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# Hippocampal GABAergic Inhibitory Interneurons

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## Abstract

In the hippocampus GABAergic local circuit inhibitory interneurons represent only ~10–15% of the total neuronal population; however, their remarkable anatomical and physiological diversity allows them to regulate virtually all aspects of cellular and circuit function. Here we provide an overview of the current state of the field of interneuron research, focusing largely on the hippocampus. We discuss recent advances related to the various cell types, including their development and maturation, expression of subtype-specific voltage- and ligand-gated channels, and their roles in network oscillations. We also discuss recent technological advances and approaches that have permitted high-resolution, subtype-specific examination of their roles in numerous neural circuit disorders and the emerging therapeutic strategies to ameliorate such pathophysiological conditions. The ultimate goal of this review is not only to provide a touchstone for the current state of the field, but to help pave the way for future research by highlighting where gaps in our knowledge exist and how a complete appreciation of their roles will aid in future therapeutic strategies.

## I. INTRODUCTION

In hippocampus, GABAergic local circuit inhibitory interneurons account for ~10–15% of the total neuronal cell population. In a 30-day-old Wistar rat it has been estimated that the total CA1 hippocampal neuronal population is ~350,000, which contains a conservative estimate of ~38,500 inhibitory interneurons (102). Despite being in the minority, this diverse neuronal population serves as a major determinant of virtually all aspects of cortical circuit function and regulation. Across all subfields of the hippocampus, the cell bodies of glutamatergic pyramidal neurons are organized in a three- to five-cell-deep laminar arrangement in stratum pyramidale (s.p.) and have orthogonal dendrites that span from the deep stratum oriens (s.o.) to the superficial layers of the stratum lacunosum moleculare (s.l.m.). This organization permits pyramidal neurons to receive afferent input from a variety of both intrinsic and extrinsic sources across well-defined dendritic domains. In contrast, inhibitory interneurons, which by definition release the neurotransmitter GABA, have their cell bodies scattered throughout all major subfields, and the positioning of their somatodendritic arbors allows them to integrate from a more restricted intrinsic and extrinsic afferent input repertoire than their pyramidal cell counterparts. The axons of many interneuron subtypes can remain local to the subfield housing their soma and dendrites, although some interneurons possess axons that cross considerable distances to innervate distinct subcellular compartments or alternatively form long range projections that extend beyond their original central location to ramify within both cortical and subcortical structures. Their axons can target well-defined narrow postsynaptic domains (i.e., soma and proximal dendrites) or can provide widespread input to large

portions of target cell dendrites. This innervation of different postsynaptic cellular compartments ensures that virtually all domains of their principal cell targets receive extensive coverage and importantly introduces the concept that each interneuron subtype performs a distinct role in the hippocampal circuit. Interneurons are primarily providers of inhibitory GABAergic synaptic input, a physiological role that utilizes $Cl^-$ influx or $K^+$ efflux via cognate $GABA_A$ or $GABA_B$ receptor activation, respectively, to transiently hyperpolarize or shunt the cell membrane away from action potential threshold. They play major roles in not only the regulation of single cell excitability, but provide well-timed inhibitory input that dictates the temporal window for synaptic excitation, and subsequent action potential initiation, thus shaping the timing of afferent and efferent information flow. In addition, they harness and synchronize both local and distributed cortical circuits to facilitate oscillatory activity across broad frequency domains.

In 1996 Freund and Buzsaki (352) published a seminal and comprehensive review of the state of the field of inhibitory interneuron research, which served as a manifesto for subsequent research in the decades that followed. Rereading their review today we are struck by the observation that at that time the field was dominated by careful and precise anatomical investigations, with only a small number of laboratories performing any cellular electrophysiological or circuit analysis of their function either in vitro or in vivo. Moreover, little was known about interneuron embryogenesis and development, and our appreciation of the roles inhibitory interneurons played in neuronal circuit disorders was primarily focused on their role in the epilepsies. Indeed, a PUBMED search of the term inhibitory interneuron up to 1996 reveals a little under 1,000 relevant publications. In contrast, between 2011 and 2016, there were >2,500 publications on hippocampal interneurons. This surge in interest has precipitated development and adoption of exciting new tools that are being used to interrogate the roles played by specific interneuron cohorts in virtually every aspect of cortical development and circuit function as well as their participation in a number of cortical circuit disorders. Indeed, this is an exciting time for inhibitory interneuron research.

During the planning phase of this review it became clear that this might be one of the last times that any attempt should be made to provide a compendium of the field of hippocampal inhibitory interneurons. Indeed, the request to write a review on “inhibitory interneurons” seems in hindsight somewhat ridiculous given their role in virtually all aspects of cortical development and function and would be akin to asking someone to write a review of pyramidal cells; the literature is simply too vast. However, we decided that we would indeed make an attempt, to document what we consider to be the most important aspects of interneuron research, to highlight the appreciation of the important roles played by this diverse cell population, and to posit questions we feel are important for future research. Accordingly, we have endeavored to cover as many aspects of hippocampal interneuron anatomy, intrinsic and synaptic physiology, circuit connectivity, and their roles in oscillations and nervous system disorders as we possibly could. However, it is impossible to discuss every aspect of these extensive fields in full, and where possible we have indicated other review articles or original research that we consider important for a true appreciation of many of these topics. It is often hard to comprehend how far this field has come in such a short time. However, as will be evident to anybody reading this review, it is also clear that only a very small number of cell types have been systematically explored in great depth, leaving the study of many other interneurons incomplete but tantalizingly tractable given the numerous emerging tools and mouse reporter lines.

## II. ANATOMY

One of the most striking features of cortical GABAergic interneurons is their remarkable anatomical diversity. The variety in morphological features of interneurons originally revealed by Golgi impregnation inspired Santiago Ramon y Cajal in the early 20th century to suggest that “. . . the functional superiority of the human brain is intimately bound up with the prodigious abundance and unusual wealth of forms of the so-called neurons with short axon . . .” (933). Cajal argued that the particular elaboration of diverse interneurons in higher primates was responsible for more complex brain functions and characterized interneurons as “butterflies of the soul.” The evaluation of diverse Golgi-stained interneurons performed by Cajal, and later his pupil Lorente de No, provided the earliest evidence for a functional significance of morphological diversity (694, 933). By meticulously cataloging the characteristic laminar distributions of dendritic processes and axonal arborizations, it was possible to predict likely sources of afferent input and postsynaptic target selection, respectively, providing a morphological basis to predict circuit function.

Indeed, it is now recognized that anatomical specialization among cortical interneuron subtypes allows for a division of labor that affords inhibitory networks exquisite spatiotemporal control over principal cell activity, rather than providing generalized inhibition (586, 1036).

Though imperfect on its own as a means for successful classification of interneuron subtypes (264, 902), neuroanatomical profiling as the primary basis for understanding interneuron diversity endured for more than half a century and remains a core feature of all modern day polythetic classification schemes. Typically, contemporary interneuron taxonomical approaches complement anatomical features with 1) developmental origins, 2) molecular expression profiles, 3) intrinsic electrophysiological membrane properties, and 4) in vivo temporal firing distributions. In this section we summarize information regarding major anatomical features including typical cell soma localization, dendritic arborizations, postsynaptic target cell-type/domain specificity, and quantitative estimates of cell numbers/output synapse numbers with relation to basic developmental origins and molecular expression profiles for widely recognized and studied interneuron subsets. Other sections deal explicitly with lineage-driven genetic programs specifying interneuron fate (sect. III), intrinsic electrophysiological features (sect. IV), and in vivo firing properties of distinct interneuron cohorts (sect. XV). Descriptions are primarily based on findings from the rodent hippocampal CA1 region, which has a highly simplified laminar architecture that significantly aids in interneuron identification and where interneuron diversity is arguably best appreciated (schematically summarized in FIGURE 1). However, the majority of interneurons described have homologs throughout the remaining hippocampus and isocortex of mouse, rat, cat, monkey, and human. Our goal in this section is not to provide a comprehensive historical survey of the existing literature describing interneuron anatomical diversity but instead to provide an updated and consolidated snapshot of the current state of knowledge for widely studied interneuron subtypes. Essentially, we adopt the molecularly and anatomically defined hippocampal interneuron subtypes outlined in previous reviews (352, 1036, 586), layer in quantitative estimates produced by Bezaire and Soltesz (102) along with developmental origins, and provide additional relevant updated information related to these features. For simplicity, we use the term interneuron generally to refer to GABAergic nonpyramidal cells.

### A. Axo-axonic or Chandelier Cells

Axo-axonic cells (AACs) are estimated to make up ~4% (~1,500 cells) of CA1 hippocampal interneurons, thus representing 0.04% of all CA1 neurons assuming interneurons account for 11% of the total neuronal population (102). Cell somas typically reside within (70%) or immediately adjacent to the s.p. both in s.o. (24%) and stratum radiatum (s.r.) (6%). Their mostly aspiny, radially oriented dendrites frequently span all layers from the alveus to the s.l.m. with minimal branching in s.r. and prominent tufts in the alveus and s.l.m., positioning them to receive excitatory input from all excitatory afferent projections innervating the hippocampal CA1 region (FIGURE 2A) (135, 582, 676). However, a subset of AACs possess exclusively or dominantly horizontally oriented dendrites within s.o. (381, 1163). The axon originates from the soma or a primary dendrite and densely arborizes throughout s.p. and superficial s.o. with terminals exclusively targeting the axon initial segments of up to 1,200 pyramidal cells (FIGURE 2A) (135, 676, 1037). Main axonal branches run horizontally along the s.p.-s.o. border and drop collaterals into s.p. where terminals are arranged in vertical or oblique rows of 2–15 boutons with each row innervating a single pyramidal cell postsynaptic axon initial segment (FIGURE 2B). These characteristic candlestick-like terminal arrays or axon cartridges are the major distinguishing anatomical feature of AACs and underlie their alternative nomenclature as Chandelier cells. CA3 hippocampal AACs exhibit anatomical features similar to those in CA1 though their axonal spread may be greater (441, 1175). In the dentate gyrus (DG), AACs reside within or immediately adjacent to the granule cell layer and typically extend dendritic trees towards the hippocampal fissure to receive afferent input throughout the molecular layer with only very sparse dendritic targeting towards the hilus (136, 461, 1040). As in the CA regions, DG AAC terminals are arranged in rows of boutons that exclusively target the axon initial segments of postsynaptic targets in the hilus and proximal CA3 including granule cells, hilar mossy cells, and displaced CA3 pyramidal cells. Neocortical AACs exhibit similar candlestick-like axonal cartridges innervating neighboring pyramidal cell axon initial segments and are found in all cortical layers with a bias towards upper layer 2/3 (540, 1033, 1079, 1097, 1218). Thus, throughout hippocampus and neocortex, selective innervation of axon initial segments by AACs provides exquisite control over principal cell spike generation.

Generally, the calcium binding protein parvalbumin (PV) is considered a core molecular marker for mature AACs with immunolabeling detectable throughout their somatodendritic and axonal compartments (FIGURE 2A) (74, 352, 563, 1036, 1041). However, while PV expression is limited to GABAergic interneurons in the cortex and hippocampus (183, 600), it is not restricted to AACs. Further complicating matters, recent evidence indicates that only 15–50% of neocortical AACs are PV immunopositive depending on cortical region examined (475, 1097). Though PV-negative AACs have not been reported in the hippocampus (e.g., Refs. 344, 582, 1163, 1175), cellular PV expression levels themselves are reportedly plastic (280). In CA1, AACs are estimated to represent 15% of PV+ interneurons with the remainder made up mostly of PV+ basket cells (PVBCs) and bistratified cells (BiCs) (discussed below) (74). Anatomically, PV+ axon terminals of AACs can be difficult to differentiate from neighboring PV expressing terminals of perisomatic targeting basket cells. However, AAC terminal identification can be confirmed by inspecting for bouton alignment with ankyrin G-expressing principal cell axon initial segments (FIGURE 2B) (e.g., Refs. 344, 1163, 1175). Among PV-expressing hippocampal interneurons, mature AACs are further distinguished by the absence of immunoreactivity for the transcription factor SATB1, which is present in most medial ganglionic eminence (MGE)-derived interneurons including the other PV expressing populations (209, 267, 1163, 1175).

Both hippocampal and neocortical AACs have origins in MGE with specification driven by the homeodomain transcription factor Nkx2.1 (1097, 1137, 1218). With the assumption that MGE-derived interneurons account for ~60% of all CA1 interneurons with relative contributions of 35/25/40% from PV, somatostatin, and neurogliaform/Ivy interneuron cohorts, respectively, AACs account for ~5% of MGE-derived hippocampal interneurons since AACs represent 15% of all PV interneurons (102, 1137). Interestingly, a large percentage of neocortical AACs are derived late in gestation (~E15–17) from Nkx2.1-expressing progenitors contrasting with other MGE-derived interneurons that are generated earlier in gestation (~E9–13) (1097). Thus using an Nkx2.1-Cre$^{ER}$ driver line with temporally late tamoxifen administration allows genetic access to large numbers of neocortical AACs (1097). Whether hippocampal AACs can also be selectively genetically targeted with this strategy has not been explicitly investigated. However, preliminary evidence indicates that hippocampal AACs are born with temporal profiles that are distinct from their neocortical counterparts (Hiroki Taniguchi, personal communication). For in depth evaluation and discussion of common transgenic mouse driver/reporter lines available for dissecting distinct interneuron cohorts, including the Nkx2.1-Cre$^{ER}$ driver line along with others outlined below, readers are referred to References 475, 1096.

### B. Parvalbumin-Expressing Basket Cells

PVBCs are estimated to comprise ~14% (~5,530 cells) of CA1 interneurons (1.5% of CA1 neurons) (102). PVBCs frequently have large pyramidal shaped or fusiform somas typically residing within (70%) or immediately adjacent to s.p. both in s.o. (24%) and s.r. (6%). PVBCs predominantly display mostly aspiny, pyramidal-shaped, or bitufted dendritic trees spanning from the alveus to s.l.m., positioning them to receive input from all excitatory afferent projections innervating the hippocampal CA1 region (FIGURE 2C) (135, 768, 1014). The axon emerges from the soma or a primary dendrite and ultimately gives rise to large numbers of collaterals forming basketlike dense pericellular arrays of synaptic boutons primarily innervating the soma and proximal dendrites of pyramidal cells (99% of output synapses), with a minority of outputs (1%) forming autapses or contacting other interneurons (FIGURE 2, C and D) (102, 211, 884, 1014). Individual PVBCs contact up to 2,500 pyramidal cells with an average of 6 synapses onto each one (102, 340, 352, 1014). The axonal arbor is highly concentrated within s.p. but can spread to varying degrees into s.o. and s.r. (885), and recent evidence suggests that output targets may be biased towards deep versus superficial pyramidal cells (656). Cell bodies of PVBCs in the DG tend to localize among deep granule cells at the hilar border extending both basal and apical dendrites that sample inputs from the hilus to the outer molecular layer (30, 593, 998, 983). The axons of PVBCs in the DG primarily innervate perisomatic regions of granule cells yielding a dense axon cloud throughout stratum granulosum (s.g.). In the neocortex PVBCs have multipolar dendrites with cell somas that tend to concentrate in deeper layers (569, 1134). As in hippocampus, neocortical PVBCs innervate the perisomatic regions of postsynaptic principal cells; however, the lack of clear lamination makes this anatomical assessment difficult and at the gross level the axon may appear to be randomly distributed. Indeed, neocortical PVBC axonal arborization territories can remain local, translaminar, and even transcolumnar.

PVBCs have origin in the MGE with specification driven by the homeodomain transcription factor Nkx2.1 (21% of MGE-derived interneurons, see assumptions above) (147, 575, 1138, 1233). As the name implies, mature PVBCs characteristically express PV, which can be detected throughout the somatodendritic and axonal compartments. Perisomatic targeting nerve terminals of mature PVBCs also express, and immunocytochemically label for, synaptotagmin 2 (386, 1030). However, while this marker is selective for perisomatic targeting PV expressing terminals, it is unclear whether it differentiates between PVBC and AAC terminals. PVBCs are estimated to represent ~60% of all PV-containing interneurons within CA1 (74). Importantly, PV expression in both hippocampus and neocortex is minimal before postnatal day (PN) 10 then increases to mature levels between PN12-P30 in rodents (14, 260, 840). Thus PV expression probed with immunocytochemistry or reported genetically based on PV promoter activity (using PV-Cre driver lines) is undetectable during embryonic and early postnatal stages. In addition, at mature stages, the degree of PV expression itself within PVBCs is reportedly plastic according to activity levels within the circuits they are embedded in, perhaps explaining in part differential staining intensities between individual cells (280).

Presently there is no genetic strategy that allows for selective targeting and manipulation of PVBCs. Though PV-Cre driver lines allow genetic access to PVBCs, these lines will additionally exhibit recombination in AACs and some PV-expressing dendrite targeting interneuron populations (see below). Moreover, addition of other commonly used metrics to confirm PVBC identity such as post hoc confirmation of PV expression immunocytochemically or spike properties also fail to differentiate among these distinct PV expressing interneuron cohorts (discussed at length in Ref. 1163). Thus caution is warranted when interpreting circuit and whole animal level experiments (e.g., optogenetic, DREADDS, or conditional knockouts) following genetic manipulation using PV-Cre driver lines. An additional complication in using PV-Cre driver lines relates to the delayed temporal expression of PV itself, which precludes genetic access at early developmental time points. Based on their MGE origin, cells destined to become PV-expressing interneurons can be targeted using Nkx2.1-Cre driver lines allowing for early genetic manipulation. However, the Nkx2.1 lineage also gives rise to dendrite targeting somatostatin (SST)-expressing interneurons, and thus use of Nkx2.1-Cre lines in isolation will result in recombination within a wide variety of perisomatic and dendrite targeting interneurons (147, 339, 1138, 1233, 1235). For reporting purposes a recently described intersectional approach using Nkx2.1-Cre in combination with SST-Flp and a newly generated intersectional/subtractive reporter line allows for simultaneous but segregated reporting of PV- and SST-expressing interneuron cohorts in red and green channels respectively (475).

## C. Bistratified Cells

BiCs are estimated to make up roughly 6% (~2,200 cells) of CA1 interneurons (0.7% of all CA1 neurons) (102). The cell bodies of most BiCs cells reside within s.p. (70%) and widely extend multipolar dendrites throughout s.o. and s.r. (FIGURE 3A) (135, 455, 561, 583, 790, 885, 1142). In contrast to PVBCs and AACs, the aspiny dendrites of these BiCs avoid s.l.m. While only a small percentage of BiCs have cell somas within s.r. (6%), nearly a quarter (24%) can be found within s.o. adjacent to s.p. and deeper towards the alvear border. Typically deeper s.o. residing BiCs extend horizontal dendritic trees that are restricted to s.o. (721, 1138, 1163). BiCs are named for their dense axonal arborizations with fine varicose collaterals split above and below s.p. simultaneously innervating both the basal and apical dendritic territories of pyramidal cells in almost equal proportion (~50% in s.o. to ~40% in s.r) (FIGURE 3A) (135, 455, 561, 583, 790, 885, 1142). While axon collaterals sparsely travel through s.p. (~10% of the axon) to connect those in s.o. and s.r., BiCs essentially avoid synapsing with the perisomatic domains of principal cells. Collaterals of individual BiCs fill the entire depth of s.o. but concentrate in deeper s.r., innervating ~1,600 postsynaptic cells with 5–10 synapses each. BiC terminals primarily target pyramidal cell dendrites with ~20% of synapses made onto spines (455). In addition, a minority of BiC terminals (~8%) make synaptic contact with other interneurons including PVBCs (455, 884).

BiCs represent ~25% of PV-expressing hippocampal interneurons with prominent immunosignal evident throughout the somatodendritic compartments (74). However, in contrast to AACs and PVBCs, BiCs coexpress neuropeptide Y (NPY) and SST, allowing them to be molecularly distinguished from the other prominent PV+ interneuron populations (75, 561, 583, 1163). Complicating interpretation of PV levels detected by immunodetection is a report that BiCs can exhibit significantly weaker PV immunoreactivity

compared with AACs and PVBCs (324). Though not extensively investigated, BiCs appear to have origin in the MGE with specification driven by the homeodomain transcription factor Nkx2.1 (9% of MGE-derived interneurons) (1138).

### D. Cholecystokinin-Expressing Basket Cells

Cholecystokinin-expressing basket cells (CCKBCs) are estimated to comprise roughly 9% (~3,600 cells) of all CA1 hippocampal interneurons (1% of all CA1 neurons) (102). Like PVBCs, the defining anatomical feature of CCKBCs is preferential perisomatic axonal targeting within s.p. to surround the soma and proximal dendrites of pyramidal cells (FIGURE 2E) (224, 352, 584, 1036, 1172). Individual CCKBCs contact roughly half as many pyramidal cells as PVBCs (~1,250), and it is estimated that the ratio of PVBC to CCKBC terminals on individual postsynaptic pyramidal cell targets is 1.6:1 (102, 340, 654, 1225). A minority of CCKBC synapses (~8%) innervate interneurons, typically other CCK-expressing interneurons, though cross-talk between CCKBCs and PVBCs has also been reported (5224, 554, 584). Despite the overlapping axonal profiles, CCKBCs are much less uniform than PVBCs in their somatodendritic architecture. While the majority of CCKBC somas reside within s.r., with a significant concentration at the s.r/s.l.m. border, substantial numbers can also be found in s.p. and s.o. (224, 258, 340, 584, 654, 1172). Moreover, while many CCKBCs have radially oriented bitufted or multipolar dendrites spanning all lamina from the alveus to s.l.m., others display horizontally oriented dendrites limited to s.r. or s.o. (181, 224, 258, 340, 584, 654, 721, 885, 1138, 1172). Though less studied, homologous cortical CCKBCs are primarily found in layer 2/3 and target the perisomatic regions of postsynaptic targets from layer 1 through 5 (569, 570, 611, 1134).

In the dentate gyrus, CCKBC somas almost exclusively reside at the s.g.-hilar border and subgranular polymorphic layer (352, 477, 499, 980). Much like dentate PVBCs, these dentate CCKBCs are typically pyramidal shaped with bitufted radially oriented aspiny dendrites. Basal dendrites branch throughout the hilus, and a prominent apical dendrite extends through s.g. then branches in the molecular layer and radially extends towards the pial surface. In contrast to other basket cells (all PVBCs and CA1–3 CCKBCs), dentate CCKBC terminals preferentially innervate proximal dendrites with minimal contacts onto postsynaptic target somas. Indeed, CCKBC axons traverse through most of s.g. to provide a dense band of terminals in the outer third of s.g. and the adjacent narrow band of the inner molecular layer innervating primarily the proximal dendrites of granule cells (352, 477, 499, 980). This anatomical profile overlaps with cells originally described as hilar commissural-associational pathway-related interneurons (HICAPs; Refs. 461, 1013, 457), suggesting that HICAPs and dentate CCKBCs are one and the same (499). However, inner molecular layer targeting HICAP-like cells display variable firing properties from accommodating action potential trains with slow afterhyperpolarizations (AHPs) (CCKBC like) to nonaccommodating with fast deep AHPs (PVBC, AAC, BiC like), suggesting that the term HICAP may encompass multiple diverse subtypes of interneurons (461, 499, 980, 812).

All hippocampal and cortical CCKBCs have origin in the caudal ganglionic eminence (CGE) (203, 651, 805, 1138, 1204). Assuming that CGE-derived interneurons account for ~40% of all CA1 interneurons with relative contributions of 30/30/25/10% from $CCK^+$ interneurons, interneuron selective interneurons, neurogliaform interneurons, $SST^+$ interneurons, respectively, and a remaining 5% of unidentified interneurons, CCKBCs account for 20% of CGE-derived interneurons as CCKBC comprise 65% of all $CCK^+$ interneurons (102, 203, 1138). As the name implies, the defining molecular characteristic of CCKBCs is the expression of the octapeptide form of the CCK neuropeptide (CCK-8) throughout the somatodendritic and axonal compartments of CCKBCs (352, 355, 467, 843). However, not all CCK immunoreactive neurons are CCKBCs, as CCK can also be detected in glutamatergic principal cell subsets (1096, 494) and additional subpopulations of dendrite targeting interneurons (352, 1036). Molecularly, CCKBCs are considered to parse into at least two subtypes: those that coexpress vasoactive intestinal peptide (VIP) and those that coexpress vesicular glutamate transporter 3 (VGluT3), though again neither of these markers is specific on their own for CCKBCs and a substantial proportion of CCKBCs express neither of them (5, 102, 1031). The terminals of CCKBCs are heavily endowed with cannabinoid type 1 receptors (CB1Rs) which serve as the molecular substrate responsible for depressing CCKBC GABAergic output in response to endogenous and exogenous cannabinoids (FIGURE 2F; Refs. 108, 350, 559, 1139) (see sect. VIII). CCKBC terminals have also been suggested to selectively express $GABA_B$ receptors

($GABA_B$Rs)in comparison with terminals from PVBCs potentially limiting GABA-mediated presynaptic inhibition of perisomatic inhibition to CCKBCs (47, 350, 354, 858). However, recent evidence from paired recordings indicates that PVBC-mediated inhibition is strongly depressed by pharmacological $GABA_B$R activation (116, 204) similar to findings for CCKBCs (657, 833). Thus, despite weak $GABA_B$R immunoreactivity in PVBCs compared with CCKBCs (1024), presynaptic release from both terminal subsets is functionally depressed by $GABA_B$R activation.

CCKBCs can be genetically targeted using CCK-Cre driver mice; however, additional CCK-expressing interneurons and even some glutamatergic principal cell subsets will also exhibit recombination (68, 1095, 1096). Intersectional approaches combining CCK-Cre mice with other interneuron specific marker or transcription factor driver lines can be used to selectively target CCK-expressing interneurons over principal cells. For example, CCK-Cre has been used in combination with Dlx5/6-Flp or VIP-Flp and dually conditional reporters to selectively reveal subsets of CCK-expressing interneurons (1095, 1096). Similarly, a novel recombinant adeno-associated virus that restricts gene expression to GABAergic interneurons based on Dlx5/6 enhancer elements can be used in combination with CCK-Cre drivers to selectively introduce recombinant proteins into CCK expressing interneurons minimizing the need for complicated breeding strategies (274). This latter approach also offers the opportunity to introduce exogenous proteins for activity monitoring (e.g., GCaMPs) and functional manipulation (e.g., ChR2, DREADDS) selectively into CCK expressing interneurons, without the need to generate dually conditional reporter lines for each protein of interest (274). However, as exciting as these refinements are, they do not allow for selective targeting of CCKBCs as a number of CCK-expressing dendrite-innervating interneurons will also be targeted using these combinatorial genetic approaches (see below). Thus again caution is warranted in interpreting circuit and whole animal observations following genetic manipulation involving CCK-Cre driver mice.

### E. Dendrite Targeting CCK Expressing Interneurons

In addition to CCKBCs, CCK expression can also be detected in a variety of dendrite targeting inhibitory interneurons that largely parse on the basis of axon termination zones across distinct pyramidal cell dendritic compartments (102, 581, 1036). CCK-expressing dendrite targeting interneurons together comprise between 3 and 5% (~1,500 cells) of CA1 interneurons (~0.4% of all CA1 neurons), largely reside in s.r., with some tendency to concentrate at the s.r./s.l.m. border. They generally extend multipolar dendrites spanning all layers, though horizontally oriented dendritic arbors mostly confined to s.r. have also been observed (181, 224, 452, 584, 654, 885, 1172). The axonal projections of Schaffer collateral-associated cells (SCAs) co-align with glutamatergic inputs from CA3, ramifying dominantly within s.r. and to a lesser extent in s.o. to primarily target the oblique and basal dendrites of pyramidal cells (FIGURE 3B ). Apical dendrite targeting interneurons (ADIs) are similar to SCAs but preferentially innervate the main apical shaft of pyramidal cells avoiding oblique and basal dendrites (584). The axons of perforant path-associated cells (PPAs) concentrate within s.l.m. overlapping with excitatory inputs from the entorhinal cortex and nucleus reuniens targeting the distal apical tufts of CA1 pyramidal cells (584, 1172). However, PPAs also extend axon collaterals across the hippocampal fissure to target the dendrites of granule cells further aligning their output with excitatory entorhinal input to the hippocampus (452, 584, 1172). All CCK-expressing dendrite targeting cells dominantly target principal cell postsynaptic targets with ~6 synapses per connection; however, a minority of terminals (~8%) innervate other interneurons (102, 224, 584, 1172). Dendrite targeting CCK-expressing interneurons are also found in the neocortex, most notably the vertically oriented bitufted double bouquet cells with ascending and descending tight radial axonal bundles targeting principal cell dendritic shafts and spines (263, 355, 556, 569, 1034, 1085, 1150).

The developmental origins for each subset of CCK expressing dendrite-targeting cell have not been systematically examined. However, in both neocortex and hippocampus, all CCK-expressing interneurons have so far been found to arise from the CGE (10% of CGE-derived interneurons based on assumptions outlined above) (102, 203, 651, 1138). Like CCKBCs, dendrite targeting CCK interneuron subtypes typically express CB1Rs (FIGURE 3B) (108, 289, 584, 594, 665, 1194). Additional molecular markers commonly associated with hippocampal and neocortical CCK-expressing dendrite targeting interneurons are calbindin (CB) (hippocampus and neocortex), calretinin (CR) (neocortex), and VIP (neocortex), though

none of these markers is specific for or ubiquitously expressed by CCK-expressing dendrite targeting interneurons (224, 556, 569, 584, 611, 612). While VGluT3 expression was originally described as being limited to CCKBCs (1031), it has also been detected in ADIs (584).

### F. Oriens Lacunosum-Moleculare Interneurons

Oriens lacunosum-moleculare interneurons (O-LMs) are estimated to comprise ~4.5% (~1650 cells) of hippocampal CA1 interneurons (0.5% of all CA1 neurons) (102). O-LMs are named for their striking anatomy with soma and dendrites restricted to s.o. and the alveus while the axon ascends with minimal branching through s.p. and s.r. to densely collateralize within s.l.m. (FIGURE 3C) (352, 719, 721, 768, 1014). This anatomical arrangement optimally positions O-LMs to function in a prototypical feedback inhibitory circuit. Indeed, the restriction of horizontally oriented O-LM soma and spiny dendrites within s.o. and the alveus dictates that the dominant source of excitatory recruitment is from CA1 pyramidal cell collaterals while the preferential axonal targeting to s.l.m. then distributes inhibition back to the distal apical dendritic tufts of CA1 pyramidal cells to gate excitatory input from the entorhinal cortex and nucleus reuniens (20, 106, 649, 720, 923, 1067). After emerging from the soma or a proximal dendrite, ~7% of an O-LM axon remains in s.o. while greater than 90% is targeted to s.l.m. (1014). The number of branches ascending through s.p. and s.r. is variable (typically between 1 and 5), but all branches generally continue to s.l.m. before collateralizing into a dense axonal cloud with fine varicosities dominantly innervating pyramidal cell spines and dendritic shafts (e.g., compare cell recoveries from References 324, 561, 642, 721, 768). In contrast to CCK-expressing PPA cells (see above) and the recently described CA1 SOM-containing back projection neuron (562), the axon of O-LM cells does not cross the hippocampal fissure to invade the dentate gyrus in the healthy brain; however, O-LM axon sprouting into the dentate gyrus has been reported in an animal model of epilepsy (894). Individual O-LMs are estimated to contact around 1,450 pyramidal cells with an average of 10 synapses per connection (102, 1014). A minority of O-LM terminals (~10%) innervate other interneurons in s.o., at the s.r/s.l.m border, and within s.l.m. (102, 299, 559, 592).

While O-LMs with classic horizontally oriented dendrites restricted to s.o. can be found in CA3, there are additional populations with multipolar dendrites extending across all strata except s.l.m. (352, 441, 442). The dentate gyrus O-LM equivalent is the hilar perforant path associated cell (HIPP) (352, 461, 499, 980, 1013). As in CA1, HIPPs are optimally positioned to participate in a feedback inhibitory loop gating excitatory drive from extrahippocampal projections to the distal dendrites of their principal cell targets. Thus HIPP fusiform cell bodies and their multipolar dendrites remain confined to the hilus optimally positioning them for recruitment by granule cell mossy fiber collaterals while the axon crosses s.g. to extensively arborize throughout the outer two-thirds of the molecular layer aligning with entorhinal cortex inputs to granule cell dendrites. The neocortical homolog of the O-LM cell is the Martinotti cell typically encountered in layers 2/3 and 5/6 with ascending axon forming a plexus in layer 1 targeting the distal dendritic tufts of pyramidal cells (569, 571, 1134, 1154, 1192).

The defining molecular characteristic of mature O-LM, HIPP, and Martinotti cells is the expression of SST (FIGURE 3C) (352, 571, 581, 716, 721, 862, 980, 1134, 1154). However, SST is not restricted to these cell populations, and in the hippocampus, O-LMs are estimated to comprise only 40% of SST-expressing interneurons (102, 324, 716, 862, 1154). Reelin is frequently coexpressed with SST in O-LM and Martinotti cells, but is not selective for or necessarily comprehensively expressed by these interneurons (203, 367, 651, 796, 899). Based on the frequent coexpression of NPY with SST, it is often assumed that O-LMs, HIPPs, and Martinotti cells represent subsets of NPY expressing interneurons (352, 610, 612, 1134). However, while limited evidence supports NPY expression in morphologically identified Martinotti and HIPP cells (352, 549, 612, 716, 1192), anatomically identified O-LMs repeatedly fail to immunostain for NPY (561, 862, 344). Further divergence in O-LM and Martinotti cell molecular profiles is evidenced by the frequent coexpression of CR with SST in Martinotti cells, a molecular signature that is absent from the hippocampus (203, 339, 1042, 1238). On the other hand, O-LMs express PV, albeit at significantly lower levels than AACs/PVBCs/BiCs, while PV and SST are considered mutually exclusive in the neocortex (324, 344, 561, 568, 582, 721, 1142, 1237). In the hippocampus, a conspicuously high level of metabotropic glutamate receptor 1α (mGluR1α) immunoreactivity along their horizontal dendrites further

helps to molecularly identify O-LM cells (75, 324, 581, 582, 1142). Similarly, somatodendritic labeling for the extracellular leucine-rich repeat fibronectin containing 1 protein (Elfn1) is suggested to be specific for O-LMs (561, 1073).

Interestingly, a subset of hippocampal SST-expressing interneurons, including a subpopulation of O-LMs, expresses serotonin 3A receptors (5-$HT3_A$Rs) consistent with developmental origins in the CGE (O-LMs comprise 4% of CGE-derived interneurons based on assumptions outlined above combined with the fact that O-LMs represent 40% of SST interneurons) (102, 203, 651, 1179). In contrast, Martinotti cells and 5-$HT3_A$R-lacking O-LM cells arise from MGE progenitors with specification driven by the homeodomain transcription factor Nkx2.1 (10% of MGE-derived hippocampal interneurons based on assumptions outlined above combined with the fact that O-LMs represent 40% of SST interneurons) (102, 203, 651, 794, 1042, 1134, 1138, 1213). Thus hippocampal SST-expressing interneurons, including O-LMs, appear to have dual MGE and CGE origins while neocortical SST expressing interneurons arise from the MGE only.

In general, SST-expressing interneurons can be genetically accessed in developing and mature brains using SST-Cre driver lines (702, 1096). However, given the diversity in SST-expressing interneurons throughout the neocortex and hippocampus, these lines cannot be used for selective targeting of O-LM, HIPP, and Martinotti cells (102, 535, 536, 716, 862, 1154). Moreover, off-target recombination in non-SST-expressing interneurons and even in pyramidal cells has been reported using SST-Cre lines (501, 787). In the hippocampus, preferential targeting for O-LMs has been reported using a driver line based on nicotinic acetylcholine receptor α2 subunit promoter activity (Chrna2-Cre mice) (649, 787).

### G. Neurogliaform and Ivy Cells

Neurogliaform cells (NGFCs) are estimated to make up just over 9% (~3,600 cells) of the entire CA1 hippocampal interneuron population (1% of all CA1 neurons) (102). In CA1, the small spherical somas (~15 µm in diameter) of NGFCs are typically found in s.l.m. with a minority of cells residing at the s.l.m./s.r. border and superficial s.r. (46, 165, 870). Several primary dendrites extend from the soma then branch extensively in a stellate fashion yielding a compact somatodendritic profile reminiscent of glial cells that is typically fully contained within the NGFC's local axon cloud (FIGURE 3D; Refs. 299, 367, 550, 578, 606, 926, 1137, 1172, 1280). The axon arises from the soma or a primary dendrite and extensively collateralizes giving rise to a remarkably dense local fine axonal plexus (FIGURE 3D). Indeed, despite occupying a relatively small tissue volume, the total axon length of an individual NGFC is estimated to be greater than three times that of a typical PVBC (102, 870). The strong affiliation of most CA1 NGFC input and output elements with s.l.m. optimally positions them to primarily serve a feedforward inhibitory role in gating excitatory input from the entorhinal cortex and nucleus reuniens. However, NGFC dendrites and axons can also cross the hippocampal fissure into the molecular layer of the dentate gyrus and penetrate into superficial s.r., indicating that CA1 NGFC recruitment and distribution of inhibition extend beyond s.l.m. (367, 550, 926, 927). Moreover, some NGFCs near the s.r./s.l.m border appear to demonstrate stronger affiliation with the Schaffer collateral pathway (606, 1138, 1172). In the dentate gyrus, NGFCs frequently reside in the outer molecular layer where they also exhibit dense axonal clouds that can penetrate the hippocampal fissure to invade the CA1 and subiculum subfields (48, 184). In addition, dentate gyrus NGFCs have been found in the hilus near s.g. (751). While neocortical NGFCs can be found throughout all layers, they are particularly enriched in supragranular layers and form a major constituent cell population in L1 (564, 858, 1017, 1074, 1086, 1134).

An unusual anatomical feature of NGFCs is their remarkably high density of small area en passant boutons that in many cases (50–75% of terminals) do not have clear postsynaptic targets (102, 858, 1172). Even at synaptic junctions with identifiable postsynaptic elements (typically principal cell spines, spine necks, or dendritic shafts), NGFC inputs exhibit a strikingly wide synaptic cleft (858). These features combined with the dense local ramification of NGFC axons are considered to underlie the ability of NGFCs to mediate volume transmission leading to slow dual component ($GABA_A$R- and $GABA_B$R-mediated) inhibition at virtually any postsynaptic element within their dense axonal plexus (550, 926, 927, 1074, 1086). In addition, the cloud of GABA generated from NGFC release can also activate presynaptic $GABA_B$R to mediate homosynaptic and heterosynaptic depression of GABAergic and glutamatergic release (48, 858, 859, 926, 927) sometimes with remarkable target cell specificity (204). Interestingly, NGFCs exhibit a

remarkably high degree of chemical and electrical connectivity with each other and promiscuously with additional non-NGFC interneuron subtypes allowing individual NGFCs to extend their influence well beyond their local dense axonal cloud through disinhibition and coordination of inhibitory networks (926, 1017, 1280, 1281).

Molecular markers associated with NGFCs include NPY, reelin, neuronal nitric oxide synthase (nNOS), α-actinin 2, and COUP transcription factor 2 (COUPTF2) (48, 367, 549, 796, 858, 926, 1137). However, molecular identification of NGFCs is complicated by considerable heterogeneity such that no one marker or combination of markers uniquely or comprehensively reveals the entire NGFC cohort. In both the hippocampus and neocortex, NPY and reelin are likely expressed by all NGFCs, although neither of these markers or their combination is selective for NGFCs. In CA1 hippocampus differential expression of nNOS by NGFCs correlates to distinct embryonic origins. Thus, in general, nNOS-expressing NGFCs derive from the MGE (4% of all MGE-derived interneurons based on assumtions outlined above and a 10% contribution of NGFCs to nNOS+ MGE-derived interneurons) while nNOS-lacking NGFCs derive from the CGE (25% of all CGE-derived interneurons based on assumptions outlined above) (1137, 1138). In contrast, neocortical NGFCs have singular origins within the CGE (651, 796, 1179).

Ivy cells (IvCs) are closely related to NGFCs and are estimated to be the largest cohort of hippocampal interneurons making up almost a quarter (23%, 8,800 cells) of the entire CA1 interneuron population (2.5% of all CA1 neurons) (102, 366, 1137). IvCs are named for the English ivy-like appearance of their axons which branch profusely close to their origin giving rise to a dense cloud of fine thin collaterals with frequent small en passant boutons much like those of NGFCs but targeting more proximal oblique and basal CA1 pyramidal cell dendrites (FIGURE 3E) (366). In contrast to NGFCs, IvC somas avoid s.l.m. and are dominantly found in and around s.p. but also populate s.o. and s.r. to lesser extents (366, 367, 1032, 1075, 1137). The aspiny multipolar dendrites of IvCs are less compact than those of NGFCs and frequently extend beyond their axonal span to largely inhabit s.o. and s.r., positioning them for feedforward recruitment by CA3 Schaffer collateral inputs and also for feedback recruitment by CA1 pyramidal cell collaterals (FIGURE 3E). However, a subset of IvCs located in superficial s.r. has been found to extend significant dendritic and axonal process into s.l.m. blurring the lines between the input and output domains of IvCs and NGFCs (1032). IvCs are generated from MGE progenitors (36% of MGE-derived interneurons based on assumptions outlined above and a 90% contribution of IvCs to nNOS+ MGE-derived interneurons) and their molecular signature is similar to MGE-derived NGFCs with prominent expression of NPY, nNOS, and COUPTF2, but unlike NGFCs, IvCs do not express reelin (366, 367, 606, 1137).

### H. Interneuron Selective Interneurons

While each of the interneuron subtypes described thus far exhibits some degree of connectivity among themselves and other interneurons, these homotypic and heterotypic interneuron-interneuron connections represent a minority of their outputs (~5–15%) compared with their innervation of pyramidal cells. In contrast, a distinct family of interneurons selectively or preferentially innervates other interneurons providing a cellular substrate specialized for network disinhibition. Initially, such interneuron selective interneurons (ISIs) were anatomically identified and characterized through immunostaining for CR or VIP with correlated light microscopy and ultrastructural analyses revealing that the major postsynaptic elements targeted by CR and VIP terminals were dendrites and somas of dendrite targeting GABAergic cells (5, 6, 425, 439, 449, 1046). More recently, a number of functional studies in both hippocampus and neocortex have taken advantage of transgenic animals and modern circuit mapping tools to functionally confirm that subsets of CR- and VIP-expressing interneurons do indeed mediate circuit disinhibition by selectively targeting other interneurons over pyramidal cells (185, 363, 652, 906, 908, 1145, 1270). In the hippocampus such ISIs are estimated to comprise almost 20% of all CA1 interneurons (2.2% of all CA1 neurons) and are separable into three subsets based on unique morphological and neurochemical signatures outlined below (102, 186, 352, 353).

Type 1 ISIs (ISI-1s) are CR-expressing multipolar cells with somas found throughout s.r, s.p., and s.o. (439, 1145). The smooth dendritic trees of ISI-1s arborize most extensively within s.r. but also infiltrate all other strata. A unique feature of ISI-1s is the regular occurrence of long dendrodendritic junctions in which two to seven dendrites from separate ISI-1s are intermingled for more than 100 μm frequently with varicose axons of additional ISI-1s (439). These braidlike structures connect clusters of ~15 ISI-1s and

likely serve to synchronize their activity through electrical and chemical synapses. The axons of ISI-1s ramify within s.r., s.p., and sparsely within s.o. seeking out somatodendritic compartments of interneuron targets. In contrast to pyramidal cell targeting interneurons, terminal distribution along ISI-1 axons (and all ISIs) is highly uneven with large lengths of axon exhibiting few boutons interspersed with sections of high bouton density upon encountering appropriate GABAergic postsynaptic elements. The preferred targets of ISI-1s are CB-expressing dendrite targeting interneurons (likely SCAs, PPAs, and CCK-expressing interneurons described above), other CR-expressing ISI-1s, and VIP-expressing CCKBCs. Upon encountering these cells, individual axons frequently form multiple contacts in a climbing fiber-like manner along their dendrites or soma. In contrast, anatomical observations indicate that ISI-1s essentially avoid PV expressing interneurons and pyramidal cells. Thus recruitment of ISI-1s by Schaffer collateral, entorhinal, reuniens, or CA1 pyramid collateral input is expected to preferentially disinhibit the apical dendrites of CA1 pyramidal cells within the termination zone of CA3 Schaffer collateral input.

Type 2 ISIs (ISI-2s) are VIP-expressing interneurons with cell somas typically found at the border of s.r. and s.l.m. (5, 6). The majority of these cells have a characteristic smooth or sparsely spiny dendritic tree comprised of a tuft restricted to s.l.m. positioning them for recruitment primarily by entorhinal and reuniens input. The axons of ISI-2s descend in the opposite direction to ramify in a mostly radial orientation throughout s.r. giving rise to a number of fine branches again with highly uneven terminal distributions. Like ISI-1s, the VIP-expressing terminals of ISI-2s preferentially form multiple synaptic contacts on the somas and dendrites of CB-expressing dendrite targeting interneurons (i.e., CCK-expressing dendrite targeting interneurons) and also innervate other VIP-expressing interneurons (likely CCKBCs and other ISI-2s or ISI-3s, see below) located throughout s.r. The output of ISI-2s further resembles that of ISI-1s in essentially avoiding PV-expressing interneurons and pyramidal cells as postsynaptic partners. Based on these features, ISI-2s appear to provide a disinhibitory network that largely overlaps with that of ISI-1s in the CA3 Schaffer collateral termination zone of CA1 pyramidal cell apical dendrites, but that is preferentially recruited by entorhinal and reuniens inputs. However, a subpopulation of ISI-2s exhibit bipolar radially oriented dendrites spanning all strata, suggesting overlap in function with ISI-1s. Further complication in parsing this subpopulation from ISI-1s is the fact ~50% of the bipolar ISI-2s coexpress CR with VIP while ISI-2s with dendrites restricted to s.l.m. do not express CR.

VIP and CR coexpressing type 3 ISIs (ISI-3s) have fusiform cell bodies typically residing in s.p. and deep s.r. (5, 6, 185, 439, 1145). ISI-3 dendritic trees are typically bipolar spanning all strata with a prominent tuft of several horizontally running branches in s.l.m. However, in some cases, all primary dendrites (up to 3) ascend towards s.l.m. (1145). In contrast to the other ISIs, the main axon primarily descends to s.o. where it emits several long horizontal collaterals producing a dense plexus within deep s.o. and the alveus co-aligning with the horizontal dendrites of oriens residing interneurons (FIGURE 3F). Indeed, initial anatomical studies revealed that the major postsynaptic targets of ISI-3s are the horizontal running dendrites of SST- and mGluR1α-expressing O-LMs with which individual ISI-3s form multiple synaptic contacts. Recent functional investigations have confirmed O-LMs as the preferred target of ISI-3s and additionally revealed less frequent connections between ISI-3s with other interneurons including BiCs and PVBCs but not with CA1 pyramidal neurons (185, 1145). Thus recruitment of ISI-3s is expected to primarily disinhibit O-LM-mediated feedback inhibition of the most distal apical dendritic elements of CA1 pyramidal cells in the termination zone of entorhinal and reuniens afferent input.

In the dentate gyrus, VIP and CR coexpressing interneurons homologous to ISI-3s are the most frequently encountered ISIs (352, 449). These dentate ISIs are typically bipolar with fusiform cell somas often located in s.g. or in the molecular layer and emit axons that primarily target the dendrites of SST-expressing HIPP cells located in the hilus. Thus, like ISI-3s, such dentate ISIs appear specialized to disinhibit the distal dendrites of local principal cells, the granule cells, in the termination zone of perforant path inputs from the entorhinal cortex. This disinhibitory motif is also common to the neocortex where a majority of vertically oriented bipolar VIP and CR coexpressing interneurons reside in layer2/3 and emit axons that preferentially innervate dendrite targeting SST expressing interneurons within the same column (168, 363, 425, 475, 553, 652, 906, 928, 1046, 1134, 1270).

In both neocortex and hippocampus, CR- and VIP-expressing ISIs represent subsets of 5-HT$3_A$R-expressing interneurons and have singular origin in the CGE (combined ISIs represent 30% of CGE-derived interneurons based on assumptions outlined above) (102, 203, 651, 796, 1138, 1179). Genetic

access for manipulation of ISIs is available through use of VIP-Cre and CR-Cre driver lines of mice (1096). Indeed, these driver lines have been successfully used in a number of recent studies to dissect circuit functions of ISIs in both hippocampus and neocortex (363, 553, 652, 906, 908, 1145, 1270). In both regions the inclusion of VIP-expressing CCKBCs when using VIP-Cre driver mice is a potential confound to data interpretation at circuit and whole animal level investigations. Similarly in the neocortex, the expression of CR by subsets of SST expressing Martinotti cells could complicate interpretation of studies using CR-Cre driver mice. The recent development of tools that allow for an intersectional approach reliant upon VIP and CR coexpression (i.e., VIP-flp with CR-Cre driver lines) offers the potential to significantly refine genetic targeting of ISIs (475).

## III. DEVELOPMENT AND EMBRYONIC ORIGINS

The remarkable diversity of cortical interneurons directly relates to their spatiotemporal origins from discrete progenitor pools within the developing embryonic telencephalon (71, 227, 1213). Indeed, although distinct interneurons require weeks of postnatal maturation to fully attain their subtype-defining characteristics, evidence accumulated over the past two decades has revealed striking correlations between the place and time of birth of interneurons and their ultimate subtype identity in the mature neocortex and hippocampus. This suggests that genetic restriction of neuronal potential at the progenitor stage is a major determinant of interneuron diversity. Interestingly, neocortical and hippocampal interneurons are generated from progenitor pools in the ventral subcortical telencephalon (subpallium) far removed from their ultimate target locations in the cortical circuits of the dorsal telencephalon (pallium). This contrasts with excitatory principal neurons that are generated in the dorsal telencephalon in close proximity to the cortical circuits they will establish by invading the cortical plate through radial migration. Thus nascent interneurons must undergo long-range ventral to dorsal (subpallial-to-pallial) tangential migration before invading target cortical circuits via radial migration. Then, through a combination of intrinsic genetic programs and local circuit activity, a given interneuron undergoes terminal differentiation towards its mature identity to fulfill its role within the circuit. In this section we briefly highlight the genetic programs, cell and molecular mechanisms, as well as local circuit activities underlying this broad developmental program of cortical interneurons starting with features of the subpallium associated with generating interneuron diversity. Due to the richness of available data, our discussion is based on findings from mouse; however, recent evidence indicates a dominantly subpallial origin for cortical interneurons in humans and primates as well (464, 714).

The developing telencephalon is first evident as a simple neuroepithelial sheet around embryonic day (E) 8.5 in mouse just as the neural tube is closing. Shortly after initial dorsoventral patterning orchestrated in part by gradients of extrinsic morphogens such as Sonic Hedgehog and fibroblast growth factors (Shh/FGFs, ventralizing influence) regulating transcription factors such as Gli3 (dorsalizing influence), a group of highly proliferative germinal zones known as the ganglionic eminences (GEs) emerge in the subpallium next to the lateral ventricle (FIGURE 4A) (476). There are three GEs morphologically defined according to their anatomical locations in the dorsoventral, rostrocaudal, and mediolateral extents of the embryonic subpallium: the medial ganglionic eminence (MGE), the lateral ganglionic eminence (LGE), and the caudal ganglionic eminence (CGE). These GEs arise in a discrete temporal order with the ventral MGE appearing first around E9 followed by the dorsal LGE around E10 with a prominent sulcus separating the two at more anterior levels. The CGE arises around E11 and was proposed as a discrete entity as the eminence that is posterior to the fusion of the MGE and LGE and, thus, is not physically separated from the MGE and LGE. Importantly, these GEs are only transiently distinguishable based on morphological criteria. For example, the prominent sulcus separating the LGE from the MGE disappears beyond E15.5 and ultimately all of the GEs fuse and give way to basal ganglia structures in the mature telencephalon. However, a more reliable map of these distinct germinal territories is revealed by gene expression profiles (see below).

Studies demonstrating that DilC18 (also known as DiI) fluorescently labeled GE derived cells migrate dorsally to the developing cortical telencephalon provided the first direct evidence for subpallial origins of cortical interneurons (35). Moreover, mutant mice lacking the homeodomain transcription factors Distaless 1 and 2 (Dlx1/2) that are expressed by most subpallial progenitors exhibited a severe reduction in subpallium-to-pallium interneuron migration resulting in a 70% reduction in neocortical interneurons (35).

Following these observations, a great number of studies using transplantation techniques, analyses of knockout mice, and genetically inducible fate mapping (GIFM) have confirmed the ventral origins of cortical interneurons and significantly refined our understanding of the discrete spatiotemporal origins for specific interneuron subtypes (147, 203, 335, 339, 391, 519, 651, 681, 794, 796, 797, 829, 914, 1042, 1068, 1097, 1137, 1138, 1179, 1202, 1214, 1233, 1273). In general, these studies have found that the vast majority (~90%) of cortical interneurons arise from progenitor pools in the MGE and CGE primarily between E9 and birth (schematically summarized in FIGURE 4B). In addition, a small diverse population of cortical interneurons is generated in a proliferative zone ventral to the MGE called the preoptic area (POA).

### A. The Medial Ganglionic Eminence

The MGE produces ~60% of neocortical and hippocampal interneurons (147, 914, 1138, 1213). In neocortex, the vast majority of PV (e.g., PVBCs and AACs) and SST (e.g., Martinotti cells) expressing interneurons are derived from MGE progenitors (147, 339, 914, 1213, 1235). In the hippocampus, MGE-derived interneurons include PV-expressing interneurons (PVBCs, BiCs, AACs), IvCs, ~60% of SST-expressing cells (e.g., O-LMs), and a subset of NGFCs (203, 914, 1137, 1138) (FIGURES 1, 4B, and 5). The majority of progenitors within the MGE, but not CGE or LGE, are molecularly defined by expression of the homeodomain transcription factor Nkx2.1, which is necessary for the generation and proper specification of mature interneuron subtypes derived from MGE progenitors. Indeed, Nkx2.1 null mice have a 50% reduction in cortical interneurons; however, death at birth precludes finer analysis of specific interneuron subtypes in mature brains (1068). Subsequent studies investigating postnatal mice with conditional loss of Nkx2.1 within MGE progenitors confirmed dramatic reductions in PV and SST interneuron populations in both neocortex and hippocampus as well as nNOS expressing IvCs and NGFCs in the hippocampus (148, 1137). Moreover, GIFM studies using Nkx2.1-Cre driver lines have confirmed that mature MGE-derived interneurons comprise these populations consistent with earlier findings from MGE transplantations (147, 212, 335, 339, 1137, 1138, 1202, 1214, 1235).

The transcription factor Lhx6 is an essential downstream effector of Nkx2.1 that is upregulated in MGE-progenitors upon exiting the ventricular zone (VZ) and persists through adulthood in most MGE-derived interneurons (212, 288, 339, 426, 433, 639, 1068) (FIGURE 4B). Loss of Lhx6 function produces deficits in MGE-derived interneurons by disrupting migration and specification to PV and SST fates (681, 1273). Downstream of Lhx6, the transcription factors Sox6 and SatB1 direct the migration, survival, specification, and functional maturation of PV and SST interneurons, respectively (52, 72, 209, 267, 826). Combined these studies highlight the critical contributions of transcription factor cascades initiated within discrete pools of subpallial progenitors in the generation of distinct cortical interneuron subtypes. Indeed, in the mice with conditional loss of Nkx2.1 mentioned above, MGE-derived interneurons are respecified towards subtype fates typically associated with CGE or LGE origins reflecting a dorsalization of the MGE progenitor zone (148, 1068). Thus Nkx2.1 serves as an example of a master regulator gene expressed in a defined proliferative region of the subpallium responsible for driving cell fate decisions by serving as a molecular switch that favors MGE over CGE/LGE fates. Importantly, Nkx2.1 expression within the MGE is driven by Shh signaling, and conditional loss of Shh replicates the MGE-derived interneuron deficits observed in Nkx2.1 mutants illustrating the continued requirement of this critical morphogen in establishing proliferative zone identity beyond initial pallial-subpallial patterning (1233, 1234, 1236).

The fact that multiple distinct cell subtypes are generated from the MGE suggests the possibility of smaller subdivisions within this progenitor pool. Indeed, based on the combinatorial expression profiles of several transcription factors within the MGE ventricular zone, it has been proposed that this region consists of up to five distinct progenitor domains (335). Thus, in a manner akin to generating cellular diversity within the spinal cord (531), spatially segregated progenitor lineages with restricted fate potential dedicated to producing particular interneuronal subtypes was considered to underlie cortical interneuron diversity. However, microtransplantation fate-mapping studies revealed mixed populations of mature interneuron subtypes generated from individual MGE subregions (335, 519, 1214). Moreover, recent clonal analysis revealed that individual MGE progenitors can give rise to both PV- and SST-expressing interneurons that disperse widely throughout the neocortex and hippocampus revealing that progenitors are not restricted to making one interneuron subtype (129, 207, 469, 766).

Though spatially segregated subdivisions of MGE progenitors are not absolutely deterministic of mature interneuron fate, transplant and GIFM studies consistently revealed biases for SST-expressing interneurons to originate from the dorsal MGE (dMGE) and for PV expressing interneurons to originate from the ventral MGE (vMGE) (335, 336, 339, 519, 1042, 1214, 1234) (FIGURE 4B). This spatial bias is nicely illustrated by GIFM studies based on Nkx6.2 which is strongly expressed in dMGE progenitors near the CGE border but absent in vMGE (339, 1042, 1214). In the mature neocortex interneurons from the Nkx6.2 lineage adopt primarily SST fates, particularly SST/CR coexpressing Martinotti cells, and rarely exhibit PV interneuron fates (339, 1042). In contrast, microtransplantations revealed that PV AACs derive almost exclusively from the ventral-most MGE progenitors (519). This dorsoventral bias in SST versus PV interneuron generation relates to the level of Shh signaling such that high Shh signaling favors SST over PV interneuron generation (1146, 1234). Indeed, a number of Shh effectors beyond Nkx2.1 are enriched in dMGE over vMGE including the above-mentioned Nkx6.2 (1214, 1258). Curiously, a major source of Shh within the subpallium is the ventricular zone of the POA far removed from the dMGE where SST interneurons are dominantly generated and close to the vMGE (FIGURE 4A). However, recent evidence indicates that dMGE progenitors receive additional Shh signal secreted from nascent MGE-derived neurons in the mantle zone of the MGE induced to express Shh by Lhx6/Lhx7 transcriptional regulation (337). Thus immature early postmitotic neurons exiting the proliferative zone themselves provide feedback signaling instructive for dMGE progenitor developmental programs and as such influence the balance of SST versus PV interneuron production (FIGURE 4B).

Complementing the spatial control of interneuron specification within the GEs is a temporal dynamic that has significant impact on mature interneuron fate (147, 519, 794, 796, 909, 1097, 1138). Within the MGE, SST-expressing interneurons destined for the neocortex exhibit a peak in neurogenesis around E11.5 while neocortical PV expressing interneuron production peaks around E13.5. In the hippocampus SST and PV interneurons both exhibit peaks in their genesis around E11.5; however, nNOS expressing IvCs/NGFCs exhibit a later peak in production around E13.5. The distinct temporal windows for different interneuron subtype generation are particularly striking when comparing PV-expressing AACs with SST-expressing hub cells which serve as organizers of early patterned network activity. Indeed, SST hub cells are generated from Nkx2.1 progenitors at the earliest time points of interneuron production (E9.5) before the MGE is even morphologically distinguishable while PV-expressing AAC neurogenesis preferentially occurs beyond E15.5 after the MGE has morphologically flattened out into a ventral germinal zone of the lateral ventricle (475, 519, 909, 1097). Remarkably, when E16.5 Nkx2.1 expressing donor cells were transplanted into the somatosensory cortex of P3 hosts, they reliably differentiated into AACs implying that late MGE progenitors are fate committed to generating AACs by an intrinsic genetic program late in embryogenesis (1097). Thus there are clear correlations between birthdate and ultimate interneuron subtype identity. However, as for spatial influences, temporal dynamics only partially predict ultimate interneuron identity as both SST- and PV-expressing interneurons are produced in varying proportions during the dominant period of MGE neurogenesis between E9.5 and E15.5 (794, 1138).

Potentially related to temporal influences on interneuron specification are recent findings illustrating that the mode of progenitor mitosis critically influences MGE-derived interneuron fate determination (904). The periventricular proliferative zone of the subpallium consists of both the VZ and subventricular zone (SVZ) populated with apical progenitors (ApPs) and basal progenitors (BPs), respectively. In vivo manipulation of these progenitor pools combined with fate mapping revealed that ApP neurogenesis within the MGE VZ is strongly biased to produce SST interneurons, while BP neurogenesis within the SVZ yields primarily PV interneurons (904). These findings are consistent with prior evidence that loss of the cell cycle regulator cyclin D2, which is enriched within SVZ BPs of the MGE, results in a 30–40% reduction in PV-expressing neocortical interneurons with no change in SST interneuron numbers (405, 406). It has been postulated that VZ ApPs could undergo asymmetric cell division to yield SST interneurons and SVZ BPs (which will produce PV interneurons), thus neatly explaining why SST interneurons tend to be born earlier and how individual progenitors give rise to mixed clones of SST- and PV-expressing interneurons (58, 904).

## B. The Caudal Ganglionic Eminence

The CGE produces ~30% of neocortical and hippocampal interneurons (203, 651, 796, 963, 966, 1138, 1179). In the neocortex NGFCs (reelin-expressing, SST negative), ISIs (VIP- and CR-expressing), and CCK-expressing interneurons (e.g., CCKBCs) are derived from CGE progenitors (651, 796, 963, 1179) (FIGURE 5). In the hippocampus CGE-derived interneurons include CCK-expressing interneurons (CCKBCs, SCAs, ADIs, PPAs), ISIs (VIP and CR expressing), a subset of NGFCs, and ~40% of SST-expressing interneurons (e.g., O-LMs) (203, 1137, 1138) (FIGURES 1, 4B, AND 5). Though a specific master regulator gene, analogous to Nkx2.1 in the MGE, has yet to be discovered for CGE progenitors, a number of transcription factors such as Gsx2, CoupTF1/2, and SP8 are enriched within the CGE and have been implicated in the generation, migration, specification, and maturation of CGE-derived interneurons (547, 688, 715, 797, 964, 1234) (FIGURE 4B). Interestingly, while the homeodomain transcription factor Prox1 is present in the SVZs of all GEs, its expression is selectively maintained in CGE-derived, and downregulated in MGE-derived, interneuron precursors (797, 964). Loss-of-function studies indicate that Prox1 is differentially required embryonically and postnatally for CGE-derived interneuron migration and differentiation/circuit integration, respectively (797). Further work should reveal the genetic programs responsible for promoting the selective maintenance of Prox1 in CGE-derived interneurons and, hence, delineate genetic cascades that instruct CGE interneuron fate determination.

Initially, in vitro culture and in vivo transplant studies implicated the CGE as a source of cortical interneurons that assumed mature fates distinct from MGE-derived interneurons (147, 829, 1233). Subsequently, elucidation of the full complement of CGE-derived interneurons within mature cortical circuits was achieved through GIFM using a Mash1-CreER driver line with expression fortuitously restricted to LGE/CGE-derived populations (203, 796, 1137, 1138). With the use of this inducible line, CGE interneuronogenesis was demonstrated to lag that of the MGE both for initial (E12.5 for CGE vs. E9.5 for MGE) and peak (E16.5 for CGE vs. E13.5 for MGE) generation (796). Thus general comparison of CGE and MGE interneuron production further highlights that distinct interneuron subtypes exhibit unique spatiotemporal neurogenesis profiles within the ventral telencephalon. However, in contrast to the MGE, the subtypes of neocortical interneurons generated within the CGE do not change significantly over time with similar proportions of reelin-expressing NGFCs and VIP/CR-expressing ISIs generated across CGE neurogenesis (796). Similarly, in the hippocampus, VIP- and reelin-expressing subsets of CGE derived interneurons are consistently produced between E12.5 and E16.5 (1138). However, CCK-expressing interneurons exhibit an early peak in production around E12.5, while CR-expressing interneuron genesis peaks late at E16.5 (1138). Thus, given that VIP is coexpressed by a subset of CCKBCs and also by CR-expressing ISIs, the relatively stable genesis of hippocampal VIP-expressing interneurons does not necessarily reflect consistent production of a single VIP-containing interneuron subtype throughout CGE neurogenesis.

The full complement of CGE-derived interneurons can also be investigated using constitutive GFP reporter lines based on serotonin 3A receptor promoter activity (5-HT$3_A$R-GFP mice) (203, 651, 1179). Indeed, GFP expression in these lines is largely confined to the CGE and is initiated in neuronal precursors shortly after exiting the cell cycle as they begin tangential migration. Moreover, in the mature neocortex and hippocampus, 5-HT$3_A$R-GFP reported cells are GABAergic interneurons that largely overlap (>90%) with those reported by the Mash1-CreER driver line described above, and have minimal overlap, to the populations reported in the Nkx2.1 lineage (203, 651). However, potential overlap between 5-HT$3_A$R-GFP/Mash1-CreER reported interneurons with populations from the dMGE reported by the Nkx6.2-CreER driver line has not yet been examined. This would seem important, as the dMGE is morphologically contiguous with the CGE. In the neocortex it seems unlikely that there would be extensive overlap between 5-HT$3_A$R-GFP/Mash1-CreER reported interneurons with populations from the dMGE as the vast majority of Nkx6.2 lineage interneurons express SST which is only minimally detected in 5-HT$3_A$R-GFP/Mash1-CreER reported neocortical interneurons (651, 796, 1042, 1179). Nonetheless, a large cohort of SST Martinotti cells generated from dMGE progenitors coexpress CR, a neurochemical marker typically associated with interneurons derived from CGE progenitors that is not observed in more vMGE generated Martinotti cells reported by the Nkx2.1-Cre line (SST positive and CR negative) (339, 1042). Thus it is possible that progenitors near the dMGE/CGE boundary specify interneurons with some hybrid MGE/CGE properties.

Nkx6.2 lineally related interneurons from the dMGE have not been fate mapped in the mature hippocampus, and a SST/CR coexpressing neurochemical signature is not detected in hippocampal interneurons (FIGURE 4B). However, ~40% of hippocampal SST-expressing interneurons are reported in 5-HT3$_A$R-GFP mice, and these cells do not overlap with SST interneurons in the Nkx2.1 lineage, suggesting dual MGE and CGE origins for hippocampal SST interneurons (203) (FIGURE 5). Surprisingly, this evidence for dual origins even extends to interneurons that are typically considered homogeneous with regard to their anatomical and basic electrophysiological profiles as O-LM cells significantly contribute to the SST cohorts of both lineages (203). Similarly, hippocampal NGFCs exhibit dual MGE/CGE origins (1137, 1138). In contrast, neocortical NGFCs and SST interneurons (e.g., Martinotti cells) have singular origins within the CGE and MGE, respectively (FIGURE 5). Why CGE-derived SST cells (including O-LMs) and MGE-derived NGFCs selectively populate the hippocampus and avoid the neocortex is presently unknown. However, these observations of dual origins for some hippocampal interneuron populations greatly complicate logical schemes devised around a parsing of interneuron subtypes based on spatially segregated progenitor pools.

### C. The Preoptic Area

The POA is estimated to produce ~10% of neocortical and hippocampal interneurons (389, 391). Mature cortical interneurons derived from the POA are highly diverse consisting of small fractions of PV-, SST-, NPY-, and reelin-expressing interneurons and may explain the small residual scattered populations of PV- and SST-expressing interneurons remaining in mice lacking Lhx6 (389, 391, 681, 1273). Indeed, though POA progenitors lying ventral to the MGE also express Nkx2.1, most interneuron precursors emerging from the POA do not rely on downstream activation of Lhx6 to specify PV and SST interneurons (335, 389, 391). Two subdomains are found in the POA based on nonoverlapping expression profiles for Dbx1 and Nkx5.1 (335, 389, 391). GIFM studies using Nkx5.1-Cre mice revealed primarily superficial multipolar mature cortical interneurons expressing NPY and reelin, but not other typical interneuron markers such as PV, SST, CR, and VIP (391, 390). In contrast, GIFM studies using Dbx1-Cre mice revealed that the ventral POA region generates minor populations of deep PV- and SST-expressing interneurons (389). Thus the POA contributes a minor yet highly diverse population of cortical interneurons some of which are MGE-like while others display more CGE-like mature phenotypes.

### D. Circuit Assembly and Connectivity

Upon exiting the ganglionic eminences, newborn interneurons must travel long distances to reach their final destination in either the neocortex or hippocampus (reviewed in Refs. 444, 744, 746). This is in stark contrast to excitatory principal cells (PCs), which are born locally in the VZ and SVZ and are tasked purely with radial migration to an appropriate laminar position (reviewed in Ref. 432). As described in detail below, an emerging model of cortical circuit formation suggests an important interplay between PCs and interneurons. Interneurons are channeled to developing neocortical and hippocampal regions and then allowed considerable freedom within migratory streams to disperse across the entire telencephalon. After leaving these streams they migrate radially among neighboring PCs, which in turn provide cues that influence their final position and synaptic connectivity. Importantly, immature interneurons are not passive participants in circuit formation, but play a key role in generating early network activity that promotes synaptogenesis. Subsequently, they are necessary for critical period plasticity, which refines functional circuits and sensory maps. Although the mechanisms are still being elucidated, the end result is mature circuitry composed of interneurons and PCs that demonstrate preferential connectivity and distinct synaptic dynamics dependent on the subtype identity of both the pre- and postsynaptic partners.

### E. Migration of Interneurons From the Ganglionic Eminences to the Telencephalon

Nascent interneurons exit the GEs via several migratory routes, which they follow before dispersal throughout the neocortex and hippocampus (38, 829, 1123, 1202, 1254) (and see reviews in Refs. 444 and 744). MGE- and CGE-derived interneurons reach the dorsal telencephalon via separate pathways: those from the MGE travel via dorsolateral routes while those from the CGE follow three distinct routes laterally, medially, and caudally. The choice of migratory path appears to be an intrinsic property of cells dependent on their region of origin and ultimate destination, and governed by different transcription factors (547, 829, 842, 1123, 1254). For example, MGE-derived interneurons transplanted into the CGE do

not join native CGE-derived cells along the caudal pathway, but rather migrate laterally and rostrally (1254). However, they can be induced to follow the caudal pathway when forced to overexpress COUPTF2, a transcription factor preferentially expressed in the CGE (547). CGE-derived interneurons themselves express differential combinations of the transcription factors SP8, PROX1, COUPTF1, and COUPTF2 dependent on which of the three migratory paths they take (1123). Finally, as mentioned, MGE progenitors preferentially express the transcription factor Nkx2.1 (147, 148, 829, 1233), which must be downregulated in migrating postmitotic cells in order for them to avoid the striatum and reach the cortex (842). Expression of Nkx2.1 represses transcription of neuropilin-2 (842), a receptor necessary for migrating interneuron repulsion by semaphorin 3F expressed in the striatum (748).

As they enter the developing neocortex and hippocampus, interneurons from both GEs converge and then disperse widely via two streams running in parallel, separated by the cortical plate (CPl) or hippocampal primordium: a deep stream in the intermediate/subventricular zones (IZ/SVZ) and a superficial one in the marginal zone (MZ) (639, 736, 795, 829, 1138). It is presently unresolved why two streams exist or whether their segregation is of specific functional importance. Antypa et al. (42) found differential gene expression profiles of migrating interneurons dependent on stream location, suggesting the choice is not random. However, choice of stream is not dependent on lineage, as both MGE- and CGE-derived interneurons can be found in either (795, 963, 1138). Furthermore, although it has been suggested that interneurons segregate by future subtype (such as CCK+ interneurons being confined to the MZ), the evidence for this is conflicting (159, 805). Interestingly, interneurons from both the CGE and MGE initially enter via the IZ/SVZ, with a subset crossing to the MZ before then resettling within the CPl or hippocampus to begin radial migration (794–796, 963, 1088, 1089, 1091). Signaling mechanisms involving netrin-1 and $GABA_B$Rs attract interneurons specifically to the MZ (689, 1047), suggesting directed movement to this stream. Within the MZ, interneurons have been observed to migrate in multiple directions, seemingly at random, over long distances (469, 1088, 1089, 1091). Thus it has been proposed that movement to the MZ serves to facilitate the balancing of subtype distributions throughout different regions of the telencephalon (1089, 1091).

Multiple mechanisms act in concert to induce interneurons to leave the tangential migratory streams and take up permanent residence in the CPl and early hippocampus. The most thoroughly described involves chemokine signaling via Cxcl12, which acts as an attractant to keep interneurons within the IZ/SVZ and MZ until they reach appropriate maturity to begin radial migration (672, 690, 973, 1191). Cxcl12 is expressed at high levels within the IZ/SVZ and MZ, and mutations of the receptors Cxcr4 and Cxcr7 result in premature accumulation of interneurons within the CPl (672, 690). Cxcr7 regulates the local concentrations of Cxcl12 sensed by Cxcr4 and controls Cxcr4 protein levels (973). As interneurons mature, Cxcr7 is downregulated, leading to Cxcr4 protein degradation, which in turn acts as a permissive cue for interneurons to leave the tangential migratory streams (672, 973, 1191). Calcium signaling, modulated by neurotransmitters, also plays an important role in the transition to radial migration. Glutamate, via AMPA and NMDA receptors, activates voltage-gated calcium channels to promote invasion of the CPl and hippocampus (78, 117, 736). In CGE-derived interneurons, depolarization via ionotropic 5-$HT3_A$Rs serves as an additional mechanism (819). Importantly, GABA either promotes or arrests radial migration dependent on cell maturity. This is due to developmental regulation of the chloride gradient (91, 872, 947, 1241), which renders $GABA_A$ depolarizing during early time points (for detailed reviews, see Refs. 89, 92). This is accomplished by regulated expression of the K/Cl cotransporter KCC2, which extrudes chloride, and Na-K-2Cl cotransporter, NKCC1, which accumulates chloride. Migrating interneurons initially express low levels of KCC2, which allows GABA to increase motility via depolarization and activation of voltage-gated calcium channels (117). However, KCC2 levels increase as interneurons mature which renders $GABA_A$ hyperpolarizing to reduce calcium influx and stop radial migration within the cortex (117, 795).

### F. Establishment of Laminar Position During Radial Migration

Developing interneurons must properly integrate within local circuits, and an emerging model proposes that PCs instruct their radial migration and synaptic connectivity. In the cortex it is well established that PCs laminate in an inside-out manner according to their birthdate: early born cells take up residence in deep layers while those born later populate the superficial layers (40). Furthermore, the PCs are

functionally organized among the lamina: corticocortical projection neurons are predominantly found in the superficial layers while subcerebral and corticothalamic projection neurons are found only in deep layers. This organization is likely due to temporal restriction of progenitor potential and specialized progenitor pools within the VZ (reviewed in Ref. 432). In the hippocampus there also appears to be a laminar organization to PCs within the tightly packed s.p., and, similar to cortex, early born cells are deeper (closer to the s.o.) with respect to those born later (reviewed in Ref. 1023). As described in detail below, the lamination of different interneuron subtypes correlates with multiple variables, including birth order and embryonic origin from either the MGE or CGE. However, such intrinsic properties may be primarily important for restricting the response of interneurons to local extrinsic signals from PCs, which invade the CPl and early hippocampus first (39, 179, 432, 796, 913, 1138).

Choice of layer in both the cortex and hippocampus most strikingly correlates with embryonic origin ( FIGURE 6A). In cortex, MGE- and CGE-derived cells are biased towards the deep and superficial layers, respectively (795, 796). Similarly, in the hippocampus, MGE-derived interneurons are biased towards the deeper s.o. and s.p., while those from the CGE are primarily found in the more superficial s.r. and s.l.m. (1138). Furthermore, MGE-derived interneurons laminate in the cortex according to birth order in the same inside-out manner as PCs: early born cells migrate deeper than those born later (310, 794, 913, 1155). In contrast, CGE-derived interneurons lack any such correlation with birth order; rather, their attraction to the superficial layers is dominant regardless of birthdate (796). These findings imply that intrinsic factors play an important role in determining laminar position. However, in a key study, Miyoshi et al. (795) found that all interneurons, regardless of birthdate or embryonic origin, are initially distributed evenly throughout all layers of cortex and only later migrate to their final laminar position. Specifically, MGE- and CGE-derived cells, born on either E12.5 or 16.5, are all indistinguishable regarding their laminar position at PN1. They only begin to sort by layer around PN3 and do not take up the stereotyped positions described above until the end of the first postnatal week (FIGURE 6B). This suggests that coordination between intrinsic cell identity and extrinsic cues found locally in the cortex is necessary to guide interneuron migration.

Several lines of evidence implicate PCs as an important source of such guidance cues. In mutant mice in which PC lamination is disrupted, interneurons are correspondingly displaced. For example, in the reeler mouse model, in which expression of reelin or associated proteins is disrupted, the lamination of PCs in cortex is inverted and the s.p. of the hippocampus is split in region CA1 (178–180, 945). In the cortex of reeler mice, MGE-derived interneurons are inverted similar to PCs: early-born cells are found ectopically in superficial layers while those born later are found in the deep layers (489, 913). Furthermore, there is a corresponding inversion of common interneuron molecular markers among the layers (913). Importantly, interneurons lacking the reelin receptor Dab1 migrate to the appropriate layer when transplanted into the cortex of wild-type mice (913). Thus loss of reelin signaling does not disrupt interneuron lamination in a cell-autonomous manner; rather, it disrupts PC lamination, which in turn instructs interneuron migration. In the hippocampus of wild-type mice, the somas of PV-expressing interneurons commonly reside close to or within s.p. Interestingly, in reeler mutants, these interneurons maintain this laminar profile and are often found within the split bands of PCs in region CA1 (121). A very similar phenomenon is observed for PV-expressing interneurons in Lis1 mutant mice, in which the PCs also split into multiple bands (338). Thus the soma and axons of PVBCs appear to be attracted to the somas of hippocampal PCs, whereas the somas of PCs may be repulsive for the axons of PV-expressing BICs. Finally, in utero knockout of doublecortin arrests radial migration of neocortical PCs out of the VZ, resulting in an ectopic cluster of PCs within the white matter below layer 6, and interneurons are specifically attracted to these clusters (935).

Recent work in the neocortex has demonstrated that PCs can modulate interneuron migration in a subtype specific manner and has begun to identify potential molecular mechanisms. In particular, Lodato et al. (687) studied the effects of knocking out Fezf2, a transcription factor necessary for the specification of subcerebral projection neurons in deep cortical layers (195, 196, 798). The loss of subcerebral-projecting PCs correlated with a shift of PV- and SST-expressing interneurons from deep to superficial layers (687) (FIGURE 6Ci). Conversely, overexpression of Fezf2 in utero produced ectopic subcerebral PCs below the white matter that preferentially attracted PV- and SST-expressing interneurons, but not subtypes primarily found in the superficial layers (687). Chemokine-signaling at least in part mediates this attraction of deep layer interneurons to subcerebral projection PCs. As described above, during embryonic development Cxcl12 interacts with the receptors Cxcr7 and Cxcr4 to maintain tangential migrating streams within the

IZ/SVZ and MZ. In the postnatal cortex, Cxcl12 and Cxcr7 expression are maintained preferentially in layer 5 (991, 1176). Importantly, Cxcl12 is expressed selectively on the somas of subcerebral projection neurons and Cxcr7 is expressed on the axon terminals of PVBCs (1221) (FIGURE 6Di). Knockout of Cxcl12 results in reduced perisomatic inhibition onto this specific subtype of PC in layer 5. Furthermore, when embryonic MGE-derived interneurons lacking Cxcr7 are transplanted into the cortex at PN1, they fail to migrate to layer 5 and instead accumulate in the superficial layers in adult animals (1176) (FIGURE 6Dii). Finally, when PCs are induced to take on a subcerebral projection identity via Fezf2 overexpression, the number of synapses they receive from local PVBCs increases (1249) (FIGURE 6Cii). Together, these data clearly demonstrate that the patterns of radial migration and synaptic connectivity of interneurons strongly depend on their own subtype identity and that of local PCs.

It was recently proposed that clonal lineage also impacts interneuron radial positioning and potential synaptic connectivity (129, 207, 1065). This was inspired by work on the development of cortical columns and recurrent connectivity among neighboring PCs. Specifically, clonally related sister PCs were found to be radially aligned in the cortex and to preferentially form synaptic connections (1259, 1260). Subsequent work attempted to identify clonally related interneurons by sparse labeling of progenitors with fluorescent markers. Colabeled interneurons in the mature cortex were assumed to represent clonally related sister cells. These studies described radially or horizontally aligned local clusters of labeled interneurons (129, 207), and strongly implied that interneurons from the same progenitor tangentially migrate together to integrate within a common local circuit. However, Ciceri et al. (207) noted that experiments using two different fluorophores suggested that many such identified clusters were likely composed of cells from different progenitors. Subsequent work revisited this hypothesis using bar-coded retroviral libraries, which allows sibling cells to be unambiguously identified (419). These studies revealed that clonally related interneurons disperse widely across the telencephalon and that spatially restricted clusters of interneurons are in fact comprised of cells unrelated by a common progenitor (469, 765, 766, 1143). These data support the general model described above in which interneurons are distributed broadly across the telencephalon and utilize local guidance cues, at least in part from neighboring cells, during circuit assembly.

### G. Contribution of Interneurons to Early Intrinsic Network Activity and Circuit Formation

Although molecular cues guide neurons to their proper location and aid in the selection of synaptic partners, the formation of neural circuits is crucially dependent on activity to trigger early plasticity mechanisms. Indeed, structures throughout the entire developing nervous system generate network activity intrinsically before the arrival of mature external sensory stimuli (4, 105). The resulting calcium influx through NMDA receptors (NMDARs) and voltage-gated calcium channels is important for dendritic arborization and establishment of early synaptic connections (597, 1044). In both the hippocampus and neocortex, the earliest activity occurs in the absence of synaptic connections in the form of spontaneous calcium plateaus, which are mediated by voltage-gated calcium channels and coordinated among cells by gap junction coupling (25, 26, 241, 384, 1262). However, this activity is quickly replaced by synapse-driven network events in which interneurons play a key role via depolarizing actions of GABA on PCs during early development (25, 60, 91, 241, 872). This is due to developmental regulation of the chloride gradient via differential expression of the cotransporters KCC2 and NKCC1, described above (91, 947, 1241). Thus, as detailed in this section, GABA acts initially as an excitatory neurotransmitter to drive network activity important for synaptogenesis and circuit formation.

In both the neocortex and hippocampus, interneurons send and receive the earliest synaptic connections, with important consequences for circuit assembly. In PCs, the earliest synaptic currents detected postnatally are mediated by $GABA_A$Rs and NMDARs; AMPA receptor (AMPAR)-mediated currents are initially absent, only appearing later during the first postnatal week (33, 92, 292, 873, 1149, 1185). In contrast, interneurons demonstrate AMPAR-mediated synaptic currents by the first postnatal day (34, 430, 480). Furthermore, at least in the hippocampus, interneurons demonstrate functional GABAergic synapses very early during postnatal development (430, 480). Thus, during the first postnatal week, interneurons and PCs form excitatory circuits that precede those between PCs. This is functionally significant, as interneurons are positioned to promote early network oscillations, which in turn provide depolarization necessary for glutamatergic synapse development via calcium influx through NMDARs (292, 1219). Indeed, perturbations of GABAergic excitation in vivo disrupt PC glutamatergic synaptogenesis, which

can be rescued by increased NMDAR-mediated transmission. For example, Wang et al. (1185) knocked down NKCC1 (which accumulates $Cl^-$) using RNA interference to render GABA hyperpolarizing/shunting throughout development, and this stunted the arrival of AMPAR-mediated synaptic events as well as dendritic branching and spine density in PCs. Similar results were obtained by blocking NKCC1 with bumetanide injections (1184, 1185) or forcing early overexpression of KCC2 (which extrudes $Cl^-$) (161). Importantly, Wang et al. (1185) rescued the development of AMPAR-mediated synaptic transmission by coexpressing a mutant NMDAR that is less susceptible to $Mg^{2+}$ block. Thus they functionally demonstrated that GABAergic depolarization and NMDARs act in concert to promote PC synaptogenesis (664).

In both the neocortex and hippocampus, network oscillations dependent on glutamatergic and GABAergic synapses emerge near the middle of the first postnatal week (25, 27, 88, 91, 92, 241, 423, 663). This activity has been most extensively studied in vitro, where it is referred to as giant depolarizing potentials (GDPs). GDPs occur as rhythmic bouts of reverberating activity within a local circuit lasting hundreds of milliseconds and travel as a wave (FIGURE 7A). While they involve recurrent excitation between interneurons and PCs, blockade of GABARs alone or optogenetic silencing of interneurons dramatically reduces or abolishes the occurrence of GDPs (FIGURE 7C) (25, 91, 241, 1198). Interestingly, GABAergic synapses between immature interneurons in the hippocampus remain hyperpolarizing and shunting throughout development (60), which may provide a means of suppressing runaway excitation. In the hippocampus GDPs are most readily initiated in area CA3, where depolarization from local interneurons leads to burst firing among recurrently connected PCs, followed by propagation to CA1 (112, 783, 1019, 1020). However, GDPs can also be initiated in CA1, where neonatal recurrent excitation is driven almost exclusively by interneurons, and propagate back to CA3 (383, 783, 1198). In the neocortex, GDPs emerge a couple of days later than those observed in the hippocampus and are primarily generated in the deep layers (25). Furthermore, they may be preceded by or coincide with a separate network rhythm that is primarily dependent on NMDARs and referred to as neocortical early network oscillations (25, 384) (FIGURE 7B). Importantly, in both the hippocampus and neocortex, these in vitro neonatal network activity patterns have in vivo counterparts (217, 423, 663).

Although all interneuron subtypes have the potential to contribute to GDP generation, those derived from the MGE may play a more prominent role than those from the CGE. In CA1 of the hippocampus, optogenetic silencing of MGE-derived interneurons reduces the frequency of spontaneous GDPs to a greater extent than silencing those from the CGE (1198) (FIGURE 7C). In the neocortex, GDPs are primarily observed in deep cortical layers, where MGE-derived interneurons are in the majority (25). Furthermore, the time course of neocortical GDP onset correlates with that of synapse development between fast spiking PV-containing interneurons (which are MGE-derived) and neighboring PCs in deep layers (25, 880). Finally, the participation of interneurons in GDPs correlates with their morphological maturity (27). At least in the hippocampus, MGE-derived interneurons appear to be morphologically and synaptically more mature than those from the CGE during the first postnatal week (1198). These data make sense in context of the fact that the MGE begins producing interneurons before the CGE and produces a majority of the total number of interneurons (651, 796, 966, 1138). However, CGE-derived interneurons certainly play a role in GDP generation. It has long been noted that endocannabinoid agonists suppress GDPs while antagonists increase their frequency, strongly implying the participation of CGE-derived CCK-containing interneurons (98, 886).

Finally, a subset of interneurons referred to as hub cells are highly interconnected within local hippocampal circuits and powerfully modulate GDPs, with some capable of triggering GDPs on their own (114, 909, 1173) (FIGURE 7Di). These cells are diverse morphologically, including both perisomatic- and dendrite-targeting interneurons that project widely within the hippocampus (114). Interestingly, a subset of hub cells born early during embryonic development also projects a long-range axon outside of the hippocampus via the fimbria (909) (FIGURE 7Dii). In mature animals, these cells target the septum and in turn receive inputs from major neuromodulatory centers as well as the septum and entorhinal cortex (1173). Thus they likely contribute to the coordination of early network oscillations across multiple related structures.

### H. The Transition to Inhibitory Circuits and the Role of Interneurons in Critical Period Plasticity

As neurons mature, the reversal potential for chloride becomes shunting/hyperpolarizing, leading to inhibitory GABAergic transmission (872). This is of course crucial for the normal operation of mature circuits, which requires tight coupling between excitation and inhibition (for reviews see Refs. 268, 271, 522). However, this transition also promotes the next stage of circuit development: critical periods during which maps of external sensory stimuli are refined and established (see reviews in Refs. 481, 668, 1082, 1127). Critical period plasticity has been most thoroughly studied in the visual system, where transiently blocking input to one eye [monocular deprivation (MD)] during a limited developmental time window weakens cortical responsiveness to that eye relative to other (309, 428, 508, 1205). Importantly, the maturation of inhibitory circuits, in particular mediated by PVBCs, is necessary for the expression of this early competitive plasticity (265, 307, 308, 482, 507, 589, 1043). The emergence of inhibition dampens intrinsically generated spontaneous activity while regulating spike-timing dependent plasticity in response to externally driven sensory input (253, 474, 613, 1125). Thus, as interneurons become inhibitory, they sculpt early circuits by supporting competition among nascent synapses.

The onset and closure of critical periods appears to depend on different threshold levels of inhibition that are achieved during postnatal development (1045). In transgenic mice with disrupted GABA synthesis at synaptic terminals, the critical period for MD sensitivity fails to open unless GABA agonists are applied (308, 482). Conversely, acceleration of interneuron circuit development by overexpressing brain-derived neurotrophic factor (BDNF) closes the critical period early (463, 507). BDNF promotes inhibitory synapse development by reducing $GABA_A$R endocytosis, and its release is stimulated by calcium entry through voltage-dependent $Ca^{2+}$ channels (VDCCs) activated by early depolarizing GABA (919). Rendering GABA hyperpolarizing during the first postnatal week by block of NKCC1 leads to reduced BDNF release and results in late closure of the critical period (265). Thus inhibition is necessary to open critical periods, but once it reaches a threshold level of maturity, the potential for plasticity is diminished and the critical period ends. However, this potential remains in mature circuits, as sensitivity to MD can be reestablished in adult mice by suppressing GABA synthesis or reducing PVBC firing rates (465, 614). Interestingly, closure of the critical period coincides with the establishment of perineuronal nets (PNNs), which are structures of the extracellular matrix that form around PVBCs and stabilize synapses (for reviews, see Refs. 1039, 1183). PNNs also facilitate the capture and uptake of the transcription factor Otx2, which in turn promotes PVBC maturation as well as further PNN development (100, 173, 912, 1063). Importantly, degrading PNNs or blocking their formation reopens or extends the critical period into adulthood (173, 912). Similarly, blocking the ability of Otx2 to bind to PNNs results in their degradation and reopens the critical period in adults (100). Thus PNNs are an important candidate mechanism for the establishment of mature inhibitory circuits and plasticity rules.

### I. PCs and Interneurons Form Selective Microcircuits Dependent on Subtype

The diversity of interneuron subtypes leads to sophisticated control of synaptic integration along the somatodendritic axis of PCs, as they differentially target distinct subcompartments (see sect. VIID) (586). However, an important question is to what extent interneurons are also selective in their targeting of neighboring PCs to form specific microcircuits. Some subtypes, such as PVBCs and NGFCs, demonstrate very high rates of connectivity to PCs: connection probabilities in paired recordings are in the range of ~50–90% (204, 331, 876, 880). Thus it has been proposed that nonselective targeting of inhibition is a general rule of cortical circuits and the identities of the pre- and postsynaptic cells are irrelevant (552, 876). However, multiple studies have challenged this view and strongly suggest that subtype specific microcircuits indeed exist, even among PVBCs (650, 656, 1230, 1252). For example, in the neocortex, PVBCs are more likely to innervate and evoke larger amplitude IPSCs in neighboring PCs that provide reciprocal excitation (1252). Furthermore, in the hippocampus, PVBCs evoke larger amplitude IPSCs in PCs located near s.o. than those near s.r. (i.e., deep vs. superficial) (656) (FIGURE 8A). Importantly, PCs can be segregated into distinct subtypes based on the projection target of their long-range axons (313, 432, 466), and recent work suggests this informs connectivity rules with local interneurons (607). In the neocortex, PVBCs are more likely to innervate PCs that project to subcerebral targets (e.g, brain stem and spinal cord) than those that project within the telencephalon (e.g., callosal) (650, 1249) (FIGURE 8B). A similar connectivity rule exists for SST-containing Martinotti cells in deep cortical layers, as they form

circuits preferentially with neighboring subcerebral projecting PCs (647, 1015) (FIGURE 8C). In medial entorhinal cortex, CCKBCs innervate PCs that project to the contralateral cortex but avoid neighboring PCs that project to the hippocampal dentate gyrus (1162) (FIGURE 8D). Finally, in CA1 of the hippocampus, PVBCs evoke larger IPSCs in PCs that project to the amygdala than those that project to the prefrontal cortex; conversely, PVBCs are more likely to be innervated by and receive the largest excitatory drive from prefrontal cortex projecting PCs (656) (FIGURE 8E). Thus, while many interneuron subtypes are certainly promiscuous in their targeting of PCs, it is likely that subtype specific microcircuits exist to carry out different cortical and hippocampal computations.

## IV. PHYSIOLOGICAL PROPERTIES OF INHIBITORY INTERNEURONS

The last two decades have strengthened early observations suggesting that the complement of both voltage- and ligand-gated channels expressed on hippocampal inhibitory interneurons differs markedly from those expressed on their glutamatergic principal cell counterparts (502, 641, 770). Given the myriad of inhibitory interneuron types (see sect. II), and the differing roles they play in their respective circuits, it is perhaps not surprising that each particular subtype of inhibitory neuron would express its own unique combination of channels and proteins to fulfill these roles. However, the repertoire of both voltage- and ligand-gated channels is extensive, and their documentation in particular cell types is largely incomplete. In fact, only a handful of studies have tackled the task of unraveling the molecular identities of channels expressed on particular inhibitory interneuron subtypes, allowing only a few channels and their physiological roles in specific subpopulations to be unequivocally identified. For example, much is known about the repertoire of intrinsic conductances present in the PVBC population; the identities and roles of fast $Na^+$ ($Na_V1.1$ and $Na_V1.6$), $K^+$ (Kv1 and Kv3), and $Ca^{2+}$ ($Ca_V2.1$) conductances, the leakage conductances as well as a number of other voltage- and ligand-gated channels in PVBCs are well documented (see below for further discussion; for review, see Ref. 502). Furthermore, how the interplay of these channels regulate PV-containing interneuron excitability, action potential phenotype, and contribute to the generation of coherent oscillations within and between neuronal circuits is reasonably well understood (67, 502). However little, if anything, is known about the identity of equivalent conductances on lesser studied interneuron subpopulations. Although there was an intense avenue of research in the early 1990s, the lack of adequate pharmacological tools has significantly hampered attempts to assign particular roles to molecularly identified voltage-gated channels within discrete interneuron populations. However, despite the absence of the true molecular identity of many of these proteins, much can be learned from the study of a cell's intrinsic conductances. In addition to providing the molecular and biophysical underpinnings of the cell's physiological phenotype, they also inform response profiles to a particular neuromodulator or transmitter and provide clues for potential drug targets to treat central nervous system circuit disorder pathologies.

### A. Action Potential Firing Patterns

Importantly, cell firing properties in response to electrotonic current injections are frequently used to aid interneuron classification. Thus, before embarking on a detailed discussion of the various passive and active membrane properties in relation to specific ion channels of discrete interneuron subtypes, we briefly describe the most common features of action potential firing associated with the interneurons outlined in section II. Fast-spiking behavior, typically exhibited by PV-expressing AACs, PVBCs, and BiCs, refers to repetitive firing without obvious frequency adaptation/accomodation (i.e., no change in interspike interval) from the beginning to end of a sustained electrotonic depolarizing current pulse beyond threshold (FIGURE 9, A–D). Indeed, in some cases, acceleration of firing with interspike interval shortening can even occur. Individual action potentials are brief with short half-widths (~0.5 ms) that remain fairly constant from the first to last spike and are followed by large/deep, fast/narrow afterhyperpolarizations. The discharge frequency of fast-spiking cells increases steeply as a function of the injected current and can reach well in excess of 100 Hz making them particularly well suited to pace and coordinate high-frequency network activity. In contrast, many interneurons, including OLMs, CCKBCs, SCAs, PPAs, and ADIs, exhibit considerable spike frequency adaptation (with increasing inter spike intervals) that limits maximal firing frequencies to levels much lower than those in fast-spiking cells (typically <50 Hz) (FIGURE 9, E–H). Such "regular spiking" accommodating cells display characteristically wider spikes with longer half-widths (~0.8 ms) that increase from the beginning to end of the discharge. Hippocampal NGFCs and IvCs

exhibit only modest frequency accommodation, with broader spikes (~0.8 ms), and achieve significantly lower maximal firing frequencies than fast-spiking cells. Indeed, in these cells, threshold is often reached by a slow ramplike depolarization beyond the initial voltage deflection driven by a sustained square wave current injection (FIGURE 9, I–K). Thus, at such threshold levels of depolarization, NGFCs/IvCs exhibit a "late-spiking" phenotype typified by considerable delay from depolarization onset to action potential discharge of the first action potential. Finally, ISIs (and in some cases members of the other families, particularly at early developmental stages) can exhibit a variety of spiking phenotypes including 1) "irregular" with single action potentials discharged randomly throughout a sustained suprathreshold current injection resulting in highly variable inter spike intervals; 2) "bursting" with three to five spikes discharged at high frequency at the beginning of the depolarizing pulse followed by single spikes of variable interevent intervals; and 3) "stuttering" with clusters of spikes separated by unpredictable periods of silence of varying durations.

## B. Resting Membrane Potential

Early electrophysiological studies of inhibitory interneurons using sharp microelectrode recording techniques were quick to demonstrate that the resting conductances and physiological firing patterns of inhibitory interneurons deviated markedly from their excitatory cell counterparts (567, 623, 624). Indeed, most studies agreed that interneuron resting membrane potentials were more depolarized and that many cells demonstrated rapid and nonaccommodating firing patterns in response to electrotonic depolarizing current steps (1130, 1131). However, these studies also immediately revealed that many divergent firing patterns existed between inhibitory interneurons, and consequently limited cell classification schemes were built around anatomical and neurochemical features in combination with the nuances of firing patterns typically driven by steady-state depolarizing currents. With the advent of whole cell patch-clamp recording techniques from cells in in vitro slice preparations becoming commonplace in the 1980s, much of these data were systematically reinvestigated. The increased resolution afforded by this technique demonstrated that many of the resting parameters (resting potential, input resistance, membrane capacitance) in subpopulations of inhibitory interneurons possessed few common features. Before considering these data, it is worthwhile pointing out that it is often difficult to get an absolute measure of these parameters when comparing data obtained across different manuscripts from different laboratories. Small changes in slice preparations, intracellular solution composition, and recording quality and resolution (e.g., access resistance, junction potentials) often alter ion reversal potentials, channel availability, and open probability, making measurement of a "true" resting potential ($V_m$) or other intrinsic conductances problematic.

Two approaches have emerged that facilitate an accurate measure of resting membrane potential that exploit the cell's intrinsic voltage- or ligand-gated conductances. With the use of a loose cell-attached configuration, an accurate measure of $V_m$ can be established by exploiting the $K^+$ reversal potential ($E_{K^+}$) (359, 1029, 1168). By setting the $K^+$ concentration in the recording pipette approximately equal to the intracellular $K^+$ concentration, $E_{K^+}$ approximates 0 mV. Thus voltage-gated $K^+$ currents will reverse direction when the pipette potential equals $V_m$, which is determined using a series of depolarizing ramp protocols (1029, 1168). This approach revealed that resting potentials of specific cell types were often more hyperpolarized than original estimates provided by the whole cell recording configuration. For example, in interneurons of the CA1 s.r., this approach yielded $V_m$ values that ranged from −59 to −93 mV (mean −74 mV) (cf. with CA1 pyramidal cells $V_m$ = −84mV; Ref. 359). In contrast, using whole cell recording techniques, the same authors found that electrodes filled with either a high $Cl^-$ solution or gluconate-containing solution resulted in $V_m$ measurements that were ~15mV more depolarized. This approach also allows extraction of both the true resting potential and the threshold for firing (359).

Tricoire et al. (1138) used this approach to measure the resting potentials of ~150 anatomically identified MGE- and CGE-derived interneuron subtypes of the CA1 subfield. Cells of the neurogliaform family (NGFC, IvC) typically possess the most hyperpolarized $V_m$ (mean −70 mV, cluster 3 in TABLE 1), whereas PV-containing cells (PVBCs, BiCs, AACs) and virtually all CGE-derived cell types (CCK-containing, long range projecting, VIP-containing) have the most depolarized resting potentials (approximately −55 to −60 mV). SST-containing cells (e.g., O-LM cells) have resting potentials intermediate to all other cells ($V_m$ = −65 mV). Despite possessing varied resting potentials, virtually all

cells had similar action potential thresholds close to −35mV (range −32 to −38 mV) (TABLE 1). A second, similar approach, that exploits the known reversal potential of NMDAR-gated single-channel currents, has also been effective in accurately determining resting and threshold properties of cells (90, 943, 1148).

## C. Voltage-Gated $K^+$ Conductances

In the early 1990s successful cloning of many voltage-gated ion channels promised a new era where one could study the biophysics of channels expressed in heterologous systems as a means to identify the molecular identity of conductances underlying a particular aspect of cell physiology, e.g., the action potential waveform, and threshold and subthreshold conductances. This optimism was short lived as it became apparent that few channels expressed in recombinant systems perfectly matched the biophysical properties of native channels (967). We now appreciate that native channels are often modified by phosphorylation and other posttranslational processes or are in intimate association with auxiliary and accessory proteins that shape their trafficking, availability, and biophysical features in unpredictable ways. Early attempts to match expression patterns of recent cloned channel transcripts with biophysical properties measured by whole cell recording techniques in in vitro slices did, however, yield some modest successes, particularly with channels formed by the Kv3 family of voltage-gated potassium channels (967) as discussed below.

Early electrophysiological recordings were quick to highlight that the physiological properties of hippocampal inhibitory interneurons differed markedly from principal cells. The rapid rise, fall, and brevity of action potentials, together with their deep AHPs, provided the first clues that the conductances underlying these important physiological features were likely distinct from those observed in their pyramidal cell counterparts. Subsequent studies provided important but limited evidence for the roles played by specific voltage-gated conductances in particular subpopulations of inhibitory interneurons, with the best characterized being the diverse repertoire of voltage-gated potassium channels. However, like many aspects of interneuron physiology, the story is largely incomplete for the vast majority of cell types with the conductances of only a small number of identified interneuron types being studied in any great detail. However, what is evident is that the spatial arrangement of numerous voltage-gated $K^+$ conductances across the somatodendritic and axonal compartments are key determinants of their spatial and temporal signal processing capabilities.

Early recordings from interneurons located within the s.o. and s.r. indicated that both transient “A-type” and numerous sustained “delayed rectifier” currents were common to virtually all interneurons (202, 678, 756, 1268, 1269). The kinetic properties of these conductances were typically rapid and possessed pharmacologies that diverged from those observed in pyramidal cells. Outside-out nucleated patch recordings from identified CA1 SST-positive O-LM cells revealed that three voltage-gated $K^+$ current types predominate in this cell type (TABLE 2) (678). A fast “delayed rectifier”, highly sensitive to 4-aminopyridine (4-AP) and tetraethylammonium (TEA) ($IC_{50}$ values <100 μM), a slow delayed rectifier blocked by high concentrations of TEA, but insensitive to 4-AP and a rapidly inactivating A-type current that was blocked by high concentrations of 4-AP but resistant to TEA. These currents contributed 57, 25, and 19% to the total macroscopic current. Single-cell reverse transcription polymerase chain reaction (RT-PCR) revealed that the fast delayed rectifier and the A-type current components were mediated by homomeric Kv3.2 and Kv4.3 channels, respectively (678).

Similar electrophysiological recordings from PVBCs revealed that macroscopic currents were dominated (~58%) by a fast non-inactivating delayed rectifier current component sensitive to low concentrations of 4-AP and TEA ($IC_{50}$ = <100 mM), similar (but not identical) to that observed in dendrite targeting SST-containing interneurons (FIGURE 10 and TABLE 2) (678). The kinetic properties of this current are remarkably rapid with the 20–80% rise time being <1 ms and showing little, if any, inactivation during a 100-ms voltage step. A second slower delayed rectifier (20–80% rise time ~6 ms) component with intermediate sensitivity to TEA and a rapid inactivating A-type current component blocked by 4-AP but resistant to TEA were also identified (756). Single-cell RT-PCR revealed a high prevalence of Kv3.1 and Kv3.2 in all PVBCs with a lower abundance of Kv4.2 and Kv4.3 transcripts.

Delayed rectifier channels assembled from Kv3 subunits are instrumental components in conferring high-frequency action potential firing in numerous hippocampal and cortical interneuron subtypes (304, 967, 1187). Their rapid activation ensures efficient spike repolarization, and their rapid deactivation allows minimal $K^+$ current accumulation during the interspike interval that would interfere with generation of subsequent action potentials. Importantly, the rapid activation kinetics enforces a narrow temporal window that minimizes $Na^+$ channel inactivation, and the consequent deep hyperpolarization serves to deinactivate other voltage-gated channels ensuring a high fraction are available for activation during trains of action potentials (967).

Although it is widely recognized that Kv3 containing channels are synonymous with cells that fire action potentials at high frequency (967), Kv3.2 is highly expressed in both fast spiking basket cells and SST-containing O-LM cells. Although O-LM cells can fire at reasonably high frequencies, their maximal firing frequency is significantly lower than that of PVBCs. A comparison of the data from two publications from Peter Jonas' laboratory (678, 756), who used identical recording techniques in O-LM and PVBCs, reveals important quantitative differences between the rapidly activating sustained $K^+$ currents in the two cell types (TABLE 2). Although many of the kinetic properties were similar, the activation and inactivation curves are less steep in O-LM cells compared with PVBCs, and the deactivation of the predominantly Kv3.2 channels in the O-LM cells is slower than the equivalent Kv3.1 containing channels in PVBCs. These subtle differences likely set the upper firing frequency of O-LM cells to be lower than PVBCs.

Kv3.2 subunits, but not Kv3.1 subunits, possess a consensus sequence for protein kinase A (PKA) phosphorylation (803, 965). cAMP and PKA phosphorylation inhibits current through Kv3.2 channels but not Kv3.1b. PKA phosphorylation of Kv3.2 channels in both PVBCs and SST-containing interneurons broadens the action potential waveform and reduces the maximal firing frequency in both cell types consequently modulating network oscillatory activity (49). Despite lacking a PKA phosphorylation site, Kv3.1 subunits have 11 protein kinase C (PKC) and 10 casein kinase sites (1166), suggesting that the phosphorylated state of both Kv3.1 and Kv3.2 could have a major impact on the firing properties of a number of interneuron populations.

In hippocampus, both Kv3.1 and Kv3.2 protein expression are developmentally upregulated between PN7 and PN21 (287, 1098). Immunohistochemistry reveals Kv3.2 expression is primarily across the somatodendritic arbor of virtually all PV-containing cells, ~85% of nNOS-positive cells, and ~50% of SST-containing interneurons. Kv3.1b is largely expressed across the soma, dendrites, as well as the axons of PV-containing interneurons and is completely absent in SST-containing or any other interneuron type (287). Kv3 expression is highest in dendrites of cells that typically possess low dendritic $Na^+$ channel densities (502, 504). Dendritic Kv3 currents act to accelerate the decay time course of excitatory postsynaptic potentials (EPSPs), imposing a narrow window for temporal integration (504, 967), and minimize the impact of clustered excitatory input to favor distributed synaptic inputs (504). In the axonal compartment, Kv3 channels ensure brief and rapid action potential firing and repolarization. Rowan et al. (957) recently demonstrated that Kv3 channels are clustered at individual presynaptic boutons and are usually spared from axonal shafts. These axonal Kv3 channels control local spike repolarization and act as key determinants of the compartmentalized control of action potential width in a synapse by synapse manner (957).

Postnatal upregulation of Kv3 containing currents in PV-containing cells is part of a coordinated sequence of events that tune PV cells for their ultimate participation in gamma oscillogenesis (277, 287, 1098) (see sect. XV). Gamma oscillations in the young hippocampus are poorly organized in part due to the immature state of PV-containing interneurons. At early postnatal stages, action potential firing is slow and unable to sustain periods of high-frequency activity. In addition, action potential propagation and transmitter release components cannot support the rapid throughput typically observed in mature cells. Consequently, during the first two to three postnatal weeks of life, action potential duration, propagation time, and duration of the transmitter release period decrease by ~50% as a result of the concurrent functional maturation of cell morphology, voltage-gated $Na^+$ and $K^+$ currents, as well as refinement of the presynaptic release machinery (277, 502).

In addition to the Kv3 subunits, both Kv1.1 and Kv1.2 are expressed in axons of PV-containing interneurons. Both Kv1.1 and Kv1.2 have low voltage activation thresholds and slower activation when compared with the Kv3 family and underlie the conductance known as the D-type $K^+$ current (245, 415). Both Kv1.1 and Kv1.2 are highly enriched at the axon initial segment where they colocalize with the voltage-gated sodium channel Nav1.6 (415, 695). When compared with the axon initial segments of principal cells, Kv1.1 and Kv1.2 are expressed at a much higher density (695), suggesting that they may play a role in establishing an increased threshold for action potential initiation in PV-containing cells. Goldberg et al. (415) observed that the slow inactivation of Kv1 containing channels in PV-containing cells of the barrel cortex causes a shift in the threshold for action potential initiation. Moreover, Kv1.1 likely functions to permit responses primarily to large events that can temporally exceed its rate of activation. In support of this, blockade of Kv1.1 eliminates the delay to first spike typically observed in these cells and converts the cell to a continuous high-frequency firing mode. In consideration of these data, Hu et al. (502) reasoned that Kv1 channels may impose a fast coincidence detection mechanism in PV-containing interneurons, allowing fast EPSPs to beat Kv1 activation leading to a rapid action potential initiation with little delay. Finally, brief repetitive stimulation of Schaffer collateral inputs to PV-containing cells results in a novel form of long-term intrinsic plasticity (160). This intrinsic plasticity results in increased excitability and recruitment of PV-containing cells, which arises through an mGluR5-dependent downregulation of currents through Kv1 channels.

Kv4.3 subunits are highly enriched in neocortical and hippocampal interneurons (678, 756, 782, 944, 999) and are thought to underlie the 4-AP-sensitive, A-type inactivating $K^+$ conductance in these cells. In hippocampus, Kv4.3 expression is highest in the somatodendritc compartments of CCK-containing, and CB-containing interneurons located in both s.r. and s.l.m. as well as SST-containing interneurons in s.p. and s.o. (119, 678, 782). In contrast, Kv4.3 is expressed in only a small percentage of PV-containing cells (119). Both Kv4.1 and Kv4.2 channels are largely absent from hippocampal interneurons (944). Native Kv4 containing channels typically associate with auxiliary subunits, which act to modify their expression levels and biophysical properties (530). The potassium channel interacting proteins (KChIPs) are $Ca^{2+}$-binding proteins, which interact with the cytoplasmic $NH_2$-terminal domain of Kv4 channels and KChIP1 is found exclusively in hippocampal interneurons where it overlaps with Kv4.3 (782, 944). Of the total Kv4.3/KChIP1 coexpression, 26% was contributed by PV-containing neurons, ~18% by SST-containing, ~20% by CB-containing, and ~34% by CR-containing interneurons (782). It is unclear what this partial overlap is actually telling us about the roles played by Kv4.3/KChIP channels in these cells, and it is possible that KChIP1 may interact with another as yet unidentified surface expressed protein.

Application of the muscarinic acetylcholine receptor (mAChR) agonist carbachol to in vitro hippocampal slices generates theta frequency subthreshold membrane potential oscillations in inhibitory interneurons (191) that are generated by the interplay of voltage-dependent $K^+$ ($I_A$, $I_{Kfast}$, $I_{Kslow}$, and $I_D$) and persistent $Na^+$ conductances (191). Using a small interfering RNA knock down approach, Bourdeau et al. (119) implicated Kv4.3 containing channels in the generation of these subthreshold membrane potential oscillations, suggesting that significant A-type current can be active at potentials close to rest and have roles in physiological processes other than action potential repolarization.

### D. Voltage-Gated $Na^+$ Conductances

Unlike voltage-gated $K^+$ conductances, relatively little is known about voltage-gated $Na^+$ channels and conductances expressed on inhibitory interneurons. What information does exist is almost exclusively derived from studies of PVBCs (for review, see Ref. 502) and SST-containing O-LM cells (FIGURE 10). The earliest study of $Na^+$ conductances in fast spiking interneurons revealed significant differences between interneurons and their principal cell counterparts (755). Although the voltage dependence of activation was similar between the two cell types, the deactivation kinetics differed, being more rapid in basket cells (~0.13 vs. 0.2 ms at −40 mV). However, the greatest differences occurred in their steady-state inactivation properties, which were steeper and shifted to more positive voltages in PVBCs (755). The molecular identities of $Na^+$ channels in interneurons suggest that at least in PVBCs the vast majority of $Na^+$ channels are formed by $Na_V1.1$ and $Na_V1.6$ subunits with a lesser contribution from $Na_V1.2$, $Na_V1.4$, and $Na_V1.7$ (502, 695, 857, 852). In contrast to hippocampal principal cells, $Na^+$ channels are largely

excluded from the dendrites of PVBCs where $K^+$ channels predominate. $Na^+$ channels instead are clustered in high density at the axon initial segment, which in PVBCs originates at locations extremely close to the soma (~20 µm away), and steadily increase in density towards distal axon sites (FIGURE 10B ). Calculations have suggested that 99% of PVBC $Na^+$ channels are contained within the axonal compartment (503).

$Na^+$ channels in PV-containing cells are targets for neuromodulation and have been implicated in pathophysiological states. While the data regarding neuromodulation of $Na^+$ channels in interneurons are sparse, Janssen et al. (528) directly demonstrated that application of exogenous neuregulin (NRG1) reduces the excitability of Erb4-expressing interneurons (of which PV-containing cells are a subset) in primary culture by raising action potential threshold and decreasing $Na^+$ channel activity by an as yet unknown mechanism. Transient cerebral ischemia also impacts $Na^+$ channel activation and surface expression in PV-containing interneurons rendering cells less excitable (1265). Reduced $Na_V1.1$ levels and PV-containing interneuron dysfunction critically contribute to abnormalities in oscillations, synchrony, and memory in human amyloid precursor protein transgenic mice and possibly in humans with Alzheimers disease (1170). Finally, a dominant loss of function mutation in $Na_V1.1$ causes Dravet syndrome, an intractable form of childhood-onset epilepsy that arises from a reduction in $Na^+$ channel density in hippocampal interneurons (1255). In mouse models of Dravets syndrome cortical interneurons cannot sustain high-frequency firing, leading to circuit disinhibition, seizures, and premature death (194, 852).

Unlike PV-containing interneurons, SST-containing cells, particularly O-LM cells, have a comparatively high density of $Na^+$ channels on their somatodendritic axis. Outside-out patch-clamp recordings from different portions of the somatodendritic domain revealed a reasonably uniform high density of $Na^+$ channels regardless of the compartment (757). The peak $Na^+$ conductance density in O-LM cell dendrites was measured at ~110 pS/µm$^2$ at −10 mV (757), about three times that seen on cortical pyramidal cell dendrites (1059, but cf. with PV-containing axons described above). Of interest, the midpoint for $Na^+$ channel activation was observed at more negative potentials in the dendrites compared with somas. However, the time constant for recovery from inactivation was identical at both locations (757). This negatively shifted activation range undoubtedly has a major role to play in lowering the threshold for spike initiation in SST-containing cells whose axons often emerge from portions of the dendritic tree.

## E. Voltage-Dependent $Ca^{2+}$ Conductances

VDCCs play myriad roles in central neurons. VDCCs located on the soma and dendrites can regulate dendritic excitability and shape the spatial and temporal properties of incoming synaptic inputs. The subsequent increase in intracellular $Ca^{2+}$ triggers a multitude of second messenger cascades and regulates transcription and translation events. $Ca^{2+}$ channels located in the axon have a pivotal role in establishing the mechanisms behind neurotransmitter regulation and release. The identities and biophysical properties of VDCCs in principal cells are well characterized, and a clear picture of their roles in these cells is firmly established. The picture is less clear for $Ca^{2+}$ channels in inhibitory interneurons. Much of what we know concerning $Ca^{2+}$ channels in interneurons has come from immunohistochemical and pharmacological studies with few studies reporting the biophysical properties of $Ca^{2+}$ channels in interneuron subtypes.

High-resolution immunohistochemical analyses of $Ca^{2+}$ channel subunit expression reveals a marked heterogeneity throughout mouse hippocampal interneuron subtypes (1174). $Ca_V2.1$ (responsible for P/Q-type VDCCs) and $Ca_V3.1$ (T-type VDCCs) subunits are uniformly expressed in almost all interneuron subtypes. The L-type VDCC subunits, $Ca_V1.2$ and $Ca_V1.3$, colocalize to CR-containing interneurons, while Cav1.3 expression is highest in PV-containing and SST-containing interneurons. $Ca_V2.2$ (N-type VDCCs) is expressed in all interneurons with the exception of CB-containing cells. $Ca_V2.3$ (R-type VDCCs) is also uniformly expressed in all interneurons except PV-containing and CR-containing where expression is much lower (1174). Surprisingly, no study has tackled an extensive characterization of the biophysical properties of any of these channel types in particular subtypes of interneurons; therefore, it is unclear whether $Ca^{2+}$ channel properties are similar or distinct from those of hippocampal principal cells.

$Ca^{2+}$ imaging studies were first to show the presence of functional dendritic VDCCs that mediate $Ca^{2+}$ influx during synaptic depolarizations and back-propagating action potentials in numerous interneuron subtypes (416, 418, 545, 961). The first direct demonstration of a high-density expression of low-voltage-activated $Ca^{2+}$ channels came from imaging the dendrites of SST-containing low threshold spiking cortical interneurons (416). In these cells dendritic T-type channels trigger low-threshold spikes and subsequent recruitment of other $Ca^{2+}$ channel types including R- and L-type channels. During trains of activity, the dendrites of low-threshold spiking interneurons behave as a single nonlinear compartment generating global $Ca^{2+}$ elevation across the entire dendritic tree (416). This is in marked contrast to $Ca^{2+}$ dynamics in PVBCs and cortical “irregular-spiking” supragranular interneurons where the voltage-gated transient potassium current $I_A$ restricts action potential propagation and limits dendritic $Ca^{2+}$ channel activation (417, 418).

In hippocampus, imaging of $Ca^{2+}$ transients triggered by back-propagating action potentials in SST-containing O-LM cells revealed contributions of T, L, N, and P/Q channel types (1111). Dendritic L-type VDCCs are implicated in Hebbian long-term potentiation (LTP) at excitatory synapses onto interneurons (see sect. VIB) (1110, 1112), and high-frequency synaptic activity of mGluR5 induces a selective and compartmentalized potentiation of L-type channels by a PKC-dependent mechanism and release of $Ca^{2+}$ from ryanodine-sensitive intracellular stores (1111).

As discussed above, the L-type $Ca^{2+}$ channel subunit $Ca_v1.3$ (and to a lesser extent $Ca_v1.2$) is enriched in PV-containing interneurons where it contributes to the low-voltage-activated $Ca^{2+}$ conductance. Both $Ca_v1.2$ and $Ca_v1.3$ are largely expressed on the cell bodies and dendrites of PV-containing interneurons and are absent from the axonal compartment (533). Functional maturation of PV-containing interneurons is retarded by antagonists and accelerated by agonists of L-type VDCCs, indicating a critical role for L-type channels in cell maturation. Moreover, currents through L-type channels facilitate CREB phosphorylation important for excitatory transcription coupling in PV-containing cells (214). In cortex and hippocampus, general expression of T-type channel subunits $Ca_v3.1$ and $Ca_v3.2$ increases during development to peak at P21 (10). In contrast, $Ca_v3.1$ expression in G42-positive cortical fast spiking basket cells is downregulated during the first few weeks of postnatal life, likely contributing to a decrease in cell excitability upon maturation (857). Although tetrodotoxin-insensitive depolarizations and action potentials are common in young (PN5–7) PV-containing cells, they are largely absent by PN25 consistent with the loss of functional T-type channels in these cells (857).

$Ca_v2.1$ (P/Q channels) and $Ca_v2.2$ (N-type channels) are widely expressed throughout all interneuron subtypes and contribute to a class of $Ca^{2+}$ channels known as high-voltage-activated channels (HVA). HVA channels are largely responsible for controlling neurotransmitter release and are intimately associated with the presynaptic machinery at individual release sites. $Ca_v2.1$ channels (P/Q type) are particularly enriched in the axon terminals of PV-containing interneurons, whereas $Ca_v2.2$ (N-type channels) are preferentially expressed in CCK-containing cell axons (see sect. IVL for their roles in neurotransmitter release mechanisms). In addition to HVA channels, $Ca_v3$ (T-type) channels have also been identified at presynaptic sites on PV-containing axons (1093). Activation of T-type channels on PV-containing axons by nicotinic acetylcholine receptors can trigger asynchronous transmitter release, which can be augmented by a concomitant $Ca^{2+}$ release from presynaptic intracellular stores (1093).

### F. The Hyperpolarization-Activated Cation Current

Hyperpolarization-activated cation channels ($I_h$ or HCN channels) are widely expressed in neurons of the mammalian central nervous system. Formed from four subunits, HCN1-HCN4, they have been most widely studied in principal excitatory neurons within the hippocampus and cortex where they regulate cell excitability and synaptic integration (709, 881, 1210). In situ hybridization analysis suggests that the majority of $I_h$ channels in inhibitory neurons are formed from HCN1 and HCN2 subunits with a smaller contribution of HCN4 subunits (976). In principal neurons, $I_h$ channel density increases as a function of distance from the soma (730). Although it is unclear whether the $I_h$ density is similarly distributed in interneuron dendrites, a multicomparment modeling study suggests that $I_h$ is dendritically expressed in O-LM cells (994).

Only a small number of studies have formally demonstrated the $I_h$ current under voltage-clamp conditions in inhibitory neurons (see below). However, its presence is often assumed based on a voltage-dependent sag that manifests during electrotonic hyperpolarizing current pulses in current clamp recordings (881, 949). Tricoire et al. (1138) noted that in recordings from ~150 CA1 interneurons that while virtually all cells displayed a voltage-dependent sag during current pulses, this sag was largest in the SST- and CCK-containing interneurons (FIGURE 9 and TABLE 1).

The first formal demonstration of $I_h$ in hippocampal interneurons came from recordings from O-LM interneurons of the CA1 s.o.-alveus (718) (FIGURE 11A). $I_h$ in these cells is activated at potentials close to −50 mV, with a mid activation point of approximately −80 mV and makes a major contribution to the total membrane conductance at rest. $I_h$ is blocked by both external $Cs^+$ and ZD7288 (FIGURE 11, A and B) and potentiated by the monoamine adrenergic agonists norepinephrine and isoprenaline (718). $I_h$ amplitude and activation kinetics are enhanced by ethanol in s.l.m. interneurons (1244). $I_h$ in O-LM interneurons is inhibited by activation of mu and delta opioid receptors (1071) as well as nicotinic receptors (435). Since $I_h$ is active at potentials close to rest, its blockade results in membrane hyperpolarization accompanied by increased cell input resistance. Block of $I_h$ also decreases spontaneous action potential frequency by prolonging the interspike trajectory (718).

In a study of PV-containing fast spiking basket cells in the DG, Aponte et al. (43) observed that the biophysical properties of $I_h$ were somewhat similar to those described in O-LM cells and had a role to play in establishing resting potential, input resistance, and the membrane time constant. In PV-containing cells, RT-PCR identified $I_h$ as the heteromeric assembly of HCN1 and HCN2 subunits. Of particular interest $I_h$ not only has a role to play in somatodendritic processes but also determines axonal properties (43, 977). In DG PVBCs, $I_h$ channels depolarize the axon and reduce the threshold for action potential initiation thereby increasing spike reliability (43). Moreover, blockade of $I_h$ by ZD7288 reduces the frequency, but not the amplitude, of mIPSCs, suggesting that $I_h$ channels are located close to individual transmitter release sites and can influence transmitter release probability (Pr).

### G. The M-Current

The M-current ($I_M$) is a noninactivating voltage-gated $K^+$ conductance comprised of the Kv7 (aka KCNQ) channels Kv7.2 and Kv7.3. $I_M$ is widely expressed in central neurons and plays a major role in regulating cell excitability, action potential firing, and accommodation as well as contributing to a medium-duration AHP in many cells. The voltage dependence of activation is such that $I_M$ is active close to $V_m$, and since it operates at subthreshold potentials, it is an important target for a number of neuromodulators in regulating cell excitability (223, 459). Although widely studied in hippocampal principal cells, only a handful of studies have investigated this current in inhibitory interneurons. Immunohistochemistry has shown Kv7 channel expression on the soma and dendritic compartments of PV-containing and SST-containing interneuron populations (222, 645). Although somewhat controversial, there is little evidence for axonal expression of Kv7 channels in interneurons.

$I_M$ has been best studied in CA1 SST-containing O-LM cells, which express Kv7.2 and Kv7.3 protein on their soma and dendrites, suggesting that native $I_M$ arises from their heteromeric assembly (645, 646) (FIGURE 11C). $I_M$ in O-LM cells is active at resting potentials close to −50 mV and is blocked by the antagonists linopirdine, TEA, and XE-991 and enhanced by the Kv7 channel opener retigabine (645) (FIGURE 11C). Using standard depolarizing test pulses, $I_M$ contributes ~15% of the total outward current activated at +40 mV. Blockade of $I_M$ increases spontaneous firing frequency by reducing the interspike interval without impacting action potential half-width. Enhancing $I_M$ activity with retigabine ceases spontaneous action potential firing (645). A current with similar properties has also been described in hippocampal fast spiking cells maintained in primary culture (434).

In the presence of mAChR agonists, SST-containing O-LM cells and CCKBCs exhibit an M1/M3-receptor dependent acceleration of action potential firing frequency concomitant with the emergence of a prominent afterdepolarization (ADP). Emergence of the ADP results from an inhibition of $I_M$ and the slow AHP, concomitant with activation of a nonselective cation conductance (182, 640, 645). A similar (but not

identical) excitatory effect of muscarinic receptor activation via M1 receptors on PV-containing cells has also been observed (182, 1251). Although not formally tested, the change in excitability triggered by M1 receptor activation in PV-containing cells is consistent with a reduction in $I_M$. Finally, BDNF strongly modulates the firing of PV-containing cells via an action on $I_M$ availability (837). Application of BDNF decreases the firing frequency and input resistance of PV-containing cells by a mechanism involving a TrkB-mediated increase of $I_M$.

### H. Acid Sensing Ion Channels

Members of the degenerin/epithelial $Na^+$ channel superfamily show wide expression throughout central neurons, with the subfamily member of acid-sensing ion channels (ASICs) being the most widely studied (1181, 1195). ASIC channels are comprised of six family members (ASIC1a, ASIC1b, ASIC2a, ASIC2b, ASIC3, and ASIC4) encoded by four genes (Accn1–4). ASIC currents possess a steep pH dependence of activation, are $Na^+$ selective, and are classically blocked by external $Ca^{2+}$ and amiloride (1181). ASIC1a, unlike other family members, is permeable to $Ca^{2+}$ ions (1195). In hippocampus, although ASICs are expressed in both principal cells and inhibitory interneurons, the latter have the larger current density (113, 205, 1196, 1277). Although the role of ASICs in inhibitory interneurons has received relatively little attention, they have been implicated in neurological disorders such as stroke, ischemic cell damage, and termination of electrographic seizure events. Two ASIC family members ASIC1a and ASIC2 are differentially expressed in hippocampal interneurons. SST-containing O-LM cells typically express transcripts for both ASIC1a and ASIC2 channels, whereas only ASIC1a is expressed in DG PVBCs (1196). In neocortex, ASIC4 expression is restricted to CR- and VIP-positive cells; however, its expression in hippocampus has not been reported (680).

Rapid acidification of the extracellular environment triggers activation of an inward ASIC channel-mediated current (at −60 mV) in O-LM and PVBCs (1196), as well as unidentified interneurons of s.r. and s.l.m. (113, 1102). In side-by-side recordings, ASIC currents were sixfold greater in O-LM cells (current density 0.75 pA/$\mu m^2$) compared with PVBCs (0.12 pA/$\mu m^2$, a density similar to that observed in principal cells). ASIC currents in O-LM cells possess markedly rapid recoveries from desensitization (0.96 s) compared with PVBC currents (42.8 s), suggesting that the latter may accumulate in a desensitized state more readily (1196). Unidentified cells types referred to as dentate gyrus “stuttering” and “accommodating” cells had current amplitudes intermediate to O-LM and PVBCs (1196). Psalmotoxin-1, a selective inhibitor of ASIC1a channels, inhibited currents in PVBCs, consistent with the expression of only ASIC1a mRNA transcripts in these cells. In contrast, ASIC-mediated currents in O-LM cells were largely resistant to psalmotoxin-1 consistent with their expression of both ASIC1a and ASIC2 transcripts (1196).

Although ASIC channels are predominantly expressed on the soma and dendrites of interneurons, there is evidence for presynaptic expression of ASICs (516). Block of presynaptic ASIC channels by an orthosteric noncompetitive antagonist 2-oxo-2H-chromene-3-carboxamidine (aka compound 5), triggers an increase in the frequency of spontaneous IPSCs onto principal cells, suggesting that presynaptically active ASICs on as yet unidentified interneurons normally act to dampen spontaneous inhibitory tone in the hippocampal circuit (516).

Classically ASIC channels are blocked by amiloride; however, native ASIC channels on s.r. and s.l.m. interneurons are also blocked by the mAChR M1 receptor agonist oxotremorine (282) and potentiated by monoamine compounds known to block N-methyl-D-aspartate (NMDA) receptor-gated channels (IEM-1921, IEM-2117, and memantine), albeit at concentrations ~10-fold higher than typically used to block NMDAR-gated currents (1102). In mouse models of electrographic seizures (kainate acid lesioning, PTZ, and reduced extracellular $Mg^{2+}$), termination of the electrographic event depends on the activity of ASIC1a channels (1277). Given that seizures trigger an extracellular acidification, it is not unreasonable to assume that this acidification activates ASIC channels on both principal and inhibitory interneurons. Indeed, Zeimann et al. (1277) demonstrated that disruption of the Asic1a gene or pharmacological block of ASIC1 increased seizure severity. Acidification of the extracellular fluid to levels achieved during electrographic events triggers activation of ASIC1a channels on interneurons, increases interneuron cell firing, and promotes increased inhibitory tone onto principal cells (1277). However, selective block of

ASIC1a on inhibitory neuron presynaptic terminals actually reduces electrographic seizure activity in low $Mg^{2+}$ and kainate-induced models of seizures by a mechanism involving presynaptic ASIC channel modulation of inhibitory tone (1102), suggesting that interneuron presynaptic ASICs are not the molecular substrate responsible for terminating electrographic seizures.

### I. TASK Channels

Twik-related acid-sensitive channels (TASK) are voltage-independent, potassium-selective channels that belong to the two-pore domain potassium channel family (76, 422). TASK-1 (KCNK3) and TASK-3 (KCNK) are the predominant subtypes found in the central nervous system and can exist as either homomers or heteromers (1083). Although both channel types are widely expressed in principal cells, higher levels of TASK3 and lower levels of TASK1 are typically expressed in hippocampal interneurons (1083, 1099). Single-cell RT-PCR and immunohistochemistry have demonstrated that TASK3 is expressed in ~50% of GAD67-positive interneurons. Of these, most (97%) PV-containing interneurons, as well as a subpopulation of SST-containing interneurons including O-LM cells, are heavily decorated by TASK3 immunoreactivity (1099, 1113). Pharmacological tools are sparse for TASK-related channels; however, they are typically activated by alkalinization and inhibited by acidification (76). Accordingly, acidification or alkalinization of the extracellular fluid impacts the input resistances and holding currents required to voltage-clamp at rest diverse populations of CA1 interneurons. Both of these effects were blocked by the anesthetic bupivacaine consistent with a role for TASK channels in establishing intrinsic resting parameters (1113). Moreover, activation of $5HT_{2A}$ receptors of entorhinal cortex interneurons increases their excitability by a mechanism involving inhibition of TASK3 channels (269).

### J. $Na^{+}/Ca^{2+}$ Exchanger

Very little is known concerning the identities of the diverse family of membrane transporters and pumps typically found on neurons throughout the central nervous system and which, if any, are present on specific inhibitory interneuron subpopulations. However, one landmark study highlighted an essential role for the $Na^{+}/Ca^{2+}$ exchanger in providing input specific dendritic compartmentalization of synaptic signaling in neocortical fast spiking interneurons (417). Most excitatory synapses are made onto spine-free, smooth dendrites of inhibitory interneurons (1035) (see sect. V). This arrangement suggests that unlike principal cells, inhibitory interneurons lack a mechanism to compartmentalize $Ca^{2+}$ transients generated by single synapses. Goldberg and colleagues (417, 418) used imaging techniques to monitor single synaptic inputs arriving onto GluA2-lacking $Ca^{2+}$-permeable AMPAR synapses of neocortical layer II/III and V fast spiking basket cells. Surprisingly, they observed that synaptic input generated $Ca^{2+}$ transients that were remarkably localized despite the absence of physical structures to limit the $Ca^{2+}$ spread (417). This “compartmentalization” of the synaptic signal resulted from the unique combination of both the kinetics of the underlying $Ca^{2+}$-permeable AMPARs and a fast extrusion mechanism provided by a proximally located low-affinity, high-capacity $Na^{+}/Ca^{2+}$ exchanger. Indeed, blockade of the $Na^{+}/Ca^{2+}$ exchanger with benzamil increased the spatial spread of $Ca^{2+}$ microdomains (417). Such an arrangement provides the molecular underpinnings of $Ca^{2+}$ microdomains in interneuron subtypes.

### K. Cluster Analysis of Physiological Parameters

As stated above, comparing results from different cell types obtained from different laboratories using different recording conditions is often problematic. Moreover, consideration of one or a few physiological feature (s) (e.g., resting potential or firing threshold) alone is usually not particularly informative in trying to determine the intrinsic properties or identity of any particular cell type. However, several recent studies have made recordings from large numbers of identified cell types using identical recording conditions (providing an internal control), thus allowing comparisons of basic membrane and active properties across interneuron subtypes derived from either both MGE and CGE (1138), only those derived from the CGE (796), cells restricted to a particular hippocampal subfield (499), or cortical NPY-expressing interneurons (549). Although briefly discussed here, readers are encouraged to seek out these original papers to truly digest the complexities and value of these approaches.

Using a polythetic classification scheme, Tricoire et al. (1138) compared electrophysiological, molecular, and lineage parameters of identified MGE- and CGE-derived hippocampal interneurons. Unsupervised cluster analyses (Wards and K-means) that included 20 features of intrinsic excitability and firing properties were performed (FIGURES 9 and 12 and TABLE 1). This data set, obtained from in excess of 140 cells, resulted in identification of six robust cell clusters. Clusters 1 and 2 were comprised solely of MGE-derived inhibitory neurons, whereas clusters 4, 5, and 6 comprised only cells of CGE origin ( FIGURE 12). Cluster 1 comprised cells expressing PV- and SST-mRNA transcripts and possessed the fastest membrane time constants (13 ms) and steady-state firing frequencies (mean 70 Hz) (TABLE 1). Action potentials were brief (half-widths of 0.5 ms) followed by large-amplitude (25 mV) and short-duration AHPs (29 ms). Cells fire action potentials at high frequency with limited accommodation compared with all other cells in clusters 2 through 6 (1138). This cell cluster comprised PVBCs, BiCs, and AACs.

Cells in cluster 2 possessed slower membrane time constants (46 ms) and firing frequencies (~20 Hz), typically exhibited significant voltage-dependent sag indicative of $I_h$, and expressed SST-mRNA transcripts. Cluster 3 was the only group to comprise cells derived from both the MGE and CGE that were characterized as expressing NPY-mRNA and possessed a late spiking firing phenotype consistent with Ivy and NGFC populations (TABLE 1). Action potential amplitudes are relatively small, duration is moderate and typically followed by a brief but large AHPs. Firing patterns are largely nonaccommodating and often accelerate as the depolarizing pulse proceeds (1137, 1138). The inability of the cluster analyses to separate NGFCs derived from either the MGE or CGE underscores the common physiological features despite being derived from disparate embryonic eminences (1137). Cells in clusters 4 and 5 had similar electrophysiological properties with high input resistances (430 and 401 MΩ, respectively) and slow membrane time constants (57 and 5 ms, respectively). Cells in cluster 4 were typically CGE-derived, dendrite targeting cells, such as SCA and associational collateral associated CCK-cells. Cells in cluster 5 possessed axons with little to no ramification within the hippocampus and were considered to represent long range projection or interneuron-targeting interneurons (5, 439). Finally, cells in cluster 6 had the highest incidence of CCK expression (typically in combination with VGluT3 and VIP) and anatomies indicative of CCKBCs (1031, 584) and mossy fiber associated cells (1138) with intrinsic features that were often intermediate to cells in all other clusters (TABLE 1).

Close inspection of these data begs consideration of whether these intrinsic physiological parameters are largely genetically determined or induced at their final settling positions within the hippocampus. The observation of no overlap of functional characteristics between MGE-versus CGE-derived cells within five of the six clusters suggests that the cell origin has high discriminative power in the cluster analyses ( FIGURE 12). Similarly, some electrophysiological properties such as time constants and spike kinetic/frequency parameters possessed very strong discriminative power, and randomization of these parameters significantly degraded the clusters. This observation is most likely influenced by the unique physiological features that PV-containing cells of cluster 1 possess, which are among the earliest born MGE-derived interneurons. Cluster 1 cells have the lowest input resistance, fastest membrane time constants, and rapid action potential kinetics/frequency parameters. The remaining MGE-derived interneurons of clusters 2 and 3 have physiological features that diverge from the PV-cell population and suggest that spatiotemporal changes in the production of MGE-derived cells can have significant influence over their ultimate physiological properties. Fine-grained inspection of electrophysiological properties of clusters 2 through 6 (in absence of cluster 1) yields few features that discriminate between the cells of these clusters, suggesting that no obvious single genetic or transcriptional feature determines the overall physiological intrinsic properties of hippocampal interneurons.

Using a GAD67-eGFP mouse line, Hosp et al. (499) took a similar morphophysiological approach to determine whether interneurons of the hippocampal DG could be “broken” into functionally distinct groups or exist in a continuum. Cluster analysis based on morphometric variables of 114 sampled cells revealed 5 distinct classes of interneurons each with distinct morphophysiological features. Based on dendritic and axonal morphological criteria alone, this approach revealed clear separation of interneurons into five well-defined subcategories. Of these morphological features, the layer specific distribution of the axon together with its length and density in the transverse plane were critical determinant features. Like the studies described above, perisomatic targeting cells (PVBCs and presumed AACs) formed a major

cluster (M1). However, with the exception of molecular layer cells (ML, corresponding to MOPP cells and NGFCs) analysis of electrophysiological parameters alone were insufficient to clearly delineate interneuron subtypes, confirming our hypothesis that there is a continuum for sampled electrophysiological parameters that are often insufficient to permit fine grain definition of individual interneuron subtypes. Combining both morphological and electrophysiological features revealed five cell clusters comprising PVBCs (BC, cluster), HICAPs, total molecular layer cells, HIPPs, and molecular layer cells. Comparison of these with the clusters identified in CA1 subfield by Tricoire et al. (1138) reveal some remarkable consistencies between cluster identities from both studies. Both the BC cluster (499) and cluster 1 of Tricoire et al. (1138) comprise almost exclusively PV-containing interneurons. Similarly, HIPP cells form a cluster equivalent to that of cluster 2 SST-containing cells in Tricoire et al. (1138). DG HIPP cells have previously been suggested to correspond to O-LM cells of the CA subfields (352). Similarly, cluster 3 of Tricoire et al. (1138) contains cells of the NGFC family as did the ML cluster of Hosp et al. (499). The HICAP cluster comprises CCK-containing interneurons similar to cluster 4 in the CA1 hippocampus. Taken together, these two independent studies using morphological and physiological features of randomly selected neurons yield cell cluster identities with remarkable consistency across different hippocampal subfields.

A similar study by Miyoshi et al. (796) probed the intrinsic properties of neocortical inhibitory neurons derived solely from the CGE. Using the 5HT3aR-eGFP mouse reporter line, they attempted to unravel the diversity of CGE-derived cell types and determine whether distinct subpopulations of cells could be grouped according to anatomical, transcriptional, and electrophysiological features. They observed that this divergent population of CGE-derived cells parsed into nine distinct subtypes based on morphology, cell layer positioning, firing patterns, and other intrinsic properties. Of these, the largest groups were either reelin-positive cells, characterized by cells with a late spiking phenotype or VIP-containing cells. The reelin cells comprised two subgroups based on cell size (small vs. large soma-dendritic-axonal arborizations) and position (primarily layer I/II vs. layers I/II/III), together with late spiking firing phenotypes in response to depolarizing stimuli. The majority of CGE-derived interneurons that did not express reelin expressed VIP. These cells were found primarily in layers II/III and fire strongly accommodating trains of brief duration action potentials. Interestingly, this study also revealed several other classes of interneurons that possessed unique anatomical and electrophysiological properties distinct from either reelin or VIP cells, underscoring that CGE-derived neocortical interneurons comprise a diverse and larger population of inhibitory interneurons than initially predicted. Close inspection of the electrophysiological properties of these cells, however, highlight few features that are distinct to one or few cell types, with only minor exceptions, and all nine identified cell types largely exhibit a continuum of intrinsic parameters. It is possible that spatiotemporal changes in the production of CGE-derived subtypes are less prominent than observed in MGE-derived interneurons, consistent with the observation that the ratio of reelin- to VIP-containing interneurons remains constant throughout development. However, two functionally distinct cell types argue against this simple notion: the “sigmoid intrinsic bursting” interneuron types (high input resistance, bursting firing pattern) are among the earliest CGE-derived interneurons, whereas the fast adapting interneurons [electrically small, high input resistance and fire spikes with short half widths (~1.0ms)] are preferentially produced at the peak of CGE-interneuron production (147, 796). It is unclear at this time whether shifts in the production of particular subtypes and their intrinsic properties represent temporal alterations in the progenitor populations or shifts in intrinsic cues within the cortex as development progresses (796).

Finally, Karagiannis et al. (549) also used unsupervised cluster analysis based on morphological properties, laminar positioning, and 32 electrophysiological features to interrogate the diversity of NPY-expressing interneurons in the rat barrel cortex. Their extensive data analysis from 200 cells suggested three main populations of NPY-expressing cells. 1) The first class are nNOS-expressing NGFCs with a dense axonal plexus and a late-spiking phenotype. This adapting NPY cluster exhibited the lowest firing frequencies of the cells tested. Action potentials were followed by biphasic AHPs comprising early and late components. This cell cluster had a remarkably diverse array of firing phenotypes perhaps suggestive of different cell types captured within the cluster that have some overlapping features. 2) The second population are SST-containing Martinotti-like cells with axons that ascend into layer 1 and represent the most excitable cell type. These cells exhibited a relatively depolarized $V_m$, were electrically more excitable than PVBCs, and exhibited pronounced sag during hyperpolarizing current steps indicative of $I_h$. These cells fired action

potentials of durations intermediate between those observed in PVBCs and pyramidal cells and demonstrated slow accommodation. 3) PVBCs with low input resistance, short membrane time constant, and high rheobase comprised the third class of distinct NPY-containing interneurons. These cells also fired brief action potentials of small amplitude followed by sharp monophasic afterhyperpolarizations. Action potentials showed an acceleration of their firing rate when depolarized above threshold and could sustain high steady-state firing frequencies. Each of these cell types possessed distinct repertoires of mRNA transcripts that correlated well with functional physiological parameters.

### L. Axonal and Presynaptic Release Properties

Although all inhibitory interneurons by definition release GABA as their primary neurotransmitter, the structural and functional properties of the axonal compartments of these cells are far from homogeneous. Neurotransmitter release is generally considered a “point to point” process i.e., liberation of vesicular neurotransmitter occurs from a well-defined presynaptic structure onto clusters of receptors housed in a postsynaptic specialization. Neurotransmitter release profiles are dictated by the combined properties of the axonal architecture, action potential duration and propagation, the biophysical properties of presynaptic voltage-gated $Ca^{2+}$ channels, and the particular neurotransmitter release machinery used to liberate synaptic vesicles (1282). Consequently, neurotransmitter release profiles can vary considerably due to the highly divergent nature of these parameters across discrete cell types and synapses.

As described in section II, the axons of many interneurons can remain local to the subfield housing their soma and dendrites (e.g., IvCs and NGFCs), or possess axons that cross considerable distances to innervate distinct subcellular compartments (e.g., CCKBCs, O-LM, and backprojecting cells) or, alternatively, form long-range projections that extend beyond their original central location to ramify within both cortical and subcortical structures. At the anatomical level, the properties of many interneuron subtypes have been studied and the length and trajectories of these cells well documented (102). However, the functional properties of axons of only a small number of cells have been described in any great detail. However, it is becoming clear that the functional properties of axons that are often excessively lengthy, branch often, and taper to extremely small diameters require functional specializations that are not typical of principal excitatory cell axons. Of particular relevance for our discussion here are cells of the PV-containing, CCK-containing, and NGFC subpopulations. These three subfamilies have axonal and synaptic neurotransmitter release properties that differ considerably from each other and serve to exemplify synchronous, asynchronous, and a hybrid form of phasic/tonic neurotransmission mechanisms used by inhibitory interneurons (FIGURE 13). The increasing understanding of their release biophysics highlights the remarkable diversity that exists even at the level of inhibitory neurotransmission.

**1. PV-containing interneurons** The best studied of these three interneuron subtypes is the PV-containing interneuron subfamily (see sect. IIB). The axons of single PV interneurons extensively arborize to form en passant boutons (~10,000 in the CA1 hippocampus), which provide synchronous robust inhibitory control of their downstream targets (FIGURES 2C, 9A, and 13). The axons of PVBCs typically innervate the soma and proximal dendrites of principal cells, while those of AACs form “chandelier”-like strings that selectively innervate the axon initial segments of principal cell targets (352) (FIGURE 2, A–D). To enforce such strong inhibitory output onto downstream targets the PV axon has incorporated numerous functional specialties worthy of discussion (502). Action potential initiation and propagation in PV cells possess features distinct from those of excitatory pyramidal cells. The action potential initiation site is extremely close to the soma (within 2 0µm), and spike initiation of the AP is reliable and seldom fails. Action potentials are brief (~0.5 ms) (TABLE 1), and propagation speeds are extraordinarily fast with orthodromic speeds of ~0.25–1.5$ms^{-1}$ being reported using direct axonal recordings (277, 503). In considering action potential propagation through this thin extensively diverging axonal compartment, it is hard to fathom that equivalent transmission could exist at the farthest reaches of this axon (~50 mm in CA1). However, a unique arrangement of voltage-gated $Na^+$ channels facilitates conduction throughout this extensive compartment. In a remarkable series of patch-clamp recordings, Hu and Jonas (503) demonstrated that the dendrites and somas of PV cells possess a low density of $Na^+$ channels (~1% of total). The $Na^+$ channel density progressively increases (~100-fold) with distance along the axon (FIGURE 10B). At distal locations the $Na^+$ conductance density was reported as ~600 pS/µ$m^2$. This “supercritical” density of $Na^+$ channels likely ensures failsafe and rapid action potential propagation. The biophysical properties of these

$Na^+$ channels (primarily $Na_V1.1$ and $Na_V1.6$), coupled with the axonal expression of Kv3-containing voltage-gated $K^+$ channels, ensures brief-duration action potentials that depolarize and repolarize rapidly, and importantly ensure rapid and efficient channel deinactivation such that a large fraction of channels are available for subsequent action potential initiation. These biophysical properties allow firing at high frequencies and rapid propagation through an increasingly small axonal compartment to ensure high fidelity of transmission to downstream targets (65, 503, 755).

On reaching presynaptic en passant boutons, the action potential wavefront activates rapidly activating $Ca_V2.1$ P/Q-type voltage-gated $Ca^{2+}$ channels. $Ca^{2+}$ entry through P/Q channels is tightly coupled to the exocytotic release machinery via formation of specialized "nanodomains" (296). The short physical distance between the site of $Ca^{2+}$ entry and the synaptic release machinery enforces a tight coupling between action potential invasion and neurotransmitter release with rapid and precise temporal dynamics (132, 477). The synaptotagmin family member syt2, which possesses rapid $Ca^{2+}$ binding kinetics (1232), is highly enriched in PV cell axons (576). The $Ca^{2+}$ binding properties of syt2 likely serve to minimize the time required between $Ca^{2+}$ entry and the liberation of neurotransmitter (502). The measured half duration of quantal release at these synapses is ~300 µs, and Pr is high (~0.6) (602). Thus, through a combination of anatomical and molecular specializations, action potential initiation, propagation, and presynaptic invasion are "tuned" to ensure rapid and reliable neurotransmission to downstream targets, consistent with a role for these cells in enforcing temporally precise feedforward/feedback-inhibitory control as well as the generation of coherent oscillations within cortical ensembles (FIGURES 13A and 20).

The brevity of action potentials combined with rapid $Ca^{2+}$ entry that is tightly coupled to release machinery ensures that neurotransmission from PVBCs to their downstream targets will proceed with high efficiency. As a consequence of these molecular specializations, the small number of $Ca^{2+}$ channels at each release site coupled to syt2-mediated neurotransmitter release favors fast temporally precise "synchronous" phasic transmitter release, thus making them rapid signaling devices capable of providing precisely timed inhibition onto their postsynaptic cells (64, 502) (FIGURE 13). Despite the specializations designed to ensure high fidelity across the axonal arborization, PVBCs can display distance-dependent scaling. In a recent study, Bartos and colleagues (1058) observed that single axons of DG PVBCs differentially inhibited close versus distant principal cell targets. Inhibitory strength declined (presumably due to lower contact numbers) and signal duration was increased with distance (likely due to changes in postsynaptic $GABA_A$ receptor subunit composition) between the presynaptic cell and the downstream targets. Of particular interest, this distance-scaling feature appears to facilitate the ability of PV-containing interneurons to synchronize large principal cell populations during gamma frequency oscillations (1058).

**2. CCK-containing cells** CCK-containing cells show an altogether distinct mode of neurotransmission that favors looser coupling and an asynchronous mode of transmitter release compared with PV-containing cells (FIGURE 13B). In addition, CCK cells fire action potentials with longer durations (>0.5 ms), which lengthen upon repetitive activation during trains further contrasting with their PV cell counterparts (182). Although studies similar to those described above for PV-containing cells have not been made for CCK cells (or for any other interneuron subtype for that matter), their action potential conduction velocities are thought to be slower than those of PVBCs since evoked unitary IPSCs occur with longer delays than that seen at PVBC synapses (FIGURE 13, A and B) (477). CCK interneuron unitary IPSC amplitudes and latencies show large fluctuations (258, 477), due to weak coupling between their presynaptic N-type $Ca^{2+}$ channels and release machinery (64, 477) (FIGURE 13B). An important feature of transmission at CCK-containing cells and their downstream targets is the transition from largely synchronous neurotransmitter release to asynchronous release during repetitive activation (21, 258, 477). Indeed, synchronicity ratios of transmission for CCK cells (the ratio between synchronous vs. asynchronous release during a train of 25 events at 50 Hz) were calculated to be between 1.1 (CCK-dendrite targeting cells) to 2.1 (CCKBCs), which are significantly lower values than those calculated for PVBCs (6.2) (258). Asynchronous release appears to be a general property of CCK-containing interneurons and correlates with the class of presynaptic CCK interneuron but is largely independent of postsynaptic target identity (258, 554). However, Ali and Todorova (21) observed that the synchronicity ratio for CCK cells residing at the s.l.m.-s.r. border was larger for postsynaptic interneurons than CA1 pyramidal cells, suggesting that postsynaptic targets may influence synchronicity of release for certain CCK cell subtypes. The precise mechanism

underlying the transition from synchronous to asynchronous modes of transmitter release is presently unclear. However, asynchronous release at a number of synapses has been attributed to the buildup of residual $Ca^{2+}$ during periods of high activity (706, 868). Elimination of dominant presynaptic $Ca^{2+}$ sensor synaptotagmin isoforms (Syt2 at the Calyx of Held or Syt1 at DG cell synapses) (576, 1066) selectively eliminates synchronous release revealing an increase in asynchronous release, suggesting that separate $Ca^{2+}$ sensors may underlie the two modes of release. At CCK cell synapses, asynchronous release increases with elevation of extracellular $Ca^{2+}$ concentration (258). The difference in $Ca^{2+}$ dependence between synchronous and asynchronous release observed at CCK synapses is consistent with the presence of two $Ca^{2+}$ sensors at these presynaptic terminals (256, 258). Functionally one can imagine that an asynchronous mode of transmitter release will endow CCK cells with prolonged inhibitory control over their postsynaptic targets, a mechanism distinct from the temporal precision enforced by PVBCs. Indeed, in paired recordings, one striking feature of asynchronous release is the long temporal window of transmitter release that continues many 100s of milliseconds after termination of presynaptic firing (258, 477), underscoring that this form of inhibition is prolonged and temporally imprecise (FIGURE 13B).

**3. NGFCs** The above examples highlight two well-established distinct modes of phasic synaptic signaling for discrete interneurons both with clearly identifiable synaptic structures consisting of anatomically well defined pre- and postsynaptic specializations, i.e., point-to-point transmission. Transmitter concentration profiles during such phasic forms of neurotransmission favor postsynaptic receptor activation and deactivation, with few if any roles for receptor desensitization. In contrast, tonic synaptic signaling results in the prolonged and persistent activation of receptors by ambient GABA in the extracellular space, which drives an equilibrium between desensitized and open states (870). Interestingly, NGFCs mediate a third form of GABAergic transmission intermediate between phasic and tonic signaling (165) (FIGURE 13C). This atypical form of neurotransmission arises from the unique axonal arborizations of NGFCs that emerges from the soma or dendrites to form a small dense plexus around the parent cell soma (FIGURES 3 , 9I, and 13C). The axonal arborization has been calculated to approximate 140,000 µm in length, compared with ~46,000 µm for a typical PVBC. Importantly, the presynaptic bouton density of NGFCs is among the highest of all hippocampal interneurons with an average bouton density close to 42 per 100 µm of axon (interbouton separation 2.5 µm) (102). Indeed, the bouton density of a single NGFC matches the release site density of five or six 6 overlapping basket cell axons (858). One feature of NGFC axons separating them from all other inhibitory interneurons is that the vast majority of presynaptic boutons are spatially located at a larger than usual distance from their target dendrites and are often not in register with any clear postsynaptic structure (858, 870). In somatosensory cortex, the separation between NGFC boutons and their dendrite targets averages 2.7 µm (range 1.1–5.0 µm) (858). This arrangement has led to the hypothesis that NGFCs release GABA in a target independent, volume- or "cloud-like"- manner to generate a nonspecific form of inhibitory control. Action potentials in NGFC cells are of small amplitudes and moderate duration. Their firing patterns are largely nonaccommodating and often accelerate during depolarizing pulses. Little is known however about the functional properties of NGFC axons and the properties underlying their neurotransmitter release. Of particular interest, in contrast to the rapid and synchronous IPSCs produced by PVBCs, transmission from NGFCs generates long-lasting IPSCs resulting from prolonged GABA transients (550, 1074, 1086) that arise from the unusual synaptic architecture where bouton density is high but close apposition to specialized postsynaptic densities is low (550, 751, 858, 1074) (FIGURE 13C). This low and prolonged GABA transient favors postsynaptic receptor desensitization and results in use-dependent synaptic depression as receptors accumulate in desensitized states (550). Second, in contrast to other interneuron subtypes that precisely target distinct subcellular domains, inhibition mediated by NGFCs generally lacks target cell and synaptic specificity. Moreover, the cloud of GABA released from NGFCs is strongly influenced by GABA uptake mechanisms ( FIGURE 13D) and acts on $GABA_A$ and $GABA_B$ receptors located on any nearby neuronal element, including the releasing cell itself, potentially producing suppression of neural activity in a widespread area dictated by their dense NGFC axonal arbor (870).

## M. Gap Junctions

The observation that sensory stimuli could trigger synchronous inhibitory activity across large populations of cortical cells suggested that networks of certain interneuron subtypes were highly interconnected (220, 541, 1072). Moreover, the observations that specific interneuron subtypes are necessary for the generation

of coherent cortical and hippocampal oscillations (333, 1200) and that interneuron subtypes fire at specific phases of the oscillatory cycle (586) suggest that synchronization among interneurons is critical for cortical circuit function (151). Although GABAergic interactions between interneurons have been implicated in the generation of synchronous activity (1190), the observation that many interneuron types were highly interconnected by connexin-36-containing electrical synapses (497, 1167) or gap junctions provided an important clue as to how large populations can be synchronized during oscillatory activity (220, 488). Within hippocampus and neocortex, dendrodendritic or dendrosomatic electrical synapses are a common feature of many interneurons (80, 370, 371, 376, 398, 1084). In contrast, electrical synapses are rarely seen between principal cells (901). Electrical synapses between interneurons are made typically only between cells of the same class or subtype. Almost all cardinal classes of interneuron (PV-containing, SST-containing, CB1R-positive, NGFCs) exhibit within class electrical synapses making extended and independent gap junction coupled networks. One interesting deviation from this canonical rule are NGFCs of layer 2/3 (but not layer 1) (206) of rat somatosensory cortex. Although these cells were highly interconnected via electrical synapses, they also made widespread electrical synapses with PVBCs, regular spiking nonpyramidal cells, AACs as well as many other unidentified interneuron cell types (1017). Estimates of connectivity suggest that >50% of cells make within class electrical synapses. PVBCs are connected via both chemical and electrical synapses. In contrast, SST-containing cells make few GABAergic synapses onto each other but are highly connected via electrical synapses. Of particular importance electrical synapses are essentially bidirectional and rapidly transmit voltage changes at speeds slightly faster than chemical synapses (970). Electrical synapses have unusual low pass filtering properties that provide essential clues to their function. The low pass coupling coefficient of connections is highly variable but is typically between 1 and 40% (with a mean coupling conductance of 1.6 nS) (220, 488). The low pass nature of the coupling severely truncates rapid events such as action potentials and favors slower depolarizations/ hyperpolarizations such as AHPs. Action potentials when propagated across gap junctions are severely truncated and manifest themselves as “spikelets” of a few millivolts that are capable of triggering rapid depolarizations that can facilitate activation of voltage-dependent conductances and trigger coordinated spiking across clusters of coupled interneurons. Such coupling is rapid and bidirectional facilitating coordinated inhibitory synaptic transmission onto downstream principal cells, as well as triggering synchronous oscillatory activity across neural networks (80, 375, 1128). Events such as the action potential AHP, which are faithfully transmitted across electrical synapses, serve to deinactivate intrinsic voltage-gated conductances across the many connected cells. This allows for simultaneous cell activation once the AHP relaxes, further enhancing synchronous activity (107, 397, 671).

## N. Persistent Action Potential Firing

In addition to fast, regular, bursting, accommodating, delayed and stuttering action potential firing patterns, an altogether unique form of firing has been observed in a small number of cell types. This novel form of slow integration is triggered in response to prolonged action potential activity and is known as persistent or retroaxonal barrage firing (300, 606, 1000, 1001, 1069, 300). In IvC, NGFCs [called perforant path associated HTr5b-GFP cells of SR/SLM border in (1000)], and PVBCs of several cortical and hippocampal regions persistent firing is generated within the distal axon compartment, requires $Ca^{2+}$ elevation and gap junction coupling, and persists for several minutes on cessation of the trigger. During persistent firing, cells fire at frequencies ranging from 20 to 130 Hz, depending on the particular region (1069). In PV-containing interneurons, steady-state persistent firing dominates at gamma frequencies close to 50 Hz (300). Although the mechanism underlying the generation of persistent firing is at present unidentified, it is not blocked by $GABA_A$, $GABA_B$, AMPA, or NMDA receptor antagonists (1000). In CA1 PPA cells, persistent firing is attenuated by blocking voltage-gated $Ca^{2+}$ channels (1001). In contrast, in PV-containing interneurons of the DG, application of $Cd^{2+}$ or inclusion of the intracellular $Ca^{2+}$ chelator BAPTA in the recording pipette boosts the duration and number of action potentials during persistent firing (300), suggesting interneuron-type specific or brain region specific differences in the contributions of $Ca^{2+}$ to persistent firing. In PV-containing cells, persistent firing depends on $I_h$ activation (300). Induction is inhibited (at least in hippocampal NPY-expressing Ivy cells) by activation of μ-opioid peptide receptors (606), which act to either hyperpolarize the NGFC or inhibit the locally connected gap-junction-network between cells. Although axonal action potential firing is required to trigger persistent firing, somatic depolarization is not. In paired recordings, persistent firing was not restricted to the

stimulated neuron; it could also be produced in the unstimulated cell, suggesting that activity can percolate through the network via electrical coupling. Consistent with this observation are the manifestation of action potential "spikelets," indicative of activity being registered by the recorded neuron through gap junction coupling to other cells in the network undergoing persistent firing. Importantly, persistent firing, which likely provides a global "brake" on local excitability, occurs in NGFCs both in vitro and in vivo, although in vivo it occurs less frequently and requires more prolonged barrages of action potential activity for initiation in neocortical NGFCs (1069).

## V. GLUTAMATE RECEPTORS

Inhibitory interneurons are embedded within complex neuronal networks of interconnected principal glutamatergic cells and GABAergic interneurons and thus participate in almost all forms of network activity. The principal form of excitation onto interneurons arises via activation of ionotropic and metabotropic glutamate receptors by glutamate, the primary neurotransmitter within the central nervous system. Despite having many common features with glutamate receptor containing synapses on principal cells, a number of notable differences and exceptions exist making them worthy of discussion here.

Ionotropic glutamate receptors are divided into three main subtypes: AMPARs, NMDAR, and kainate (KA) receptors. Historically these receptors have been defined based on agonist and antagonist pharmacological properties (1133). Each of these three receptor subtypes is composed of distinct subunits whose combinations confer unique biophysical properties to the native receptor. For more extensive discussion on glutamate receptors and specifically those found on interneurons, interested readers are pointed to recent reviews (11, 1133).

### A. AMPA Receptors

Throughout the central nervous system, the vast majority of fast synaptic neurotransmission arises via AMPARs (1133). Native AMPARs are typically homomeric or heteromeric assemblies of the four subunits, GluA1–4 (572, 822, 955). Of these subunits, incorporation of GluA2 is key to the overall biophysical properties of the receptor. The M2 reentrant transmembrane loop of the AMPAR subunit forms the lining of the channel pore, and amino acids in the so-called "QRN" site determine the ion selectivity of the channel (1133). Unlike GluA1, GluA3 and GluA4 subunits which contain an unedited glutamine (Q) most GluA2 subunits contain a fully edited arginine (R) at this site which has important consequences for single channel conductance, $Ca^{2+}$-permeability, and channel block by polyamines (1133).

Although most mature AMPAR on principal neurons are typically comprised of GluA1/2 or 2/3 heteromers, which are $Ca^{2+}$-impermeable (CI) and possess nearly linear current-voltage relationships, early evidence indicated that many interneurons expressed AMPARs that differed markedly in these properties from their principal neuron counterparts (517, 874). In situ hybridization and RT-PCR coupled with electrophysiological approaches subsequently revealed the presence of both inwardly rectifying, GluA2-lacking $Ca^{2+}$-permeable (CP) AMPARs and GluA2-containing CI-AMPARs on inhibitory interneurons throughout the cortex and hippocampal formation (11, 51, 107, 388, 539, 769, 960). Until recently, little attention was paid to what interneuron type (with the exception of noting which hippocampal or cortical subfield the cell body resided in) expressed a particular AMPAR subtype. Moreover, both CP- and CI-impermeable AMPARs had been observed in recordings from single CA3 stratum lucidum (s.l.) interneurons, which targeted each receptor subtype to postsynaptic sites innervated by distinct afferent projections (1119). Mossy fiber axons of DG granule cells innervated GluA2-lacking CP-AMPAR dominated synapses, whereas inputs from associational fibers of CA3 pyramidal cells onto the same cell innervated GluA2-containing, CI-AMPAR dominated synapses. The mechanisms whereby single interneurons can manufacture these distinct AMPARs and target them to specific dendritic domains remain poorly understood, but such selective targeting has been observed at numerous cells throughout the mammalian central nervous system (for review, see Ref. 1120).

Early quantitative electron microscopy studies indicated that asymmetric synapses onto interneuron dendrites were enriched for GluA subunits, with little evidence for the "silent" synapses observed on principal cell dendrites that lacked AMPAR subunits and appear critical for synapse maturation (846). Quantitative immunogold electron microscopy of the AMPAR subunits expressed at Schaffer collateral

inputs onto CA1 s.r. interneurons revealed no differences in GluA1, GluA2, or GluA3 subunit expression between synapses onto PV-containing interneurons versus "non-PV" synapses (1242). However, GluA4 expression was significantly higher at PV synapses than non-PV synapses. It is unclear exactly what population (s) are captured by the "non-PV" cell data set, which likely comprised both MGE-derived (e.g., SST- and nNOS/NPY-containing) and CGE-derived (e.g., CCK-, NPY, VIP-containing) interneuron types. Subsequent analysis of mRNA transcripts using fluorescent in situ hybridization revealed a high abundance of GluA1 and GluA3 in PV cells, equivalent to expression levels on principal cells. However, GluA4 was significantly higher and GluA2 significantly lower at PV cell synapses than observed at principal cell synapses. In contrast, both CCK-containing and NOS/NPY-containing interneurons showed comparatively low but consistent levels of all four GluA transcripts compared with principal cell synapses (1242).

The expression profile of GluA4 is particularly interesting since it imparts novel kinetic properties to the AMPAR. Unlike mature hippocampal and cortical principal cells, which do not typically express GluA4, PV-containing interneurons possess a high level of GluA4 and a lower level of GluA2 subunit expression (388, 630, 886, 1242). However, immature synapses onto PV-containing interneurons lack GluA4 and are comprised of GluA1 homomers (886). GluA4 expression increases over the first two postnatal weeks to generate receptors comprised of GluA1/GluA4 heteromers by adulthood (99, 388, 800, 886). These GluA1/4 containing AMPARs generate synaptic currents that possess unusually rapid kinetics, have high $Ca^{2+}$ permeability, and show strong inward rectification due to block by intracellular polyamines (644). This receptor arrangement is critical for circuit recruitment of PV-containing interneurons to enforce temporal control over principal cells for efficient generation of large scale oscillatory activity (for review, see Refs. 67, 502). GluA1 or GluA4 loss-of-function experiments show compromised gamma oscillations and impairments in hippocampal-dependent working memory (364). Similarly, overexpression of the GluA2 subunit slows the AMPAR kinetics and disrupts long range synchrony underscoring the importance of synaptic AMPARs with rapid kinetics in these cells (365).

Using a combination of genetic and electrophysiological approaches, Matta et al. (763) provided a comprehensive picture of AMPAR expression profiles at Schaffer collateral synapses onto CA1 interneuron populations based on their embryonic origins within either the MGE or CGE throughout development (FIGURE 14). Schaffer collateral synapses onto MGE-derived interneurons (e.g., PV-, SST-, and nNOS-containing interneurons) typically express CP-AMPARs, whereas CGE-derived interneurons (CR, VIP, CCK, reelin, and some nNOS interneurons) mostly express CI-AMPARs. These origin specific AMPAR profiles are consistent across a broad developmental age range and importantly demonstrate that, at least at SC synapses onto CA1 subfield inhibitory interneurons, GluA2 expression is not developmentally regulated as seen at some principal cell synapses (492). Whether this MGE- versus CGE-origin specific AMPAR expression exists at other synapses remains to be demonstrated, but suggests that embryonic origin provides a strong predictor of glutamate receptor expression.

### B. AMPAR Auxiliary/Interacting Proteins; TARPs

Most if not all AMPAR subunits exist in a complex with a number of channel auxiliary subunits that bind to a variety of targets on the pore forming subunit to modify receptor expression and recycling, as well as their biophysical and plastic properties (1243). Of these accessory proteins, most AMPARs complex with transmembrane AMPA regulatory proteins (TARPs) (1107). The TARP family comprises six isoforms, which differentially modify almost every function of native AMPARs (1133). In hippocampal principal cells, the vast majority of AMPARs interact with the TARP type 1 γ2 and γ8 isoforms, which alter surface expression, synaptic targeting kinetics, and plasticity (524, 525). Surprisingly, very little is known about the role of TARPs in regulating AMPAR function in inhibitory interneurons. A recent study combining FISH and immunohistochemistry and quantitative electron microscopy illustrated that TARPs γ2 and γ3 are enriched in PV-containing interneurons compared with CCK- and nNOS/NPY-containing interneurons. In contrast, only low expression of γ8 TARP was observed across all interneuron subtypes tested (1242). In γ2 knockout mice, AMPAR density was markedly reduced at excitatory synapses onto PV-containing interneurons but surprisingly was unaffected at synapses onto the cell cohort labeled as "non-PV," suggesting a TARP functional redundancy at the latter synapses. In contrast, AMPAR number was unchanged at synapses onto both PV- and non-PV cell groups in both γ3 and γ8 knockouts (1242). These

data suggest a prominent role for the γ2 in AMPAR expression at excitatory synapses onto PV-containing neurons. In contrast, it is unclear what role if any TARPs are having at excitatory synapses onto other non-PV interneuron subtypes.

### C. AMPAR Auxiliary/Interacting Proteins; Neuronal Pentraxins

The neuronal pentraxin family (NPTX1, NPTX2, and NPTXR) is a family of $Ca^{2+}$-dependent lectins that are highly enriched at excitatory synapses throughout the adult brain (1140). All three NPTXs form disulfide-linked assemblies that bind to the $NH_2$-terminal domain of AMPARs and promote receptor clustering (1008, 1229). Of these, NPTX1 and NPTX2 (or Narp) are secreted proteins, whereas NPTXR possesses a transmembrane domain and can function to anchor NPTX complexes to plasma membranes. NPTX2 is an immediate early gene highly enriched at excitatory synapses onto PV-containing interneurons and promotes activity dependent accumulation of GluA4-containing AMPARs (189). This regulation by NPTX2 critically dictates PV-containing interneuron recruitment to maintain E/I balance in the face of perturbations in network activity (189). However, studies of NPTX2 in regulating excitatory drive onto PV-containing cells revealed only a homeostatic role for NPTX2 and required mice to be pretreated with stimuli that induce NPTX2 expression. In a subsequent study, the developmental upregulation of GluA4 in PV-containing interneurons was observed to require the coordinated expression of both NPTX2 and NPTXR (886). Loss of function of both pentraxins prevents the developmental incorporation of GluA4, resulting in small amplitude and slower AMPAR mediated EPSCs, which disrupted both downstream feedforward inhibitory drive and circuit maturation with a prolonged critical period for giant depolarizing potentials (GDPs) and perturbations in gamma and sharp wave oscillations in vivo, together with a lower threshold for electrographic seizure activity (886).

### D. AMPAR Auxiliary/Interacting Proteins; SAP97

The membrane-associated guanylate kinase, MAGUK, family member synapse associated protein 97 (SAP97) is typically associated with components of the postsynaptic density at glutamatergic synapses onto principal cells where its interaction with GluA1 (666) and NMDARs (233) regulates both presynaptic activity and postsynaptic receptor expression levels (937, 968). SAP97 is developmentally expressed in cortical PV- and SST-containing interneurons, with virtually all cells expressing SAP97 in early postnatal periods (P15) followed by a decline to ~40% of cells in adulthood (12). SAP97-positive PV cells in visual cortex receive a twofold higher frequency of mEPSCs with more rapid kinetics than SAP97-negative PV-containing interneurons (12). Overexpression of exogenous SAP97 increases the frequency of fast mEPSCs, which is correlated with dendritic complexity and altered passive and active membrane properties (12). Although the precise mechanism is at present unclear, SAP97 regulates both synaptic input and intrinsic excitability of cortical interneurons. Given the role for SAP97 in regulating GluA1 expression, it is highly likely that early in development excitatory synapses onto PV-interneurons are comprised of GluA1 homomers that require SAP97 for their correct expression. As development progresses, the role of SAP97 may be minimized as its expression diminishes and increased expression of the neuronal pentraxins NPTX2/NPTXR coordinates the incorporation of GluA4 into GluA1/GluA4 heteromeric receptors observed at more mature synapses (886).

### E. AMPAR Auxiliary/Interacting Proteins; Erb4/Neuregulin

The receptor tyrosine kinase Erb4 binds members of the NRG and epidermal growth factor families to regulate a variety of cellular processes including migration, proliferation, synaptic transmission, and plasticity (142). In hippocampus, Erb4 primarily localizes to the postsynaptic density of glutamatergic synapses contacting dendrites of CA1 s.o. and s.r inhibitory interneurons. (319, 1104, 1180). Erb4 expression is highest in PVBCs and AACs while expression is observed only in a small fraction of CR- and SST-containing interneurons (319). Erb4 colocalizes with PSD95 and interacts with GluA4 (886); however, it is unclear what instructive role, if any, Erb4 has for AMPAR expression. Erb4 knockouts show a marked reduction in miniature EPSC frequency (but not amplitude), suggesting a role for Erb4 in controlling glutamatergic synapse formation on interneurons (319) but not necessarily a role in AMPAR trafficking or function. Similarly NRG1, which binds to Erb4, plays a role in stimulating formation of new glutamatergic synapses as well as strengthening existing synapses onto interneurons by a mechanism thought to involve PSD95 stabilization (1104).

## F. N-Methyl-D-Aspartate Receptors

The NMDAR family represents the second major ionotropic glutamate receptor type found at virtually all central synapses and is involved in fast synaptic transmission. Unlike AMPARs, they are typically activated and deactivated with slower kinetics and consequently are involved in a second prolonged component of synaptic transmission. Their unique kinetic properties, coupled to a strong voltage-dependent block by extracellular $Mg^{2+}$ at negative membrane potentials, have placed them center stage as coincidence detectors involved in many forms of synaptic plasticity at excitatory principal cell synapses (1133). Similar to AMPARs, NMDARs are heteromeric assemblies formed from five principal subunits, GluN1, GluN2A, GluN2B, GluN2C, and GluN2D. GluN1 is a core component of all native NMDARs and is an absolute requirement for channel function. Heterotetramers formed between GluN1 and differing combinations of the four GluN2 subunits provide a myriad of channel types each with distinct biophysical properties, pharmacology and expression profiles (1133). NMDARs are unique among glutamate receptors in that they require the simultaneous binding of two agonists to activate the native receptors; glycine (or D-serine) to GluN1 and glutamate to GluN2 (587). Native receptor subunits are also subject to many forms of alternative splicing and posttranslational modifications making for a dizzying array of receptor possibilities expressed at central neuron synapses (interested readers are directed to the comprehensive review in Ref. 1133).

Like AMPARs, NMDAR subunit expression and receptor composition varies between interneuron subtypes (261, 661, 763, 1048, 1177) and in many cases directly correlates with the type of AMPARs expressed at the synapse (11, 661, 769). Early studies of NMDAR function in interneurons recognized a diversity of kinetic profiles and relative contributions of NMDARs at synapses onto specific interneuron types (769, 799). However, as for AMPARs, very little attempt was made to correlate this with particular interneuron subtypes until more recently. In the hippocampal CA1 subfield, NMDARs at Schaffer collateral synapses onto MGE-derived interneurons express GluN2B-containing receptors early in development (763). These receptors possess slow kinetics and are blocked by the GluN2B preferring antagonist ifenprodil. Of particular interest GluN2B-containing receptors are coexpressed with GluA2-lacking CP-AMPARs (FIGURE 15). The AMPA:NMDA amplitude ratio at these synapses is high (~5), suggesting that NMDARs make only a relatively small current contribution at these synapses (FIGURE 15A). Indeed, of all interneurons studied, MGE-derived PV-containing interneurons have the smallest observable NMDAR conductance (763). Later in development synaptic GluN2B subunits are replaced by GluN2A subunits as indicated by a speeding up of receptor kinetics together with a loss of ifenprodil sensitivity (763) (FIGURE 15B). This developmental subunit switch is also triggered by high-frequency synaptic stimulation and requires a rise in intracellular $Ca^{2+}$ through CP-AMPARs, but intriguingly not through NMDARs themselves or by activation of mGluRs, both of which are required for a similar subunit switch in pyramidal cell synapses (762, 763). In contrast, Schaffer collateral synapses onto almost all CGE-derived interneuron subtypes express GluN2B-containing NMDARs across all developmental stages tested that persist through adulthood and do not exhibit any plastic subunit switch following high frequency stimulation (763) (FIGURE 15, A and B). The one exception to this rule so far identified is CGE-derived CCK-containing SCA interneurons, which also demonstrate the GluN2B-GluN2A switch (763). At CGE cell synapses GluN2B-containing receptors associate with GluA2-containing, CI-AMPARs. The AMPA:NMDA amplitude ratio at these synapses is close to unity, indicating a greater role for NMDARs at synapses onto CGE-derived interneurons (763).

The expression of GluN2C and GluN2D subunits on interneurons is less clear. Recent evidence from in situ hybridization studies shows GluN2D expression in cortical and hippocampal PV-, SST-, CB- and CR-positive interneurons as well as in VIP-positive irregular spiking interneurons (799, 920, 1177). Indeed, functional GluN2D-containing NMDARs are found at synapses onto a number of hippocampal interneurons (898, 1177). Early in development, blocking NMDAR activity by ifenprodil increases the decay of synaptic currents in wild-type mice, consistent with the uncovering of NMDARs containing the GluN2D subunit, a phenomenon absent in GluN2D loss of function mice (1177). Expression of slow gating GluN2B and GluN2D dominated NMDARs early in development likely provides a wider temporal window for synaptic integration, potentially important for network maturation, whereas GluN2A expression at later ages enhances the precision of synaptic responses.

Synaptically driven $Ca^{2+}$ entry into cells is undoubtedly a tightly controlled feature, and the above discussion highlights a major divergence in glutamate receptor-mediated calcium influx between interneurons with distinct origins. In MGE-derived interneurons, the expression of GluA2-lacking CP-AMPARs together with a low NMDAR conductance suggests that the primary route of $Ca^{2+}$ entry is through AMPARs, with a smaller contribution of GluN2B or GluN2D NMDARs. In contrast, at synapses onto CGE-derived interneurons, the primary route of $Ca^{2+}$ entry is likely through GluN2B-containing NMDARs. The consequences of these differential routes for $Ca^{2+}$ entry during phasic transmission are at present unclear but may provide clues to the types of plasticity and second messenger mechanisms that are triggered in MGE- versus CGE-derived interneurons (see sect. VI) (214).

Important physiological roles for interneuron NMDARs have been described at cellular (573, 574, 661, 763), network (599, 574), and behavioral levels (82). In MGE-derived hippocampal interneurons of young mice, GluN2B-containing NMDARs play an important role in modulating excitation-spike coupling. The slower kinetics of GluN2B-containing NMDARs influence the synaptic integration properties to regulate both the summation and timing of action-potential generation (763). Similarly at mossy fiber synapses onto CI-AMPAR interneuron synapses, which exhibit high NMDA/AMPAR ratios, a train of stimuli triggers multiple action potentials at each stimulus followed by a large late NMDAR-dependent depolarizing envelope that persists long after the stimulus. In contrast, in synapses with low NMDA/AMPAR ratios, EPSPs trigger only single action potential firing with no substantial after depolarizing phase (661).

Integration of developing interneurons into the nascent circuit critically depends on NMDAR activity. Genetic deletion of GluN2B in hippocampal interneurons leads to a reduction in the frequency of AMPAR-mediated mEPSCs observed onto CA1 s.o. interneurons (574). This decreased excitatory drive promotes hippocampal seizures and subsequent lethality (574). In contrast, elimination of GluN1 from CGE-derived CA1 s.l.m. NGFCs arrests maturation of both pre- and postsynaptic elements such that a higher frequency and amplitude of EPSCs is observed, coupled to an exuberance of cell morphology (Chittajallu and McBain, unpublished observation). Selective ablation of NMDARs later in development in PV-positive interneurons alters theta and gamma oscillations with consequent impairments in spatial and short- and long-term memory tests, indicating a critical role for NMDARs in PV-interneuron-mediated circuit entrainment (82, 599). Loss of NMDARs in PV-containing interneurons at early postnatal ages triggers behavioral deficits associated with schizophrenia including psychomotor agitation, anhedonia, reduced pre-pulse inhibition of acoustic startle, deficits in nesting/mating, and social withdrawal (82), supporting an NMDAR hypofunction theory of schizophrenia (for reviews, see Refs. 234, 235). However, given that PV-containing interneurons possess the smallest NMDAR currents (763), it is hard to reconcile the hypothesis that PV interneuron synaptic NMDAR hypofunction is an underpinning for schizophrenia (825), suggesting that alternative roles for NMDARs other than conventional synaptic transmission must exist in these cells early in development. Indeed, tonic extrasynaptic NMDAR-mediated currents have been identified on PV-containing interneurons of the prefrontal cortex (925) and CA1 s.r. (946), suggesting a novel role for extrasynaptic NMDARs on interneurons in addition to their role in synaptic transmission.

As described in section III, cortical interneurons originate in the ventral telencephalon and migrate tangentially into the neocortex and hippocampus (747). A number of in vitro (78) and in vivo (117, 736) studies have proposed a role for NMDARs in interneuron migration based on changes in cell migration following pharmacological antagonism of NMDA receptors (117). However, the density of PV-positive interneurons in somatosensory cortex of transgenic mice with selective deletion of GluN2B from GAD67-positive interneurons was comparable to wild-type mice (574). In contrast, similar genetic manipulation resulted in increased cell death of adult born olfactory bulb granule cells (573), indicating that NMDARs play different roles in cell survival across different brain regions or developmental stages. Elimination of GluN1 and GluN2B, but not GluN2A, in cortical CGE derived interneurons produces cell type specific (reelin-positive, but not VIP-containing cells) stunting of dendritic and axonal morphology (261). In contrast, elimination of GluN1 in CA1 s.l.m. NGFCs results in cells with more complex dendritic arbors, with dendrites shifting from a stellate form to one polarized towards the termination zones of afferents from the entorhinal cortex and thalamic nucleus reuniens (Chittajallu and McBain, unpublished observation).

## G. Kainate Receptors

Kainate receptors (KRs) are homo- or heteromeric tetramers assembled from GluK1, GluK2, GluK3, GluK4, and GluK5 (1133). Although all subunits are widely expressed throughout the central nervous system, interneurons predominantly express GluK1 and GluK2 (with lower levels of GluK3) at either pre- and postsynaptic sites (143, 332; for review, see Refs. 11, 171).

KR-mediated currents through either homomeric or heteromeric GluK1 or GluK2-containing KRs have been observed in numerous interneuron subtypes (230, 332, 348, 867, 883, 920). Functional mapping of KRs using uncaging methods revealed a continuous density of KRs across the dendrites of CA1 s.o. O-LM and "trilaminar" (sic) interneurons (1245). Of interest, BiCs have KRs on all dendrites residing in the s.o. but not on those that extended into s.r., while other interneurons in s.o. had "hotspots" or were completely devoid of KRs.

In CA1 s.r. interneurons, exogenous kainate evokes inward currents in both GluK1 or GluK2 knockouts, suggesting functional receptor subunit redundancy (816). In contrast, KR-mediated inward currents in CA3 s.r. interneurons are absent in GluK2 loss-of-function mice but not GluK1 knockouts, consistent with a role for GluK2 containing KRs on specific CA3 interneuron populations (332). KR activation by exogenous kainate robustly increases interneuron excitability, triggers action potential firing, and boosts spontaneous inhibitory drive onto pyramidal cells (230, 348). Despite this evidence for functional KRs on various interneurons, only a few studies have identified KR-mediated synaptic currents on interneurons. In principal cells KR mediated EPSCs tend to be kinetically slow, are activated by repetitive high frequency stimulation, and manifest as slow tail currents typically following the AMPAR mediated component at negative holding potentials. Similarly, evoked or spontaneous KR-mediated synaptic events onto inhibitory interneurons often appear as small slow tail currents in the EPSC waveform (229, 230, 348, 349, 1215). However, Cossart and colleagues (229, 420) observed spontaneous KR-mediated synaptic events with slow kinetics (decay tau's ~10 ms) onto CA1 s.o. interneurons, primarily O-LM cells, that occurred in the absence of a detectable AMPAR component. These studies were the first to suggest that KR synaptic events may exist in isolation from synapses containing AMPARs, and importantly these events comprise a significant fraction of the total spontaneous EPSC population (~30%). Similar KR-mediated synaptic events were observed in s.r. and s.l.m. interneurons (1215). Goldin et al. (420) suggested that KRs, but not AMPARs, on SST-positive O-LM cells entrain spiking at theta frequencies, suggesting an important role in oscillatory activity. Indeed, GluK1 antagonists reduce the frequency of hippocampal theta oscillations in vivo (515). However, Oren et al. (867) found no evidence for spontaneous KR-mediated events in recordings from the same cell population and concluded that the vast majority of spontaneous EPSCs in s.o. O-LM cells were AMPAR mediated (1215). Indeed, evoked GluK1-containing KR synaptic events make only a modest contribution (~10% of the total current) when synaptic transmission is driven by repetitive activity (867).

KRs are also expressed on axonal presynaptic terminals of certain interneuron types, where they serve to regulate neurotransmitter release. In hippocampus, exogenous kainate reduces the amplitude and Pr of evoked IPSCs onto CA1 pyramidal cells (208, 231, 734, 951) (however cf. with Refs. 231, 332). Lerma et al. (952) have suggested that this occurs via a metabotropic KR mechanism, although little corroboration of this hypothesis exists. In paired electrophysiological recordings, GluK1 containing KR activation decreases presynaptic release from CCK-containing but not PV-containing interneurons that is observed at release sites onto pyramidal but not interneuron targets (256). As discussed in section IVK, CCK-containing interneurons release transmitter via a combination of synchronous and asynchronous modes. Activation of presynaptic KRs preferentially reduces synchronous, but spares asynchronous transmitter release (256). Such a mechanism may act as a switch to move between phasic modes of transmitter to prolonged inhibition when glutamate levels are elevated during periods of intense activity. Presynaptic modulation by KRs has also been linked to the endocannabinoid (eCB) system (701, 793). High-frequency stimulation of CA1 Schaffer collateral afferents transiently depresses inhibitory transmission onto pyramidal cells via a mechanism involving glutamate spillover activating presynaptic GluK1-containing receptors on CB1R-positive interneuron presynaptic terminals (701). This spillover mechanism requires the concerted activation of the eCB system, presynaptic CB1Rs and GluK1-containing KRs (701).

## H. Kainate Receptor Auxiliary/Interacting Proteins; Neuropilin- and Tolloid-like Proteins

Neuropilin- and tolloid-like proteins (Neto1/Neto2) are auxiliary KR subunits capable of regulating almost every parameter of receptor function. In overexpression studies in heterologous cells, Netos regulate KR desensitization and deactivation kinetics, channel open probability, ligand affinity, and subcellular localization (225, 226, 1057, 1243). At dentate gyrus mossy fiber axons to CA3 pyramidal cell synapses, Neto1 regulates binding affinity, kinetics, and synaptic targeting of native GluK2-containing postsynaptic KRs (1056, 1094, 1224). Direct evidence for Neto2-mediated regulation of endogenous KR function remains lacking despite association with native KR complexes. Neto1 and Neto2 colocalize with GluK subunits (1/2/5) in SST-, CCK-, and PV-containing interneurons (Wyeth, Pelkey, and McBain, unpublished observation). Neto1, but not Neto2, regulates postsynaptic KR currents in all three interneuron subtypes as well as the KR-mediated recruitment of inhibitory drive onto pyramidal cells. Presynaptic GluK1-containing KRs on CCK/CB1R-containing interneurons are regulated by both Neto1 and Neto2, with Neto1 being required for presynaptic KR function and Neto2 modulating KR affinity (Wyeth, Pelkey, and McBain, unpublished observation).

### I. Delta Glutamate Receptors

The delta subfamily of glutamate receptors comprises two family members, GluD1 and GluD2. Although they share some sequence homology with other glutamate receptors, they do not bind glutamate and normally do not function as ionotropic receptors but rather serve as scaffolding proteins (1133). The GluD2 subunit is expressed predominantly in cerebellar Purkinje cells and plays an important role in long-term depression at parallel fiber-Purkinje cell synapses (595), and acts as a synaptic organizer via interactions with both pre- and postsynaptic elements (546). Although GluD2 is not thought to act as an ion channel, it does interact with the metabotropic glutamate receptor mGluR1, which can trigger currents through GluD2 (9). The role of GluD1 is poorly understood but also possesses a channel pore domain and promotes synapse formation in vitro (621). Hepp et al. (484) showed wide expression of both GluD1 and GluD2 throughout the hippocampal formation. RT-PCR from interneurons of the s.r. and s.l.m. revealed highest expression of GluD1 (representing >90% of GluD transcripts) with a much lower expression of GluD2. In ~30% of cells tested, transcripts for both GluD1 and GluD2 were detected (484). Despite this widespread distribution in interneurons, the role(s) of either subunits is completely unexplored at this time; however, global knockout of GluD1 results in mice that exhibit hyperaggresiveness and deficits in social interaction consistent with features of schizophrenic behavior (1239).

### J. Metabotropic Glutamate Receptors

mGluRs are a family of G protein-coupled receptors that are widely expressed throughout the central nervous system. The eight members of this family are grouped into three classes based on sequence homology, agonist/antagonist selectivity, and G protein coupling characteristics (for reviews, see Ref. 839). Group I mGluRs comprise mGluR1 and mGluR5, group II includes mGluR2 and mGluR3, and group III includes mGluRs 4, 6, 7, and 8. In general terms, group I mGluRs are expressed in the postsynaptic domain and signal via $G_q/G_{11}$ to activate phospholipase C, resulting in the generation of inositol 1,4,5-trisphosphate and diacylglycerol to mobilize intracellular $Ca^{2+}$ and activate PKC. Groups II and III are usually expressed in presynaptic or axonal compartments and are predominantly coupled to $G_{i/o}$ proteins, which downregulate adenylyl cyclase formation. Liberation of the Gβ/γ subunits positively or negatively modulate a number of ion channels (e.g., activation of $K^+$ channels and inhibition of $Ca^{2+}$ channels) and other downstream effector mechanisms. Of course, many exceptions exist to this general activation scheme, and it is becoming widely appreciated that many other distinct downstream pathways (e.g., JNK1, MAPK, cGMP, ERK, mTOR/p70 S6 kinase) are triggered by mGluRs in a cell type specific manner (for a more complete discussion, see Ref. 839).

**1. Group I mGluRs** Before the advent of reasonably selective ligands, activation of mGluRs was observed to directly depolarize interneurons and alter the frequency of sIPSCs and sEPSCs onto cells, suggesting complex pre- and postsynaptic roles for mGluRs in regulating interneuron excitability (270, 393, 768, 789, 869, 917). Application of the nonselective mGluR ligand trans-ACPD to CA1 s.o. SST-containing O-LM interneurons (768) and CB-positive interneurons (1156) triggered slow oscillatory inward currents (768, 1156, 1217). Somogyi and colleagues subsequently demonstrated that the mGluR1α isoform is particularly enriched in CA1 SST-containing interneurons (75, 326); however, the overlap between mGluR1α and SST

is incomplete. In addition, VIP-, CR-, and dendrite targeting CCK-containing interneurons also express mGluR1α (176, 324). Whether PV-containing interneurons express mGluR1α has been controversial (75); however, a recent study using both immunohistochemistry and quantitative immunoelectron microscopy has shown both mGluR1α and mGluR5 to be expressed on both DG and CA1/CA3 PVBCs (447). The splice variant mGluR1b is enriched in unidentified interneurons of the CA3 subfield but not CA1 (325). mGluR5 is expressed on the soma and dendrites of subsets of SST-containing interneurons and PVBCs (1156). Group I mGluRs exhibit highest expression around the perisynaptic annulus of glutamate synapses (710) and have been implicated in the generation of slow oscillatory activity and long lasting plasticity of interneurons (see sect. VI).

**2. Group II and III mGluRs** GABA release from interneuron axons is modulated by presynaptic mGluRs. Electron microscopic immunocytochemistry has revealed the expression of group III family members, mGluR4, mGluR7a, mGluR7b, and mGluR8a in the presynaptic active zone of GABAergic terminals onto hippocampal CA1 and CA3 interneurons (but not onto pyramidal cells) (592, 1004). Early studies revealed that inhibitory postsynaptic currents were strongly depressed by the group III agonist L-(+)-2-amino phosphonobutyric acid (L AP4) in unidentified CA1 s.r. interneurons (995). Kogo et al. (592) demonstrated that both low concentrations (selective for mGluR4 and mGluR8) and high concentrations (thought to activate mGluR4, 7, and 8) of L-AP4 depressed evoked IPSCs onto SST-containing O-LM interneurons to a similar degree by a presynaptic mechanism, suggesting that several group III mGluRs are involved in presynaptic depression of inhibitory transmitter release onto interneurons. The high variability of block of IPSCs observed likely indicated that different GABAergic terminals onto interneurons express different combinations of group III mGluRs.

Activation of presynaptic mGluRs reduces transmitter release by altering $Ca^{2+}$ entry into the presynaptic terminals (283, 514). Transmission at most central synapses is supported by $Ca^{2+}$ entry through either P/Q- or N-type voltage-gated $Ca^{2+}$-channels. Modulation of inhibitory transmission by group III mGluRs occurs via a reduction of $Ca^{2+}$ influx through N-type channels but not P/Q channels (969). Imaging of interneuron axonal boutons demonstrated that neighboring varicosities often showed heterogeneous sensitivity to group III mGluR activation, consistent with the target cell dependence of mGluR expression (969, 1004, 1005). mGluR-mediated depression of inhibitory transmission is accompanied by a reduction in presynaptic Pr, thus enhancing paired pulse facilitation at these synapses. Such a mechanism is likely important during patterned activity where pooled glutamate from the surrounding neuropil can activate mGluRs on GABAergic terminals to directly modulate the inhibitory tone of the network. This mechanism would depend not only on the inhibitory cell types activated but the rate and pattern of excitatory activity flowing through the network and the type of mGluR expressed on the presynaptic terminal (700).

mGluRs show exquisite targeting to distinct interneuron terminals. Ferraguti et al. (326) demonstrated that mGluR8 had a unique expression profile among all interneuron types. mGluR8-positive boutons, which also expressed VIP or mGluR7, are selectively targeted to muscarinic receptor M2-containing interneurons. In vivo recording of an mGluR8 decorated, M2-positive interneuron revealed a new trilaminar cell type with complex spike bursts during theta oscillations and firing during sharp wave ripples. The trilaminar cell had a strong projection to the subiculum as well as innervating both pyramidal cells and interneurons in the CA1 subfield.

In contrast to group III mGluRs, very little is known about the expression profile of group II mGluRs in interneurons. Poncer et al. (916) demonstrated that transmission between CA3 s.r. interneurons and pyramidal cells was reduced by the group II agonist DCG-IV. Although the interneuron cell type (s) within the s.r. cohort were not identified, the action of DCG-IV was precluded by prior application of an N-type $Ca^{2+}$-channel blocker, suggesting that they were recording transmission from CCK-containing interneurons. In contrast, inhibitory transmission from s.o. interneurons (which use P/Q $Ca^{2+}$ channels for transmission) was insensitive to DCG-IV, indicating a lack of group II mGluRs on this cell type. Little information exists regarding the localization of mGluR2/3 on interneuron axons; however, on glutamatergic axons, mGluR2 is typically expressed outside the presynaptic active zone at extrasynaptic locations (839).

Surprisingly, since this flurry of papers on mGluRs in the late 1990s/early 2000s, there have been few studies (if any) that have systematically probed pre- or postsynaptic mGluR expression on specific cohorts of well-defined interneurons in mouse reporter lines, leaving a large gap in our understanding of mGluR regulation of specific interneuron excitability and synaptic transmission.

## VI. SYNAPTIC PLASTICITY OF GLUTAMATERGIC TRANSMISSION ONTO INTERNEURONS

### A. Short-Term Pre- and Postsynaptic Mechanisms

Repetitive activation of most central synapses results in a short-term increase (facilitation) or decrease (depression) of subsequent postsynaptic events (938). The mechanisms underlying this short-term plasticity can have origins in presynaptic or postsynaptic elements or both. Short-term plasticity is an important feature of network dynamics and whether a synapse facilitates or depresses in response to repetitive activation has significant impact on information flow. At the simplest level, short-term facilitation of glutamatergic synaptic responses transiently brings the postsynaptic membrane voltage closer to threshold for action potential firing. Furthermore, synaptic facilitation will act to increase the recruitment of NMDARs by removing the voltage-dependent $Mg^{2+}$ block, expanding the temporal window of excitation as well as recruiting an essential route for $Ca^{2+}$ entry. In contrast, short-term depression acts to enforce a narrow temporal window for successive synaptic events to summate and to trigger action potential activity, thereby progressively weakening any influence that the presynaptic cell may have during repetitive activation. How these features of transmission impact circuit dynamics will be discussed in greater detail in section VIID.

Whether a synapse weakens or strengthens during repetitive activity is determined in part by the identities of both the post- and presynaptic cells. Numerous reviews have tackled the issue of target cell specificity of short-term synaptic transmission and interested readers are directed to these for a more detailed discussion (104, 636, 772, 817, 888, 1120). There is now overwhelming evidence that a single axon possesses different release properties at adjacent boutons onto differing postsynaptic targets (888). Markram et al. (749) using triple patch-clamp recordings were first to demonstrate that a presynaptic train of action potentials in a cortical layer 5 pyramidal cell simultaneously triggered short-term facilitation of transmission onto an interneuron target and depressing synaptic events onto a pyramidal cell target (FIGURE 16A). This differential mode of transmission was not simply a consequence of the postsynaptic target cell type (i.e., pyramidal cell vs. inhibitory interneuron) since a similar study demonstrated that a cortical layer 2/3 pyramidal cell presynaptic to two different inhibitory interneuron targets provided the same basic observation (FIGURE 16B). A train of action potentials in the presynaptic pyramidal cell triggered short-term facilitation onto a bitufted interneuron and depression of transmission onto a multipolar interneuron (940). That such exquisite regulation of transmitter release properties could exist in a single axon raises the question of what could be the local mechanism responsible? Whether a synapse facilitates or depresses in response to a train of stimuli is generally determined by the Pr. In general, synapses with a low initial Pr show facilitation upon repetitive activation, whereas those with high Prs typically demonstrate short-term depression (938). The type of presynaptic machinery and the interterminal $Ca^{2+}$ dynamics are largely thought to determine release at individual synapses. An elegant study by Koester and Sakmann (591) demonstrated that frequency-dependent facilitation between pyramidal cells and bitufted cells is more sensitive to presynaptic $Ca^{2+}$ buffering than is depression onto multipolar cells. This likely reflects differing diffusional distances between $Ca^{2+}$ entry sites and the release machinery or disparities between $Ca^{2+}$ channel types or densities. Indeed, a 10-fold variation in single action potential evoked $Ca^{2+}$ transients was observed across different boutons of a single layer 2/3 pyramidal neuron despite all boutons using P/Q-type $Ca^{2+}$ channels (591) (FIGURE 16C). $Ca^{2+}$ transients were larger at high Pr synapses onto multipolar cells than those observed at low Pr synapses onto bitufted cells (590). A recent study by Rowan et al. (957) demonstrated that axons of cerebellar stellate cell (SC) interneurons possess variable action potential widths at presynaptic bouton sites within the same axon branch. Localized expression of Kv3-containing voltage-gated potassium channels at individual boutons

dictate site-specific spike repolarization at each release site. Thus the clustering and variable density of channels that shape the action potential waveform endows axons with exquisite control of transmission in a bouton to bouton manner (957).

In the CA1 hippocampus, transmission between CA1 pyramidal cells and PV-containing interneurons shows marked short-term depression during repetitive activation, while the same presynaptic input to SST-containing interneurons shows facilitation. Elfn1 is expressed at pyramidal cell synapses onto SST-containing cells but not PV-containing interneurons in both the CA1 and dentate gyrus (1073, 1106). Although the mechanism is not completely understood, Elfn1 is thought to act as a retrograde signaling device to determine presynaptic Pr. Viral vector-mediated Elfn1 knock down (1073), or knockout of Elfn1 (1106) reduces the magnitude of short-term facilitation, confirming a role for Elfn1 in establishing a low Pr. However, the absence of Elfn1 does not convert pyramidal neuron-SST-containing interneuron synaptic activity to match that of pyramidal neuron-basket cell connections, which have an extremely high initial Pr and show marked paired pulse depression. Rather, loss of Elfn1 normalizes transmission across the train of stimuli, with only weak facilitation remaining (1073), suggesting that other factors must be involved in establishing the high Pr of pyramidal neuron-basket cell synapses.

Elfn1 expression increases during postnatal development and is instructive in recruiting presynaptic mGluR7-containing glutamatergic processes onto SST-containing interneurons (1106). Elfn1 directly interacts with mGluR7 and may function as an endogenous transynaptic activator of mGluR7 (1106). Indeed, loss of Elfn1 reduces the amount of presynaptic mGluR7 which leads to an increased Pr (172). However, it is unclear how mGluR7 and Elfn1 interact to modulate transmitter availability. Losonczy et al. (700) suggested that excitatory inputs onto O-LM cells are tonically modulated by persistently activated mGluR2/3/8; however, they failed to implicate mGluR7 in this process. Elfn1 may also act by engaging a GluK2-dependent KR-mediated mechanism to regulate facilitation (1073). Given the myriad proteins that are expressed in the pre- and postsynaptic elements during developmental maturation, there likely exist a large number of as yet unidentified candidates that determine the short-term dynamics of transmitter release.

An entirely postsynaptic form of short-term plasticity exists at glutamatergic synapses made onto CP-AMPARs. As described in section VA, CP-AMPARs are both $Ca^{2+}$ permeable and blocked in a voltage-dependent manner by cytoplasmic polyamines, such as spermine and spermidine (1133). This intracellular block imparts inward rectification to the current-voltage relationship, precluding current flow at more depolarized potentials. The relief of polyamine block is both use and voltage dependent, providing these synapses with a novel form of postsynaptic short-term plasticity (959, 1121). Repeated activation of the receptor during a train of activity essentially “flushes” the polyamine from the pore allowing greater current flow and a larger resulting EPSC. Block of the channel pore by polyamines is sensitive to cytoplasmic levels of ATP, which chelates polyamines, suggesting an additional mechanism to modulate postsynaptic channel availability (57, 1121). In the CA1 hippocampus, CP-AMPARs are primarily expressed at synapses onto interneurons derived from the MGE (PV-, SST-, and nNOS/NPY-containing interneurons) and largely absent from CGE-derived cells (763), suggesting that this novel form of plasticity is intimately linked to the circuit functions provided by MGE-derived interneurons.

## B. CA1 Hippocampal Interneuron LTP

Long-lasting potentiation and depression (LTP and LTD) of glutamatergic synaptic transmission onto glutamatergic principal cells has been a major focus of neuroscience research over the last 30 years (431, 487, 509). Although a number of potentially distinct, but overlapping mechanisms have been identified at synapses onto principal cells, the vast majority of these plastic changes rely on activation of the NMDAR, which acts as a coincidence detector, and the primary route of $Ca^{2+}$ entry that triggers downstream second messenger cascades to ultimately influence AMPAR trafficking (509). In contrast, studies of long-term plasticity of glutamatergic synaptic transmission onto inhibitory interneurons have been less intense and the results often less than clear in determining the underpinning mechanism(s). Although NMDAR-dependent plasticity has been observed at synapses onto interneurons (see below for further discussion), interneurons lack $Ca^{2+}$/calmodulin-dependent kinase IIa (686, 1012), which is an essential component of the NMDAR-dependent cascade that underlies LTP at glutamatergic synapses onto principal cells (682), suggesting that alternative mechanisms must exist for LTP/LTD onto interneurons. Instead, the major

"types" of interneuron plasticity center on activation of mGluRs and CP-AMPARs. Interested readers are directed to several excellent reviews that discuss the history and the nuances of this research (619, 620, 625, 802).

As discussed in section II, many distinct types of interneurons can be found in the CA1 hippocampus alone. This diversity in part has hampered a clear description of long-lasting plasticity of glutamatergic synaptic transmission onto inhibitory neurons since it now appears likely that different cell types and classes possess distinct and nonoverlapping types of plasticity. This together with the complication that few studies have rigorously identified the cell types being studied much beyond what subfield they were recorded from, as well as the differing recording techniques and conditions, has made for slow progress in our understanding of the types of plasticity observed onto identified interneuron subtypes.

Two predominant types of LTP exist at glutamatergic synapses onto CA1 interneurons. The first, an NMDAR-independent form of LTP was identified in SST-containing interneurons of the s.o. (primarily O-LM cells) and subsequently observed in PVBCs, and AACs (867, 896). High-frequency afferent stimulation or a 5-Hz stimulation coupled with postsynaptic hyperpolarization triggers an LTP that requires a postsynaptic $Ca^{2+}$ elevation, but appears to have a presynaptic expression locus coupled to increased Pr (867). This form of LTP requires cooperative interaction between group I mGluRs or M1 mAChRs by an as yet unknown mechanism (648). This LTP predominates at synapses comprising CP-AMPARs and has been termed "anti-Hebbian" (633). The "anti-Hebbian" tag is derived from the observation that CP-AMPARs act as coincidence detectors between an excitatory afferent input and synapses that are hyperpolarized or inactive (617, 618, 625). The requirement for hyperpolarization during the induction period serves to increase the driving force for $Ca^{2+}$ entry, as well as remove the use- and voltage-dependent polyamine block typical of these receptors (see sect. VIA for further discussion). One can imagine a scenario where an interneuron simultaneously receiving high-frequency excitatory input concomitant with a hyperpolarizing GABA or neuromodulatory input would trigger such an "anti-Hebbian" form of plasticity. However, it does suggest that a complex interplay of presumably multicellular events must be at play to satisfy all of the requirements for plasticity induction.

The same presynaptically expressed LTP can be triggered at these synapses by theta-burst stimulation and postsynaptic depolarization and requires activation of group I mGluRs (896). This induction paradigm triggers mGluR1 and mGluR5 activation and also requires postsynaptic $Ca^{2+}$ elevation together with Src/ERK and TRP channel activation (634, 896, 1110). The postsynaptic locus for induction and presynaptic locus for expression of this NMDAR-independent form of LTP implies retrograde signaling between the post- and presynaptic sites. At this time it is unclear what this signaling mechanism may be, but the use of nitric oxide, cannabinoid, and TRPV1 receptor antagonists has failed to implicate any of the more "conventional" retrograde messenger systems (834). So far, NMDAR-independent LTP has largely been observed at synapses between CA1 pyramidal cells and their downstream interneuron targets and does not typically occur at Schaffer collateral synapses onto interneurons residing in the s.r. (867).

An NMDA-dependent form of LTP exists at synapses onto some s.o. interneurons (869), low-threshold spiking interneurons of the somatosensory cortex (705), and at Schaffer collateral synapses onto a subset of aspiny interneurons residing in the CA1 s.r. (631). This form of LTP shares many of the features observed at Schaffer collateral synapses onto principal cells and appears to have its primary induction and expression loci within the postsynaptic compartment. However, as mentioned above, interneurons lack the $Ca^{2+}$/calmodulin-dependent kinase IIa pathway essential for LTP in principal cells (686, 1012). Indeed, CA1 s.o. interneurons in the αCaMKII T286A mutant possess normal NMDAR-dependent LTP unlike principal cells (632). Potential $Ca^{2+}$ sensors may be βCaMKII (1186), CaMKI, and CaMKIV (1026) or perhaps the $Ca^{2+}$ binding proteins PV, CB, and CR themselves (144), although evidence for this is sparse.

### C. CA1 Hippocampal Interneuron LTD

One of the first reports of long-lasting plasticity at excitatory synapses onto hippocampal interneurons came from observations that a high-frequency stimulation paradigm that typically triggers LTP at synapses onto principal cells induced LTD at synapses onto s.r. interneurons (774). This LTD was heterosynaptic, i.e., unstimulated synapses onto the same interneuron were also depressed (774). Like LTP at synapses onto interneurons, this LTD required group I mGluRs. Activation of group I mGluRs triggers arachidonic

acid formation and release of 12-(S)-HPETE by a mechanism involving 12-lipoxygenase. 12-(S)-HPETE functions as a retrograde signaling messenger, and its liberation from the postsynaptic compartment allows it to diffuse to the presynaptic site and activate the nonselective cation channel TRPV1 (395). This LTD and sensitivity to 12-(S)-HPETE are absent in TRPV1 loss-of-function mice, confirming a role for TRPV1 channels in interneuron LTD. It is worthwhile pointing out that these same interneurons that demonstrate high-frequency stimulus-induced LTD also show NMDAR-dependent LTP. However, these two mechanisms are not simply the reverse of each other and appear to share few common cellular features for induction and expression. How they interact to regulate interneuron circuit function has yet to be formally tested.

## D. CA3 Hippocampal Interneuron Plasticity

**1. CA3 pyramidal–s.r. interneuron synapses** In a manner similar to that observed at synapses onto CA1 inhibitory interneurons, high-frequency stimulation of afferents in CA3 triggers differing forms of plasticity at excitatory synapses onto CA3 inhibitory interneurons. High-frequency stimulation of CA3 afferents onto unidentified s.r. interneurons triggers an NMDAR-independent form of LTD at CP-AMPAR synapses that arises only when the postsynaptic membrane potential is hyperpolarized in a manner akin to that described as "anti-Hebbian" in CA1 (627). Induction of this plasticity requires $Ca^{2+}$ entry through postsynaptic CP-AMPARs and activation of presynaptic mGluR7 (for review, see Ref. 625). Intriguingly, with NMDARs unblocked, the same induction paradigm triggers an NMDAR-dependent form of LTP or LTD that is entirely dependent on the postsynaptic membrane potential (626). Taken together, these studies suggest a complex interplay by $Ca^{2+}$ entry via CP-AMPARs, NMDARs, and pre- and postsynaptic mGluRs to trigger either LTD or LTP all modulated by modest changes in postsynaptic membrane potential.

**2. Mossy fiber-stratum lucidum interneuron synapses** The axons of DG granule cells, the so-called mossy fibers, form somewhat unique synapses compared with others within the mammalian cortex and hippocampus. Mossy fiber boutons onto downstream principal cell targets (primarily CA3 pyramidal cells) are extremely large (~10 μm in diameter) and possess numerous well-defined presynaptic release sites with low Pr, which engulf their postsynaptic dendritic targets to form the so-called thorny excrescence synapse (7, 201). In contrast, small filopodial extensions emanate from these larger mossy fiber boutons to form either en passant or terminal synapses onto inhibitory interneurons within the hilar or CA3 subfields. These filopodial extensions are small in diameter and possess only a single high Pr release site (641, 662). High-frequency stimulation of mossy fibers triggers a presynaptic form of LTP at synapses onto CA3 pyramidal cells but triggers LTD at naive synapses onto s.l. interneurons (722, 889). At CI-AMPARs, this LTD is NMDAR dependent and possesses a postsynaptic locus of induction and expression that relies on NSF/AP2-dependent AMPAR internalization (662). At CP-AMPAR synapses, the same induction protocol triggers presynaptic NMDAR-independent LTD (662). Like the many forms of interneuron plasticity described above, mGluRs are key regulators of this form of plasticity. mGluR7b, which is highly enriched at mossy fiber synapses onto s.l. interneurons (but not CA3 pyramidal cells), functions as a metaplastic switch controlling bidirectional plasticity. Glutamate liberated by the induction paradigm triggers activation of presynaptic mGluR7b, which reduces presynaptic $Ca^{2+}$ entry through P/Q $Ca^{2+}$ channels by a mechanism involving PKC (887, 890; for reviews, see Ref. 772), resulting in LTD. As a consequence of binding glutamate, mGluR7b is rapidly internalized, and subsequent rounds of the induction protocol now induce a presynaptic form of LTP via a cAMP-dependent mechanism identical to that observed at mossy fiber principal cell synapses (891). Thus the presence or absence of mGluR7b at these synapses acts as a bidirectional switch that dictates the direction of plasticity at these synapses by governing whether a PKC- or cAMP-mediated LTD or LTP is triggered, respectively.

**3. Mossy fiber-stratum lacunosum moleculare interneuron synapses** At mossy fiber synapses onto CA3 s.l.m interneurons, high-frequency stimulation induces a bidirectional form of NMDAR-independent plasticity. Stimulation of afferents onto CI-AMPAR synapses triggers an LTD, which relies on postsynaptic mGluR1 activation and requires an $IP_3$-mediated elevation of intracellular $Ca^{2+}$, or entry through L-type $Ca^{2+}$ channels and PKA and PKC activation. When postsynaptic mGluR1s are blocked, the same induction paradigm now triggers LTD, which requires $Ca^{2+}$ entry through L-type $Ca^{2+}$ channels (377, 378).

In CA3 s.r. and s.l.m. interneurons that receive both CA3 pyramidal cell recurrent collateral and mossy fiber inputs, there appears to be a compartmentalization of synaptic plasticity (379). NMDAR-dependent plasticity at s.r. inputs on CI-AMPAR synapses requires postsynaptic $Ca^{2+}$ elevation and activation of $Ca^{2+}$/calmodulin-dependent protein kinase II and PKC. While mossy fiber LTP onto the same cells also requires PKC formation, this LTP is independent of CaMKII activation instead of relying upon a cAMP PKA signaling cascade.

**4. Mossy fiber-dentate gyrus basket cell synapses** To complicate matters even further, mossy fiber inputs onto CP-AMPAR containing synapses on DG PVBCs express an NMDAR-independent form of LTP in response to high-frequency stimulation (23). LTP induction requires a postsynaptic elevation in $Ca^{2+}$ and PKC activation but is expressed presynaptically. Pharmacological block of either perisynaptic mGluR1 or mGluR5 prevents this Hebbian form of LTP; however, exogenous application of either mGluR1 or mGluR5 agonists alone is insufficient to induce LTP, suggesting that convergent activity via CP-AMPARs and mGluRs are required for its induction (447).

Like many interneurons, PVBCs receive afferent inputs from converging sources. In the DG, PVBCs receive feedforward excitation via entorhinal cortex perforant pathway inputs and feedback excitation from mossy fiber afferents. Repeated coactivation of the two inputs triggers associative LTP at mossy fiber synapses, which requires $Ca^{2+}$ entry via CP-AMPARs (972). In contrast, perforant pathway synapses made onto CI-AMPARs do not show associative LTP. Sambandan et al. (972) suggest that this associative form of plasticity is an essential mechanism that acts to adjust inhibition to maintain sparse cell activation and an acceptable signal-noise level in the circuit.

It is worthwhile pointing out that although LTP and LTD undoubtedly exist at glutamatergic synapses onto interneurons, they are not universally observed in all interneuron types. Indeed, progress has been extremely slow in defining clear rules for interneuron plasticity, since synapses onto many interneuron types lack any clear form of plasticity and simply follow the “passive propagation” of plasticity induced at excitatory synapses onto principal cells, which acts to increase their afferent output into the hippocampal network (619, 720, 771). This together with the differing recording techniques used and the ease with which whole cell recordings flush essential components out of the postsynaptic compartment have made the study of interneuron plasticity difficult. In the future it will be essential to revisit many of these earlier studies and determine the true identity of each cell type to determine whether logical rules exist at particular cell types. For example, consideration of the literature suggests an intriguing possibility about the rules underlying which cells will express which type of plasticity in the CA1 hippocampus. Kullmann and Lamsa (619) recognized that the cells in which NMDAR-dependent LTP was most readily observed tended to possess the largest NMDAR-mediated conductances. In addition, presynaptically expressed NMDAR-independent “anti-Hebbian” LTP requires either mGluR or mACh receptor activation and occurs primarily at synapses comprised of CP-AMPARs. Of interest, these two forms of LTP appear to largely correlate with cellular origins in either the MGE or CGE. As described in section V, Matta et al. (763) observed that MGE-derived CA1 interneurons exclusively express CP-AMPARs at Schaffer collateral synapses, and this subset comprises PV-, SOM-, and NPY-containing interneurons, all of which express “anti-Hebbian” NMDAR-independent LTP. Cells derived from the CGE typically possess large synaptic NMDAR conductances through GluN2B-containing NMDARs. In hippocampus, CGE-derived interneurons comprise both CCK- and VIP-containing interneurons and largely reside in the CA1 s.r. (763), consistent with those cells that express the NMDAR-dependent LTP. This differential expression of LTP between MGE- versus CGE-derived interneurons has not been rigorously determined, but given the known synaptic properties of these cells, it seems extremely likely that developmental origin will determine which type of LTP an interneuron expresses.

## VII. GABA RECEPTORS

Since the discovery of the γ-aminobutyric acid (GABA) in the central nervous system over 60 years ago, its role as a major inhibitory neurotransmitter has been well established. GABA exerts its cellular actions predominantly via the ionotropic $GABA_A$ receptors ($GABA_A$Rs) and metabotropic $GABA_B$Rs (863). The vast majority of studies have focused on the functional properties and physiological roles of GABAR signaling on principal excitatory cells. However, it is evident that interneurons also impinge on each other

providing inhibitory control of inhibition itself (186). As highlighted previously, the CA1 hippocampus contains many different subtypes of interneurons that together serve as activity dependent sources of GABA. Therefore, the possible interactions between pre- and post-synaptic interneuron partners are potentially vast and like the delineation of their subtypes, providing a complete description of all these interactions is by no means a trivial endeavor. Here, we will briefly summarize the current state of knowledge regarding the known connectivity between interneurons, particularly in the hippocampus, as evidenced by GABAR mediated responses on the varied subtypes (FIGURE 17). In this section we will highlight the functional properties of GABAergic inhibitory transmission between interneurons and describe some of the physiological roles attributed to the resulting disinhibition produced by such interactions within neural circuits.

$GABA_A$Rs belong to the cys-loop family and are pentameric hetero-oligomers that assemble to form anion selective channels and predominantly flux chloride. To date 19 individual mammalian genes encoding homologous $GABA_A$R subunits have been identified consisting of α1–α6, β1– β3, γ1-γ3, ε, δ, θ, π, ρ1−3 (for review see (1011). $GABA_A$Rs in the brain, including the hippocampus, are pentameric and generally consist of two α subunits, two β subunits and either a γ or δ subunit (828, 1011). As will be outlined, the inclusion of certain subunits can influence the cellular localization and fine-tune numerous biophysical and pharmacological properties of the $GABA_A$R complex thus shaping the physiological nature of inhibition.

## A. $GABA_A$R-Mediated Inhibition Between Interneurons

**1. Interneuron targets of PV-expressing cells** PV-expressing interneurons in CA1 and DG innervate each other as evidenced by the identification of synaptic boutons originating from this subtype at symmetric synapses, indicative of an inhibitory phenotype, along the somatodendritic axis of postsynaptic PV labeled interneurons (8, 440). This mutual connectivity occurs in various cortical regions (374, 455, 906) and appears to be a generalized circuit phenomenon. In hippocampus, PVBCs provide $GABA_A$R inhibition onto each other (65, 211, 258, 594, 980, 1257), whereas there is no such connectivity between their AAC counterparts (594). $GABA_A$R responses can be observed between PVBCs and AACs but due to their lack of connectivity never in the reverse direction (594). Thus, within the various PV-expressing populations of interneurons, specific connectivity rules exist.

The α1 subunit is prevalent in all subfields and lamina of the hippocampus (382) and is the most common $GABA_A$R subunit. Some of the highest expression levels are encountered in PVBCs, AACs, and BiC populations (74, 382, 692, 788), and this subunit is particularly enriched at PV-PV interneuron synapses (585). The α1 subunit influences the activation and deactivation kinetics of $GABA_A$R-mediated responses, and the unitary $GABA_A$R IPSCs between mature PVBCs posseses fast decay kinetics (65, 258). The expression of α1 increases during postnatal development of PV interneurons and is accompanied by speeding of the decay of $GABA_A$R IPSCs (277). Furthermore, in α1 knockout mice, $GABA_A$R IPSCs onto CA1 interneurons possess significantly slower decay times that in part maybe due to "compensatory" increases in α2 and α3 subunit expression in numerous interneurons including PV subtypes that normally express little or no α2 and α3 (421, 990).

Benzodiazepines (BZs) are positive allosteric modulators of $GABA_A$R function (i.e., require the presence of GABA to exert their actions) and their binding site is located between the α (either 1, 2, 3, or 5 isoforms) and γ subunits (for review, see Ref. 1010). Zolpidem, a non-BZ, also binds to the BZ site to act as a positive allosteric modulator of $GABA_A$R function. However, it has higher affinity for receptors containing the α1 subunit than those with α2, α3, or α5 subunits. Thus, at low nanomolar concentrations, the actions of zolpidem are selective for α1-containing $GABA_A$Rs, and this agent has served as an experimental tool to probe for expression of this subunit. Indeed, the effect of low nanomolar concentrations of zolpidem on $GABA_A$R-mediated responses onto interneurons is abolished or largely reduced following genetic ablation of α1 subunits or mutation of the histidine residue [replaced by arginine, a1 (H101R)] in this subunit that is critical for binding of zolpidem (54, 421). In agreement with immunohistochemical studies demonstrating enriched α1 subunit expression in PV interneurons (382, 692, 788), zolpidem potentiates $GABA_A$R-mediated responses between members of this subtype (277, 972).

The fast uIPSC kinetics of α1-containing $GABA_AR$-mediated responses results in precise temporal inhibition between PVBCs similar to that imposed by PVBCs onto principal cells (64). PVBCs are fast signaling devices that enable large ensembles of PCs to be precisely temporally coordinated, thus generating network activity patterns (see sect. XV). Under certain modeling conditions, networks of PV interneurons are sufficient to drive oscillations (66, 1190), and the propensity to do so is particularly sensitive to the strength and prevalence of their inhibitory interconnectivity (323). Additionally, altering the kinetics of the $GABA_AR$-mediated conductance onto PVBCs in this computational network influences the coherence and frequency of the resultant oscillatory behavior (66, 67). Empirically, conditional genetic deletion of the γ2 subunit in PV-expressing interneurons results in loss of fast α1-containing synaptic $GABA_AR$-mediated IPSCs and disrupts the coupling of theta and gamma oscillations in the CA1 hippocampus (1222), resulting in deficits of hippocampal-dependent spatial memory tasks (667). Thus fast α1γ2-containing $GABA_AR$-mediated inhibitory input onto PV interneurons is critical for the generation and characteristics of coordinated network activity that underlie varying cognitive processes.

Anatomically defined inhibitory synaptic inputs originating from PV cells have also been observed targeting other interneuron subtypes such as CCK interneurons (8, 554). In DG, PVBCs mediate $GABA_AR$ responses onto CCK HICAP cells (980), but functional evidence of an analogous connection in CA1 is yet to be described. Interestingly, a subpopulation of entorhinal cortical interneurons, some of which express PV, send long-range inhibitory projections into the hippocampus and elicit $GABA_AR$-mediated responses onto various hippocampal interneurons (69, 781). Conditional expression of channel rhodopsin has revealed that PV-long range mediated inhibition of CCK-expressing interneurons provides a temporally defined gating of Schaffer-collateral excitatory input onto CA1 PCs, rendering them permissive for the expression of synaptic plasticity underlying various learning behaviors (69). Additionally, the prevalence and role of local interactions between PV-expressing interneurons in CA1, a subpopulation of which are perisomatic targeting, have also been examined with conditional optogenetic approaches. Functional $GABA_AR$-mediated inhibitory inputs are observed onto BiCs and O-LM interneurons with a higher synaptic strength onto the former (703). Inhibiting PV interneuron activity increases the firing rate of BiCs, resulting in a switch from perisomatic to dendritic inhibition of CA1 PCs (703). Thus such interneuron interactions result in dynamic shifts between distinct modes of inhibition impinging on PCs impacting the processing of CA3 Schaffer-collateral inputs.

**2. Interneuron targets of CCK-expressing cells** $GABA_AR$-mediated inhibitory transmission between homologous pairs of CCKBCs (258, 594), CCK SCAs (19, 21), and CCK HICAPs (980) have all been identified. Thus, as observed for PV subtypes, homotypic interactions between CCK-expressing interneurons are also prevalent within the hippocampus. In contrast to the temporally precise PV interneuron inhibition, CCK interneurons produce marked asynchronous $GABA_AR$-mediated responses onto connected principal cells due to a relatively weak coupling between N-type calcium channels and the GABA release machinery in their presynaptic terminals (21, 64, 477). Interestingly, this mode of release is also evident at CCK-CCK synapses including those between CCKBCs resulting in a more temporally variable, prolonged inhibition compared with that seen at PV-PV synapses (258). In CA1 and dentate gyrus, axonal boutons originating from CCK interneurons are closely apposed to somatic, dendritic, and axonal compartments of PV interneurons (8, 554). Indeed, $GABA_AR$-mediated IPSCs can be elicited on PV cells by CCK interneuron activity in both these regions (506, 980, 1257) and possess the archetypal asynchronicity (506). Disruption of CCK interneuron firing results in decreased inhibitory drive onto these postsynaptic targets altering the temporal characteristics of PV interneuron firing (506). It is hypothesized that this interaction desynchronizes pyramidal cell output to manifest as a deficit in gamma oscillations (506).

**3. Interneuron targets of SST-expressing cells** Unlike the prevalent homotypic interactions of PV and CCK interneurons within the CA1, it remains unclear whether SST-expressing subtypes are mutually connected. However, in dentate gyrus, the O-LM equivalent, SST-expressing HIPP interneurons impart $GABA_AR$ inhibition onto each another, albeit with a lower connectivity rate when compared with other homotypic interactions between CCK HICAP-CCK HICAP and PVBC-PVBC pairs that occur in this region (980). However, SST, O-LM, and HIPP subtypes anatomically contact other interneurons such as PV, CCK, and CR expressing subtypes (557). Paired electrophysiological recordings of presynaptic

identified O-LM interneurons reveal action potential-dependent $GABA_A$R-mediated responses on various interneuron subtypes including CCKBCs, SCAs, PPAs, and NGFCs (299). This relatively widespread inhibitory influence of SST interneurons has also been described in cortical circuits (906). Manipulations of SST interneuron activity can modulate the rate and precision of PVBC firing (980), likely influencing information flow through the dentate gyrus. Furthermore, the disinhibition of CA1 NGFCs by O-LM interneurons modulates the balance between feed-forward and feedback inhibition of the distal dendrites of PCs (299), revealing a role for interneuron connectivity in gating modes of inhibition onto PCs.

**4. Interneuron targets of NGFCs** Electrophysiological recordings from pairs of NGFCs demonstrate a marked functional connectivity with each other (48, 550, 926, 1074). Like PV-expressing interneurons, NGFCs express high levels of α1 subunit, and unsurprisingly, the $GABA_A$R-mediated responses impinging on this subtype are sensitive to low nanomolar concentrations of zolpidem (367, 550). However, in contrast to the fast synaptic inhibitory responses that occur on PV cells, inhibition between NGFCs results in $GABA_A$R-mediated IPSCs with decay times an order of magnitude larger that have been termed $GABA_{A,slow}$ (48, 167, 870, 1086). These remarkably slow kinetics are not fully attributable to dendritic filtering, asynchronous release, spillover, nor the properties of the $GABA_A$Rs themselves (however, see Refs. 483, 1264) but are primarily due to the spatiotemporal profile of GABA release from this interneuron subtype (see sect. IVL) (167, 550, 870, 1074). In CA1, NGFCs and their related IvCs (366) are the most abundant subgroup (102) of interneurons and are distributed in the s.l.m., s.r., and s.p. layers (see sect. IIG). Together, their cumulative prodigious axonal arbors cover large regions of the hippocampal real estate. To what extent NGFCs/IvCs communicate with other specific interneuron subtypes requires further investigation, although in CA1 and dentate gyrus they have been shown to mediate $GABA_{A,slow}$ on unidentified s.l.m. and molecular layer interneurons, respectively (48, 926). Modeling of networks consisting of interconnected interneurons mediating $GABA_{A,slow}$ and $GABA_{A,fast}$ is sufficient to produce theta and gamma rhythms, thus implicating NGFC cross-talk to other interneuron subtypes in such network phenomenon (1199). Furthermore, the role of $GABA_{A,slow}$ in the generation of network oscillations has been described (167, 483), but the relative contributions of NGFC-mediated $GABA_{A,slow}$ onto principal cells versus that onto other interneurons in mediating these phenomenon has not been directly or individually assessed.

**5. Interneuron specific cells** One of the most compelling observations illustrating the potential importance of inhibitory control of interneurons lies in the existence of a defined subpopulation of so-called ISI cells. As the name suggests, ISI cells display a remarkable selectivity of their postsynaptic partners primarily targeting other interneurons whilst typically avoiding principal cells. In the CA1, ISI cells can be further subdivided based on anatomical location and immunocytochemical marker profile (see sect. IIH). ISI-3 interneurons express VIP and CR, and recently, the postsynaptic partners of ISI-3 interneurons have been identified at a functional level. Employing transgenic reporter mice and conditional optogenetic expression strategies, ISI-3 cells located in s.p. and s.r. possess a relatively high connectivity to O-LM interneurons (185, 1145) whilst providing no input onto principal cells (1145). This interaction paces O-LM interneuron output, modulating their firing rate and timing with implications for dendritic electrogenesis, burst firing in PCs, and the generation of oscillatory activity (703, 1145). The targeting of SST interneurons by VIP cells appears to be a generalized motif across brain structures including somatosensory, visual, and auditory cortices, and this specific disinhibitory microcircuit is important in sensory processing that, in some circumstances, demonstrates behavioral state dependence (363, 553, 660, 905, 906, 908, 1246, 1270). In addition to entorhinal cortical long-range inhibitory projections described earlier, a population of GABAergic medial septal neurons specifically innervate hippocampal interneurons via long-range projections providing regulation of theta frequency synchronization (351, 438, 1118). This additional dialogue provides an alternative long-range mode of disinhibition to that locally imparted by ISI-3 cells which together modulate the function of O-LM cells (185).

### B. Extrasynaptic Tonic Inhibition of Hippocampal Interneurons

Although $GABA_A$Rs are prevalent at synaptic sites, a significant population exists at peri- and extrasynaptic locations. The subunit composition dictates the trafficking of the receptor complex, and generally speaking, $GABA_A$Rs containing α1–3 and γ subunits versus those comprised of α4–6 and δ

subunits are predominantly located at synaptic and extrasynaptic locations, respectively (81, 317, 410). The α5 and δ subunits containing extrasynaptic $GABA_A$Rs possess a much higher affinity and minimal desensitization to GABA than synaptic receptors. Thus, as opposed to fast phasic inhibition mediated by relatively large GABA transients at synaptic $GABA_A$Rs, ambient low concentrations of GABA can persistently activate this extrasynaptic population of receptors permitting the presence of an ongoing inhibitory tone. GABA found in the extracellular space can be derived from a number of nonvesicular mechanisms including astrocytic release and reversal of GABA transporters. It has also been suggested that vesicular release during trains of action potential discharges provide an appreciable source of GABA resulting in tonic inhibition via $GABA_A$Rs (411).

Extrasynaptic $GABA_A$R subunits are highly expressed in dentate granule cells and in hippocampal interneurons (893). However, with respect to the latter, subtype specificity of expression is apparent. The δ subunit is particularly abundant in PV interneurons (320, 788, 1256) and NGFCs (316, 858) with little or no detectable levels observed in SST-, CB-, or CR-expressing subtypes (788). The extent to which a given neuron is influenced by tonic inhibition can be experimentally assayed by monitoring changes in membrane potential (or holding current required to maintain a specific membrane potential) upon application of $GABA_A$R antagonists such as bicuculline, gabazine, or picrotoxin (660). Additionally, 4,5,6,7-tetrahydroisoxazolo[5,4-c]pyridin-3-ol (THIP) possesses an extremely high efficacy for δ-containing $GABA_A$Rs that is much greater than that of GABA itself. This “superagonist” serves as a useful experimental tool to test for the presence of tonic inhibition. This distinct inhibition mode has been described in interneurons with soma located in the m.l. of DG and CA1 s.r. (409, 659, 1038, 1256). In agreement with the selective expression of δ subunits in certain hippocampal interneuron subtypes, THIP-mediated currents are present in dentate gyrus PV-containing but not other DG interneurons including HIPP and other SST-containing interneuron populations (1109, 1160, 1256). As expected, ablation of the δ subunit reduces THIP-mediated currents in interneuron populations, including PV subtypes (739). Ectopic expression of the δ-subunit in SST HIPP cells results in the presence of $GABA_A$Rs containing this subunit at nonsynaptic locations, including perisynaptic sites near symmetric synapses and an emergence of THIP sensitivity (1109).

Tonic inhibition controls neuronal excitability and hence action potential output in pyramidal and dentate granule cells (317, 660, 996). The role of tonic inhibition of interneurons has been experimentally determined by conditional ablation of the δ subunit. In DG, removal of this subunit increases inhibitory input onto granule cells and reduces the susceptibility to kainate-induced seizures (659). Conversely, increasing tonic inhibition in hilar SST cells via ectopic expression of α6 and δ subunits reduces experimentally induced bursting of IPSCs impinging on granule cells (1109). Conditional δ ablation specifically from PV-expressing interneurons increases the frequency of γ oscillatory activity in the CA3, illustrating a negative modulation of such oscillatory activity by tonic inhibition (320, 739). Therefore, changes in tonic inhibition of interneurons can regulate excitability and oscillatory behavior throughout the hippocampal circuit. The cellular effect of tonic inhibition is likely more complex than to simply provide a dampening of interneuron activity resulting in disinhibition of downstream principal cells. For example, in unidentified CA1 interneurons of the s.r., tonic inhibition is biphasic resulting in an increase or decrease in action potential output due to depolarizing and shunting responses, respectively, that are in turn dependent on the conductance level of tonic inhibition (1038). Whether this is a generalized phenomenon found in all interneurons that are susceptible to tonic inhibition remains to be determined.

The most potent endogenous modulators of $GABA_A$Rs are the neurosteroids allopregnanolone (ALLO) and tetrahydrodeoxycorticosterone (THDOC). Although the binding site is located between α and β subunits (498), it is the δ subunit that generally dictates sensitivity to these neurosteroids (629). Thus THDOC-mediated effects are seen in interneuron subtypes expressing δ such as NGFCs and PV interneurons (316, 320, 788, 858, 1256) with little or no effect in SST cells that are devoid of this subunit (1160). Interestingly, expression of the δ subunit itself can be altered in part due to changes in the levels of circulating neurosteroids that occur during stress, puberty, menstrual cycle, and pregnancy (726, 732, 733, 807). In particular, plasticity of δ subunits on PV-expressing interneurons is linked to alterations of γ oscillatory activity that may explain memory and cognitive dysfunctions known to occur during estrus and pregnancy (320, 321).

### C. $GABA_B$ Receptor-Mediated Inhibition

In contrast to the ligand-gated $GABA_A$ receptors, $GABA_B$Rs are heterodimers of seven transmembrane G protein ($G_i/G_o$)-linked proteins that are comprised of a $GABA_B$1 (either $GABA_B$1a or $GABA_B$1b) and a $GABA_B$2 subunit. Activation of postsynaptic $GABA_B$Rs and subsequent direct G protein interaction with GIRK (Kir3) channels predominantly results in membrane hyperpolarization inhibiting neural excitability. Immunoreactivity for $GABA_B$Rs demonstrates a relatively ubiquitous distribution on somatodendritic compartments of varying interneuron subtypes including SST-, NPY-, CCK-, CR-, and CB-expressing subtypes, although differences in relative expression levels are apparent (115, 116, 345, 616, 691, 926, 1024). PVBCs of the dentate gyrus, but not their dendrite-targeting counterparts, express functional postsynaptic $GABA_B$Rs (116) (FIGURE 18). Computational modeling predicts the possible importance of this signaling in modulating the temporal nature of output in the former subtype (116), perhaps explaining the differing firing patterns observed between PVBCs and dendritic targeting interneurons during network oscillations. Particularly high levels of $GABA_B$Rs are found on somatodendritic regions of CCK cells (115, 1024). However, the relative size of $GABA_B$R-mediated currents among the various CCK subtypes significantly differ with larger responses noted in CCKBCs compared with those observed in SCAs or PPAs (FIGURE 18) (115). Thus, as with PV cells, postsynaptic $GABA_B$R-mediated signaling preferentially occurs in perisomatic versus dendritic targeting CCK subtypes (FIGURE 18).

In general, postsynaptic $GABA_B$R activation occurs via spillover of GABA from the synapse that in experimental paradigms requires either strong electrical stimulation/trains of stimuli resulting in GABA release from multiple neurons to overcome GABA uptake mechanisms or stimulation under conditions where GABA uptake is pharmacologically blocked (427, 523, 982). $GABA_B$R postsynaptic potentials/currents have been identified in numerous interneuron subtypes (115, 116, 137, 578, 622, 811). Not all interneuron subtypes exhibit postsynaptic $GABA_B$R responses, and a division of labor between subtypes in providing putative $GABA_A$R- or $GABA_B$R-mediated IPSPs (628, 993) indicates the presence of selective microcircuits responsible for activation of postsynaptic $GABA_B$Rs. Thus it is unclear whether the functional connectivity rules as defined by $GABA_A$R signaling outlined above also apply to interactions between interneurons that are mediated via $GABA_B$R signaling (844).

Activation of presynaptic $GABA_B$Rs on various interneurons results in negative modulation of transmission of varying degrees due to activation of GIRK channels and/or inhibition of voltage-gated calcium channels coupled to vesicular release. Such modulatory mechanisms occur on various interneuron subtypes resulting in decreased GABA output at synapses onto both excitatory and inhibitory neurons (116, 478, 916), the former providing another synaptic route for disinhibition. Intriguingly, NMDAR-dependent LTP of excitatory inputs onto CA1 pyramidal cells and dentate gyrus granule cells is sensitive to a concomitant presynaptic $GABA_B$R-mediated decrease of GABA release resulting in disinhibition of pyramidal cells and enhanced NMDAR activation (255, 810, 939). Although the interneuron subtype(s) involved remains to be determined, these data confirm a potential role for disinhibition in gating synaptic plasticity, albeit via a distinct mechanism from that described previously. On the other hand, this form of disinhibition can result in hyperexcitability of principal cells (345, 808, 809) and may play a part in pathological discharges akin to those seen in epilepsy. Again, the interneuron subtype(s) involved remains a mystery, but recently CCK-expressing interneurons have been implicated in this proconvulsant phenomenon at least in CA3 (290). Thus short-term dynamic and more persistent changes in presynaptic $GABA_B$R-mediated inhibition of GABA release are implicated in both physiological and pathophysiological scenarios.

NGFCs, by virtue of their ability to elicit volume transmission (see sect. IVL3), are a major source of GABA that culminates in $GABA_B$R activation. Therefore, this interneuron subtype may play a significant role in some of the disinhibitory mechanisms involving this receptor. It is evident that NGFCs mediate postsynaptic $GABA_B$R-mediated responses on other NGFCs and principal cells even after a single action potential (48, 927, 1086). As mentioned, dentate gyrus NGFCs impart $GABA_{A,slow}$ responses on molecular layer interneurons (48), but whether these same interactions result in additional postsynaptic $GABA_B$R responses was not tested. Volume transmission by NGFCs also results in presynaptic $GABA_B$R activation on axon terminals of both PCs and other interneurons in a paracrine manner to modulate

neurotransmitter release in cortical circuits (204, 858). More recently, ongoing activity of SST interneurons in the somatosensory cortex was shown to mediate depression of glutamate release from pyramidal cells via presynaptic $GABA_BR$ activation (1154). However, whether similar modulatory mechanisms exist in the hippocampus is unclear.

The rich tapestry of interconnectivity mediated by GABAR signaling between diverse interneuron subtypes, including both local and long range, provide additional arrays of layered microcircuits. Although this intercommunication has the potential to be widespread, it is clear that specific connectivity rules exist serving discrete network functions. As is the case for principal cells, varied inhibitory modalities coexist even onto a single interneuron subtype. This is dependent not only on the identity of the presynaptic interneuron but also on the functional properties of postsynaptic GABARs, with the latter being dictated by subtype (i.e., $GABA_A$ vs. $GABA_B$), cellular location (i.e., synaptic vs. extrasynaptic; pre- vs. postsynaptic), and subunit composition. Dynamic modulation of such interactions serves to gate the mode and timing of inhibition impinging on principal cells, hence sculpting their input/output relationships central for synaptic plasticity induction/expression and generation of network oscillations.

### D. Circuit Dynamics of Dendritic Versus Perisomatic Inhibition

As described in section II, local circuit interneuron axons possess considerable diversity in the targeting of their downstream postsynaptic domains (352, 582, 1036) (FIGURE 1). At one end of this continuum are two subsets of PV-containing perisomatic targeting interneurons. PVBCs innervate the soma and first 20–30 μm of the proximal dendrites of principal cells, and AACs target the pyramidal neuron axon initial segment (FIGURE 2). In contrast, SST-containing hippocampal O-LM cells or cortical Martinotti cells send their largely unbranching axons across several subfields to target the most distal dendritic portions of pyramidal cells (FIGURE 3). The target-specific diversity of local circuit interneurons ensures that virtually every compartment of the dendrites-soma and axon initial segment are selectively targeted. But to what end? Transmission onto perisomatic versus dendritic targets provides fundamentally different forms of inhibitory synaptic control. Perisomatic inhibition efficiently controls $Na^+$-dependent action potential generation, whereas dendritic inhibition influences local voltage-gated conductances, shunts excitatory inputs lying distal to their location, and regulates the generation of $Ca^{2+}$-dependent action potentials and synaptic plasticity (522, 790, 721).

While principal neurons of the hippocampus and cortex are highly enriched for both inhibitory and excitatory synaptic inputs, these inputs are not distributed evenly across cells. The vast majority of excitatory synapses onto pyramidal cells are made onto spines located on the mid proximal to distal dendritic portions of the cell. In contrast, as stated above, inhibitory inputs are made onto almost all portions of the dendritic tree as well as the perisomatic regions including the axon initial segment. This synaptic arrangement undoubtedly has consequences for the functional control of principal cell outputs. Pouille et al. (924) combined optogenetics and dynamic patch-clamp techniques to explore the consequences of distal dendritic versus proximal GABAergic inputs on excitatory synaptic integration and action potential firing in hippocampal and cortical pyramidal cells. Of interest, they observed that when inhibition and excitation arrived at the same dendritic compartment, inhibition caused a rightward shift in the firing rate function related to excitatory conductance (FIGURE 19). In other words, the postsynaptic cell could still achieve the same maximal firing rate, albeit in response to a greater excitatory conductance input. When inhibition was placed at locations proximal to the excitatory conductance, the firing rate of the cell is again reduced; however, proximal inhibition alters the electrotonic properties (i.e., shunting) of the path between the excitatory conductance input and the axon initial segment output to both increase threshold and decrease the maximal firing rate for a given excitatory conductance input. This rather elegant example serves to illustrate the different functional impact inhibitory input location can have on principal cell output (924).

This anatomic arrangement of dendritic and perisomatic inhibition, together with the particular cell intrinsic properties (i.e., the complement of voltage-gated conductances), action potential dynamics, neurotransmitter release properties, and short-term plasticity of both excitatory and inhibitory transmission provides the anatomic and functional basis for almost all feedforward and feedback inhibitory control of cortical networks (FIGURE 20). In the CA1 hippocampus, excitatory afferents (of both intrahippocampal and subcortical origins) target both excitatory and inhibitory neurons. In general, excitatory afferent inputs

onto interneurons are stronger than the equivalent inputs onto principal cells (522). This arrangement ensures that any input that activates monosynaptic excitatory input onto principal cells will almost always trigger disynaptic inhibitory input to generate feedforward inhibition of the principal cells (FIGURE 20). In most circuits the short latency of feedforward inhibition enforces a narrow temporal window for action potential firing in principal cells (922). In a series of experiments combining somatic and dendritic recordings from hippocampal CA1 pyramidal cells, Pouille and Scanziani (922) elegantly demonstrated that the bulk of feedforward inhibitory inputs arise through perisomatic fast spiking basket cells and that inhibition onto dendritic compartments was modest by comparison. This differential inhibitory input provides two integration windows for EPSP summation with a broader integration window existing for EPSPs arriving at dendritic sites. In fact, this is a motif shared across many cortical and hippocampal circuits (257, 372, 403, 404, 922). Recently, Basu et al. (68) challenged the narrow hypothesis that PVBCs are the main providers of feedforward inhibition and demonstrated that CCK-containing interneurons can also play a prominent role in providing feedforward inhibition driven by perforant path and Schaffer collateral inputs to CA1 pyramidal cells (see also Ref. 1165). Given the surprising number of interneurons whose cell bodies and dendrites occupy space in the CA1 s.r. and can therefore be targeted by both intra- and extrahippocampal afferents, it is highly likely that many interneuron subtypes contribute in discrete ways to enforce different aspects of feedforward inhibitory control over both principal and interneuron targets.

In most cortical networks, the dynamic between excitatory and inhibitory inputs is strongly modulated by the short-term plasticity properties of the respective components, such that progressive changes in the excitation:inhibition ratio results in a progressive degradation of the excitation and inhibition balance (372, 404). For example, in somatosensory cortex, although both EPSCs and feedforward IPSCs depress in response to repetitive stimulation, the magnitude of the depression is greater for inhibition than excitation resulting in an increased action potential jitter and a loss of temporal precision (372). In contrast in CA3 circuits, mossy fiber synapses onto CA3 pyramidal cells provide a strong monosynaptic drive that demonstrates unusually strong facilitation in response to repetitive stimulation (538, 641). Mossy fiber-driven feedforward inhibition facilitates to maintain a fixed excitatory:inhibitory balance during trains of activity. Of interest, in contrast to other cortical circuits, erosion of this feedforward inhibitory input does not lead to a loss of temporal precision of action potential generation in CA3 pyramidal cells, but can trigger a prolonged plateau depolarization following action potential firing (1114). This suggests that temporal precision in the mossy fiber-CA3 circuit is primarily determined by the rapid kinetics of the excitatory input itself and that feedforward inhibition serves largely to prevent excessive depolarization triggered by this large and rapid excitatory conductance (1114).

The output of principal cells is similarly differentially influenced by distinct inhibitory interneuron subpopulations via feedback inhibitory control of spiking activity. The output features of principal cells, i.e., spike frequency and timing, are critical for correct cortical functioning and are regulated by recurrent excitatory drive onto interneurons that then target the very same principal cell populations. Pouille and Scanziani (923) provided the first demonstration that recurrent inhibition onto CA1 pyramidal cells occurs via a dynamic rerouting of inhibitory drive that commences via perisomatic inhibitory input followed by a delayed primarily dendritic inhibition. This circuit arrangement is predicated on several pre- and postsynaptic features of the small circuit loop: excitatory synaptic kinetics, properties of short-term plasticity of excitation onto different interneurons, intrinsic properties of interneurons, and the temporal dynamics of disynaptic inhibition. Trains of action potentials from CA1 pyramidal cells drive excitation onto two populations of interneurons termed “onset transient” and “late persistent” interneurons (923). Synaptic events with rapid kinetics exhibiting short-term depression in response to trains of action potentials drive the early-onset transient form of perisomatic inhibition, presumably primarily via PV-containing interneurons back onto CA1 pyramidal cells. The rapid depression of excitatory drive onto this interneuron population ensures that they are active for only short periods, providing a coincidence detection mode of inhibitory control. In contrast, slowly facilitating excitatory input onto a different population of “late persistent” interneurons recruits dendritic inhibition onto CA1 pyramidal cells. As a result of slow facilitation, these interneurons [presumably SST-containing O-LM cells, BiCs and CB1R-positive CCK-containing cells (404)] are engaged in a later inhibitory epoch reflecting an integration mode that drives distal dendritic inhibitory inputs proportional to spike rates late in the series.

All of the above discussion treats inhibitory control as a point-to-point function in a seemingly Euclidean or linear manner. Of course, this is an extraordinarily simplistic point of view since multiple converging afferent excitatory and local inhibitory inputs are likely to be simultaneously engaged during any period of ongoing activity. Moreover, as discussed above, interneurons make highly extensive reciprocal connections between each other (374, 398, 522). The combination of afferent and efferent synaptic temporal dynamics coupled with each interneuron's intrinsic properties will have many functional consequences for cortical integration and function. Indeed, the very idea that inhibition exists as a precise regulator of specific cell types and domains has been challenged by a number of studies.

In many cortical circuits, lateral inhibition is thought to sharpen stimulus selectivity by sharpening the tuning of neuronal receptive fields in a cell type and circuit specific manner (522). However, recent evidence suggests that certain forms of inhibition are promiscuous and less selective in downstream targeting than initially thought (331, 552, 876, 918). Using a combination of optogenetics, high-resolution imaging, and electrophysiological techniques, Yuste and colleagues (552) found that neocortical PV- and SST-containing interneurons indiscriminately target virtually all principal cells within a 200-μm radius of their cell body, to provide what has been termed "blanket inhibition." Such an arrangement would ensure that individual or small groups of interneurons would target overlapping domains to globally inhibit large numbers of pyramidal cells within their vicinity, thus diminishing excitatory output. In keeping with the discussion above, one can envision that recruitment of PV- versus SST-mediated blanket inhibition would have significantly different temporal dynamics with distinct influences on cortical information processing (see sects. IIB and IIII for further discussion). PV-containing interneurons would provide rapid and early blanket inhibition of the somatic and axonal initial segment domains of principal cells, whereas the slowly facilitating inputs onto SST-containing interneurons would ensure a later shift toward global dendritic forms of inhibition (552). In this scenario NGFCs would present a novel, nonspecific form of blanket inhibition. In the CA1 hippocampus, the vast majority of NGFCs are located within the s.l.m., where they appear to tile the entire extent of the region to cover the distal dendrites of principal cells (1137, 1138). Given that NGFCs release GABA in a hybrid manner with features of both synchronous and volume transmission (see sect. IVL3), large areas of the hippocampal dendritic landscape could become bathed in GABA yielding massive indiscriminant inhibition, suggesting a more permissive binary role for inhibition in sculpting excitation than one designed around its timing. Given that the s.l.m. is the target subfield for excitatory afferents from both the temporoammonic entorhinal cortex and thalamic nucleus reuniens, such blanket inhibition could act to shunt the distal dendrites of principal cells functioning as a gate to block entorhinal/thalamic input and favoring activity arising through the Schaffer collateral pathway into s.r.

Based on the discussions above, the very notion of blanket inhibition provided by either PV-perisomatic targeting or SST-dendritic targeting cells seems counterintuitive to the primary roles typically assigned to these cells. Moreover, how could excitatory principal cells respond to incoming afferent activity if they are constantly blanketed by inhibition? A recent series of manuscripts have shed potential light on this apparent conundrum. VIP-containing interneurons selectively target other inhibitory interneurons (see sect. IIH) with SST-containing interneurons serving as a primary target, while principal cells are largely spared VIP-containing interneuron input (553, 652, 906). VIP-containing interneurons therefore provide a mechanism for lateral disinhibition, i.e., inhibition of inhibitory interneurons, which allow principal cells temporary relief from inhibitory control. Karnani et al. (553) rather elegantly show that activation of VIP-containing interneurons in vivo makes "local and transient holes in the inhibitory blanket" provided by SST-containing interneurons, thereby allowing patterns of principal neuron activation to propagate within specific networks. The radial extent of single VIP-cell disinhibition of SOM-interneuron driven lateral inhibition is ~120 μm, which is consistent with the known axonal arborization of VIP-containing inhibitory neurons (569). Such a mechanism whereby small numbers of VIP-containing interneurons disinhibit "pockets" of principal cells provides an attractive mechanism to permit transient activation of precise selective circuits within normally inhibited cortical circuits.

## VIII. ENDOCANNABINOIDS

The endogenous cannabinoid (eCB) system primarily consists of the lipid-derived messengers N-arachidonoyl-ethanolamide (anandamide) and 2-arachidonoylglycerol (2-AG) that exert their cellular actions through two major receptor subtypes, CB1R and CB2R (17, 272). These G protein-coupled

receptors are predominantly expressed in the brain and immune system, respectively (727). The CB1R is one of the most highly expressed G protein-coupled receptors in the CNS (485, 486) mainly located at synaptic terminals on PCs and interneurons in the hippocampus (559, 560, 754). In fact, CB1R expression in hippocampal interneurons shows a remarkable selectivity for the CCK-expressing subtypes (559). Anandamide and 2-AG are partial and full CB1R agonists, respectively, with the latter being present at much higher concentrations and therefore is the major known contributor to eCB signaling in the brain (1053). In this section we aim to give a brief introduction to the distinct mechanisms by which eCBs modulate neural circuits with particular focus on those pertaining to the control of interneuron function within the hippocampus and highlight the pathophysiological consequences of dysregulation of eCB system. We also refer readers to a number of excellent and recent reviews regarding this topic (17, 175, 558, 704, 1028).

### A. Cellular Mechanisms of eCB/CB1R-Mediated Regulation of CCK Interneurons

One of the most well-described synaptic mechanisms resulting from activation of CB1Rs is termed depolarization-induced suppression of inhibition (DSI) (18, 343, 855, 1212). Depolarization of postsynaptic neurons that express the necessary cellular machinery for eCB synthesis initiates an as yet unknown cellular cascade to produce diacylglycerol lipase-α (DAGLα) in response to increases in $[Ca^{2+}]_i$ through VDCCs. DAGLα enzymatically converts DAG to 2-AG that is released in a retrograde manner to activate presynaptic CB1Rs reducing $GABA_A$R-mediated transmission from CCK interneurons by inhibition of presynaptic N-type VDCCs (1077) (for reviews, see Refs. 548, 1028). DSI is regulated by enzymatic degradation of 2-AG via monoacylglycerol lipase (MAGL) expressed in presynaptic terminals and astrocytes (275, 437, 1171). Thus, under most conditions, it is relatively short-lived, lasting on the order of seconds (18, 1212). Activation of glutamatergic afferents and NMDAR-mediated $Ca^{2+}$ influx is itself sufficient to trigger the eCB signaling cascade even in the absence of postsynaptic VDCC activity (854). However, physiologically DSI is likely triggered through a combination of postsynaptic VDCC and NMDAR activation due to NMDAR-mediated depolarization of the postsynaptic membrane.

Another route of 2-AG generation involves metabotropic receptor signaling coupled to the $G_{q/11}$ effector protein, for example, via mGluR5, $CCK_{2R}$, and M1 mAChR subtypes (558). Sometimes referred to as metabotropic-induced suppression of inhibition (MSI) (704), this alternative pathway, unlike DSI, does not require an increase in postsynaptic $[Ca^{2+}]_i$ but instead occurs via PLCβ1 activation to generate DAG, thus initiating the eCB cascade. Although these distinct pathways exist, under many physiological contexts they can act in concert since PLCβ1 function is in itself regulated by $[Ca^{2+}]_i$ therefore representing a form of coincidence detection between DSI and MSI to ultimately control CCK interneuron output (470, 472).

Similar eCB-mediated cellular mechanisms, particularly involving activation of group I mGluRs, can also depress GABA release from CCK interneurons over more sustained periods of time and various presynaptic cellular cascades must concomitantly occur for the successful expression of such eCB LTD (199, 200, 729). Many forms of long-lasting synaptic plasticity require de novo protein synthesis for their maintenance (907). In fact, the presence of ribosomal machinery in CCK-containing interneuron boutons provides a rapid and local ability to respond to CB1R activity, independent of transcription, resulting in long-term changes of CCK interneuron function (1253). Interestingly, eCB-LTD of CCK interneuron output effectively primes dendritic regions of the postsynaptic PC allowing for greater excitation-spike coupling and LTP induction of their excitatory inputs (198, 199), and such metaplasticity is critical for temporal memory encoding (1231).

In addition to “on-demand” eCB production, CCK interneuron inhibitory release is also susceptible to a combination of on-going basal eCB synthesis and constitutively active CB1Rs, which both promote tonic inhibition of GABA release (21, 654, 699, 833, 1275). At its extreme, this can be rather powerful resulting in virtual silencing of CCK-interneuron inhibition (699). The balance between synthesis and degradation of 2-AG, for example, which occurs via changes in presynaptic MAGL activity (471, 833, 878, 1055) finetunes this tonic influence. Thus eCB signaling can be triggered by a number of distinct pathways that synergistically interact and via retrograde action ultimately converge onto presynaptic CB1 receptors to impact synaptic transmission of CCK interneurons over a wide variety of timescales.

### B. Specificity of CB1 Receptor Regulation Among CCK Interneuron Subtypes

Although the overwhelming majority of CCK interneuron boutons in the hippocampus express CB1Rs (559), the susceptibility to DSI, mGluR-mediated, and tonic eCB regulation of GABA release appears to be more pronounced in CCK-perisomatic subtypes (basket cells) than in their dendritic-targeting counterparts (e.g., SCAs) (654). Furthermore, increases in $[Ca^{2+}]_i$ upon CB1R antagonist application is restricted to somatically opposed boutons with no response in their dendritic targeting counterparts, thus extending this differing propensity to the tonic inhibitory influence of eCBs (665). High-resolution imaging of CCK boutons indicates a larger abundance of CB1Rs and the effectors of GABA release (VDCCs and bassoon) at perisomatic- versus dendritic-targeting CCK interneuron boutons (289). Although care must be taken when extrapolating anatomical data to function (665), these differences provide a possible explanation for the dichotomy of CB1R-mediated synaptic modulation between these CCK interneuron populations. Furthermore, distinct mechanisms and sensitivity to CB1R presynaptic modulation at VGlut3-positive versus VGlut3-negative CCKBC inputs to PCs has been postulated as a consequence of differing neurochemical signatures and morphologies of these respective synapses (864). Thus, taken together, this selectivity enables eCBs to control particular aspects of hippocampal network behavior that are sculpted by specific subsets of CCK interneurons.

### C. "Noncanonical" Modulation of Interneuron Function by eCB Signaling

Within the population of hippocampal interneurons, the selective expression of CB1Rs in CCK cells indicates a privileged role of eCBs in regulating inhibition mediated by this cell type. The additional presence of CB1Rs at PC synaptic terminals, albeit at lower expression levels, nevertheless renders them susceptible to eCB-mediated depolarization- and metabotropic-induced suppression of excitation (704, 856). Thus network inhibition can also be affected via heterosynaptic CB1R-mediated modulation of excitatory afferents onto a potentially wide variety of interneuron subtypes (495, 948). Interestingly, disruption of cholinergic induced γ oscillations in the CA3 by CB1R activation occurs in part via decreases of excitatory recruitment of putative PVBCs (495). Furthermore, interneurons including CCK-, PV-, and SST-containing subtypes express low levels of DAGLα providing a route by which CB1R-mediated negative-feedback regulation of their excitatory input may be controlled (490, 785, 900).

The reach of eCBs can also circumvent the classic CB1R pathway. Anandamide is also an agonist at the $Ca^{2+}$-permeable vanilloid receptor of the transient receptor potential family (TRPV) (1117). Although the presence of TRPV1 receptors in hippocampus is controversial (177; but see Refs. 162, 785, 929), TRPV1 and TRPV3 receptor-dependent presynaptic forms of LTD have been described at excitatory inputs onto the majority of s.r. interneurons tested (130, 395). In addition, plasticity of postsynaptic $GABA_A$R expression contributes to anandamide/TRPV1 receptor-mediated changes in the inhibitory influence on PCs (193). In combination, these TRPV1 receptor-mediated plasticity mechanisms serve to disinhibit PCs. As described previously for CB1R eCB-LTD of inhibitory input onto PCs (198, 199), the TRPV receptor-mediated disinhibition also magnifies the predisposition of PCs to undergo LTP of their excitatory inputs, demonstrating similar roles for both 2-AG and anandamide in mediating metaplasticity (93, 130), hence regulating information transfer within the hippocampus. Interestingly, 2-AG is not active at the TRPV1 receptor, and therefore a complex relationship between eCBs and network inhibition likely exists (272). For example, anandamide/TRPV1 receptors activation antagonizes 2-AG/CB1R-mediated tonic reduction of GABA release from CCKBCs (655). Finally, an unknown CB1R/TRPV1 receptor-independent alteration of the excitatory drive onto interneurons has been described (294). Together, these "noncanonical" signaling modes contribute further to the possible cellular pathways mediating eCB regulation of interneuron and hence hippocampal function.

### D. Physiological Implications and Abnormal eCB Signaling in Neurological Disorders

During development, CB1R activity regulates proliferation, migration, as well as morpho- and synaptogenesis (95, 96, 723, 815). Indeed, CB1Rs are expressed at early embryonic stages in a CGE progenitor population destined to become CCK interneurons (805, 1165). Of particular societal relevance are the findings that placental transfer of the main psychoactive ingredient of marijuana delta-9 tetrahydrocannabinol ($\Delta^9$THC) during perinatal pregnancy results in numerous behavioral deficits in offspring, some of which (e.g., abnormal social behavior) may relate to deficits in hippocampal CCK

interneuron function including cell loss and alterations of CB1R-mediated tonic inhibition in the surviving CCK interneurons (1165). The availability of conditional CB1R knockout mouse lines permits specific neural components to be examined (1278). Interestingly, intersex social interactions of mice are decreased or increased following CB1R ablation specifically in glutamatergic versus GABAergic neurons, respectively (13, 1100), thus demonstrating remarkably distinct roles of eCB signaling dependent on cell type.

Again with particular relevance to hippocampal function, cognitive decline including memory impairment represents a well-characterized effect of cannabis use in humans (131). In rodents, administration of $\Delta^9$THC or genetic CB1R knockout disrupts hippocampal-dependent tasks requiring various forms of learning and memory (for review, see Ref. 1278). Interestingly, single in vivo exposure to $\Delta^9$THC precipitates a reversible decrease in the propensity to initiate eCB-LTD of hippocampal inhibitory transmission (761). Cannabis use in humans and $\Delta^9$THC administration in rodents results in a reduction in CB1R expression (289, 491). Furthermore, CB1R knockout specifically in GABAergic interneurons results in deficits in spatial memory acquisition and novel object recognition performance (13). However, conditional knockout of CB1Rs in hippocampal astrocytes that express low levels of this receptor (827) completely abolishes the $\Delta^9$THC-induced deficits in spatial working memory, suggesting an indispensible role for eCB signaling in this glial cell population with respect to such hippocampal-dependent behaviors (13, 460). Taken together, it is evident that CB1R-mediated signaling is critical for both the deleterious effects of $\Delta^9$THC and the physiological role of eCBs in learning and memory, but further clarification of the cellular players is clearly necessary.

Changes in CB1R expression have also been observed in various neurological disorders. For example, in the pilocarpine model of temporal lobe epilepsy, an initial downregulation of CB1R expression is followed by a long-lasting upregulation, with the latter corresponding to the temporal emergence of seizures (312, 731). The chronic effects are characterized by a permanent redistribution of CB1R expression between hippocampal subfields (311). At the cellular level, febrile-induced seizures precipitate an increase in CB1R expression at CCKBC terminals with no change at excitatory synapses (197). These cell-specific alterations are accompanied by a potentiation of DSI and increased eCB-mediated tonic inhibition of inhibitory output that likely precipitate hyperexcitability of the network (197). Interestingly, brain region and cell-type specific temporally biphasic changes of CB1R expression are observed in humans with epilepsy (413, 707, 731).

In addition to changes in CB1R expression, alterations at other loci within the eCB pathway are also apparent. Fragile X syndrome resulting from FMR1 gene silencing is a major hereditary cause of intellectual retardation and autism precipitated by a plethora of circuit abnormalities (221). In a mouse model of Fragile X, an increased eCB-LTD of inhibitory input onto hippocampal and striatal principal cells is precipitated that is due to altered coupling between mGlu5 and DAGLα leading to increased 2-AG synthesis (724, 1092, 1266). The resulting enhanced disinhibition of PCs amplifies the predisposition to LTP of their excitatory inputs precipitating enhanced excitability (198, 1266), although additional cellular mechanisms independent of the eCB system cannot be discounted (221). Nevertheless, CB1R antagonism effectively normalizes the augmented eCB-LTD of GABA release (424) and can ameliorate memory impairments found in this mouse model (145, 424). In contrast, eCB-LTD of striatal and prefrontal cortical excitatory synapses is absent due to a reduction in mGlu5-mediated 2-AG synthesis (543), illustrating brain region and synapse specific changes. Intriguingly, inhibition of MAGL to increase levels of 2-AG was sufficient to rescue eCB-LTD at these synapses and also reverses deficits in open-field exploratory and elevated plus maze behaviors normally observed in Fragile X mice (543). Thus pharmacological interventions leading to opposing effects on eCB signaling reveals a complex scenario with regards to possible therapeutic intervention to treat the numerous behavioral deficits associated with mouse models of this neurological disorder.

Mice with neuroligin-3 (NLG-3) mutations associated with autism display social deficits and altered spatial learning (305, 529). At a synaptic level these mice possess deficits of tonic but not phasic eCB-mediated inhibition of CCKBC output demonstrating an interaction between NLG-3 and eCB pathways (342). Recently, another protein implicated in autism, Alzheimer's disease, and Huntington's disease called p21-activated kinase (PAK) (401, 713) was found to indirectly and negatively control basal anandamide

but not 2-AG levels (1227). PAK1 knockout mice show impaired tonic inhibition onto hippocampal PCs due to enhanced presynaptic CB1R activation (1227). Interestingly, in both studies, the changes in tonic eCB signaling are specific to inhibitory synapses with their excitatory counterparts being spared (342, 1227). Further investigation of the interactions between eCBs and other cellular signaling pathways should reveal additional targets for therapeutic intervention. Finally, on a celestial note, a recent study in which rodents exposed to irradiation mimicking cosmic ray exposure of astronauts during space travel reveal a decrease in eCB-mediated tonic inhibition of CCK interneuron transmission in the hippocampus that are not caused by changes in CB1R expression but partly due to lower levels of basal 2-AG (653). Therefore, these changes may underlie the emergence of cognitive deficits that potentially could jeopardize mission performance during prolonged space exploration (882).

## IX. ACETYLCHOLINE RECEPTORS

### A. Muscarinic Receptors

Basal forebrain cholinergic input to the neocortex and hippocampal formation plays a major role in regulating arousal and sleep wake cycles, attention, and memory formation as well as being a primary regulator of oscillatory activity (473). The hippocampal formation primarily receives its cholinergic input from the medial septum and diagonal band of Broca (MS/DBB) (293). Fibers from the MS/DBB extensively ramify throughout all layers of the hippocampus to target principal cells, inhibitory interneurons, and astrocytes. In the mouse, cholinergic fibers densely innervate the CA1 subfield with the highest density of fibers innervating s.p. and the border between s.r. and s.l.m. The bulk (~90%) of cholinergic axons lack any specialized presynaptic release sites, and it is thought that transmission influences its downstream targets by volume transmission, suggesting that areas of high axonal density will “pool” the highest concentrations of released ACh (1152). ACh acts through both pre- and postsynaptic metabotropic muscarinic (mAChR) and ionotropic nicotinic (nAChR) receptors to regulate both principal cell and inhibitory interneuron activity (640). Early studies highlighted that the increased inhibitory tone onto pyramidal cells following ACh application was due to direct excitation of inhibitory neurons instead of a secondary increased excitatory drive from pyramidal cells (79, 911). Convergence of local interneuron activity and cholinergic modulation of multiple cell types has a complex role to play in the modulation of neocortical and hippocampal principal neuron oscillatory activity that relates to behavioral state (138).

Early studies of mAChR activation on interneurons recognized that application of ACh agonists triggered complex changes in cell excitability that did not always clearly correspond to cell identity. In neocortex, application of cholinergic agonists strongly depolarizes SST-containing Martinotti cells, but not PVBCs, and triggers biphasic responses in CCK-containing interneurons (566). Similar experiments in hippocampal CA1 using exogenous agonists or extracellular stimulation of cholinergic fibers triggers either a membrane hyperpolarization, depolarization, or biphasic responses often accompanied by changes in the AHP/ADP that does not correspond to specific anatomical subtypes of interneurons. These data suggest a complex interplay of muscarinic receptor (s) modulation of temporally overlapping intrinsic conductances in different subpopulations of interneurons (777, 778, 1203).

The advent of numerous mouse interneuron reporter lines coupled with more thorough anatomical recovery and cell identification has however begun to reveal stereotypic responses to mAChR activation in a handful of hippocampal interneuron subtypes. In CA1 hippocampus, in response to muscarinic agonist exposure, SST-containing O-LM cells show an acceleration in firing frequency that is coupled to conversion of the spike AHP to an ADP. This arises primarily via M1/M3 mAChR activation of a nonselective cation current ($I_{CAT}$) and inhibition of both $I_M$ and the slow AHP ($I_{AHP}$) currents (646). This mAChR modulation tunes the intrinsic oscillatory properties of O-LM cells to increase firing reliability (642, 646).

mAChRs on CA1 CCKBCs and SCAs increase action potential duration and frequency, reduce spike adaptation, and promote conversion of the AHP to an ADP via activation of both M1 and M3 mAChRs (181, 182). In these cells activation of M3 mAChRs controls the spike frequency increase and M1/M3 receptor activation triggers conversion of the AHP to an ADP. CCKBCs typically demonstrate an M1/M3 membrane depolarization, whereas SCA cells undergo a biphasic membrane voltage change driven

separately by M1 and M3 receptor activation of GIRK channels and inhibition of $I_M$, respectively (181). Of interest, mAChR activation triggers long-lasting repetitive firing in both cell types in response to synaptic stimulation as well as amplifying 0.5–2.0 Hz subthreshold membrane oscillatory activity facilitating recruitment at theta frequencies.

mAChRs differentially modulate somatodendritic and axonal mAChRs on CA1 hippocampal and prefrontal cortex PVBCs and BiCs (182, 1250). Activation of soma-dendritic M1 mAChRs depolarizes and increases the firing frequency of PV-containing interneurons (182). While CA1 PV-containing interneurons also show a conversion of the AHP to an ADP, PV-containing interneurons in the prefrontal cortex do not (1250). M2 mAChRs are expressed on the presynaptic terminals of PV-containing interneurons (454). IPSCs generated at synapses between PVBCs and cortical pyramidal cells (608), DG granule cells (478), and hippocampal CA3 (1076) and CA1 pyramidal cells (643) are all inhibited by M2 mAChR-mediated reductions in presynaptic $Ca^{2+}$-transients leading to decreased Pr (643).

All of the above studies relied primarily on agonist application to trigger mAChR. Electrical or optogenetic stimulation of ACh release in mouse interneuron reporter lines have added another perspective to the role played by both mAChR and nAChR modulation of interneurons. Widmer et al. (1203) demonstrated that bulk electrical stimulation of cholinergic fibers in hippocampus triggered complex responses in interneurons that included hyperpolarization, depolarization, or both, with no clean segregation between anatomically distinct subtypes. However, optogenetic studies using channelrhodopsin to trigger release of ACh and archaerhodopsin to suppress excitation of specific interneuron subtypes demonstrated that VIP/CCK-containing perisomatic targeting interneurons depolarize and increase their firing rate on mAChR activation, leading to an increase in sIPSCs onto pyramidal cells (84, 85, 821). In contrast, PVBCs depolarize, hyperpolarize, or produced biphasic responses following optogenetic release of ACh. The extent of the depolarization is smaller in PV-containing interneurons than that observed in VIP-containing CCKBCs, consistent with the observation that PV-containing cells are not the primary target for cholinergic driven increases in PC sIPSCs (84, 85, 821). Of interest, depolarizing responses required greater cholinergic terminal stimulation than did muscarinic mediated hyperpolarization, suggesting that presynaptic firing properties coupled to axon densities and pooled ACh concentrations may be important determinants of the type of cholinergic modulation observed on specific interneuron subtypes (86). While M4-mAChRs were responsible for the hyperpolarizing response via activation of an inward rectifying $K^+$ conductance, the depolarizing response was resistant to block of M1, M4, and M5 receptors consistent with a role for M3 mAChRs in generating the membrane depolarization as shown previously in the agonist experiments described above (86).

### B. Nicotinic Receptors

Like mAChRs, ionotropic nAChRs are differentially expressed across inhibitory interneuron populations. Although 11 nicotinic receptor subunits have been identified (1062), only α7 and α4β2 receptors have been identified on inhibitory interneurons. Early studies in the neocortex demonstrated that nAChR agonists strongly depolarize and excite CCK- and VIP-containing interneurons, while only weakly exciting PV-containing cells (565, 921). In hippocampus, PVBCs are similarly resistant to nicotinic receptor agonists. α7-Containing receptors are enriched in interneurons of the s.r., including CCK-containing interneurons (22, 542, 779). It has been suggested that nAChR expression is a hallmark feature of cortical interneurons derived from the CGE (651). In the s.o., both MGE- and CGE-derived SST-containing O-LM cells express both α7 and non-α 7 receptors (139, 779), suggesting that at least some MGE-derived interneurons also express nAChRs (203, 1138). Electrical stimulation of cholinergic axons generates rapid kinetic synaptic events onto CA1 interneurons that is thought to arise primarily via activation of α7 receptors (22, 347). However, subsequent studies indicate that the pharmacological profile of the responses indicates α4β2 containing receptors rather than α7-containing (322, 921). Consistent with this observation, nicotine-sensitive neocortical CCK-containing interneurons express transcripts for α4/5 and β2 but only low levels of α7. In contrast, hippocampal CCK-containing interneurons primarily express α7 mRNA transcripts (801), indicating potential cell type and regional heterogeneity in receptor expression profiles. A recent study using optogenetic techniques to release ACh has challenged this observation and suggests that α4β2 nicotinic receptors are the primary target for acetylcholine release onto hippocampal CCK- and VIP-containing interneurons leaving the role of α7 nicotinic receptors in question (83, 84). Synaptic events

triggered by light-activated ACh release have significantly slower kinetics compared with the presumed α7 events evoked by extracellular electrical stimulation and were small and subthreshold in nature. Whether this reflects a technical issue related to the use of optogenetics (which does not trigger neurotransmitter release in a manner identical to electrical stimulation) remains to be determined. Interneuron nAChR activation by optogenically released ACh is modulated by presynaptic M2 mAChRs, suggesting a dynamic interplay between mAChRs and nAChRs controls ACh regulation of inhibitory interneurons. A recent study has added a new dimension to our understanding of cholinergic modulation of inhibitory transmission. Pabst et al. (875) demonstrated that optogenetic release of ACh from septohippocampal projections triggers an increase in GABAergic tone onto DG granule cells. However, released ACh does not excite inhibitory interneurons directly but instead activates hilar astrocyte intermediaries, which subsequently release glutamate onto downstream hilar interneuron targets to drive an increase in inhibition. It is unclear if this mechanism is shared across other hippocampal and cortical subfields, but if so it would act to expand the repertoire of modulatory pathways available to cholinergic pathways in the mammalian CNS.

nAChRs also modulate transmitter release directly from inhibitory interneuron terminals (725). Activation of presynaptic nAChRs on perisomatic basket cells, presumably PV-containing interneurons, triggers a robust action potential independent release of GABA via α3/β4 nAChRs coupled to T-type $Ca^{2+}$-channels and $Ca^{2+}$-induced $Ca^{2+}$ release from intracellular stores.

## X. DOPAMINE RECEPTORS

Subcortical dopaminergic axons from the ventral tegmental area ramify widely throughout the hippocampal formation (1169), and a role for dopamine in hippocampal novel memory formation and synaptic plasticity is well established (684). However, much of what we know concerning dopamine receptor distribution in the hippocampus and cortex is biased towards studies of principal cell expression of D1 and D2 receptors. In contrast, only a handful of studies have tackled the distribution of dopamine receptors on specific inhibitory interneuron subpopulations.

Although a number of autoradiographic and mRNA studies have indicated dopamine receptor subtype expression in “scattered” cells outside of the pyramidal cell layers (741), a general lack of reliable antibodies for dopamine receptor subtypes has hampered elucidation of their expression patterns. With the use of a D1R-eGFP mouse line, D1 receptor expression has been shown in DG presumed molecular layer PPA cells, as well as presumed PVBCs and AACs in the hilus (380). Within the CA1 and CA3 hippocampus proper, the vast majority of D1R-expressing interneurons reside in s.r., with lower numbers in s.p., s.o., and s.l.m. Although the exact identities of these interneurons are unknown, many are CR- or CB-positive, but PV-negative (380). Although a similarly labeled D2R-eGFP mouse line failed to reveal D2 receptor expression in inhibitory neurons (380), Drd2-Cre:riboTag and Drd2-Cre:RCE mouse lines show multiple cell populations expressing D2R in the CA1 and CA3 subfields. Combined immunohistochemistry reveals D2R-expressing interneurons primarily localized to s.o. and s.l.m. comprised of PV-, CB-, CR-, NPY-, SST- and nNOS/reelin, coupTFII-containing cell types, indicating widespread expression of D2Rs throughout diverse interneuron populations (930).

The D4 receptor is of particular interest because of its suggested role in schizophrenia and high affinity for the antipsychotic drug clozapine. D4Rs are expressed at extremely low levels throughout the hippocampus, with in situ hybridization and immunohistochemistry approaches revealing D4R expression in a small number of presumed interneurons (36, 44, 262). Within the CA1 hippocampus, ~25% of PV-containing interneurons are D4R-immunopositive and ~50% of D4R-expressing interneurons are positive for the neuregulin ErbB4 (36). Triple immunofluorescence indicates that D4R- and ErbB4-immunoreactivity overlap within a subset of PV-containing interneurons and converge to positively modulate KR-induced gamma oscillations (36). D4Rs are also enriched in interneurons within the prefrontal cortex (813). D4R activation of PFC layer I-V interneurons in a GAD-GFP transgenic mouse line (862) reduces excitatory transmission onto these cells via a mechanism involving calcineurin-dependent AMPAR trafficking (1261). One can imagine that a D4R-mediated reduction in the excitatory drive of as yet unidentified PFC interneurons would result in an imbalance in the excitation:inhibition dynamics within circuits essential for executive function.

## XI. SEROTONIN RECEPTORS

Subcortical serotonergic innervation of the hippocampal formation originates from the median raphe nucleus, with a somewhat minor projection coming from the dorsal raphe. These two projections are thought to give rise to two distinct afferent fiber types (601, 677): one with large boutons that cluster along dendritic branches and a second with thin axonal projections with numerous small evenly distributed varicosities, respectively. The projection from the dorsal raphe is thought to release serotonin at nonsynaptic sites to target cells expressing the metabotropic G protein-coupled 5-HT1 and 5-HT2 receptor subtypes, whereas the medial raphe nucleus afferent pathway innervates specific interneuron subtypes expressing the ionotropic 5-HT$3_A$ receptors (352). Studies using a 5-HT$3_A$R-eGFP mouse line demonstrated that neocortical and hippocampal interneurons derived from the CGE, but not the MGE, express 5-HT3Rs (651, 1179). 5-HT$3_A$R expression is observed in early embryonic stages ~E14.5 and persists throughout the animals lifespan making it an excellent marker for cells of CGE origin. Indeed, Rudy and colleagues (651, 1134) have gone so far as to use this 5-HT$3_A$R expression as a defining feature for classification schemes of the CGE-derived group of neocortical interneurons. It is important to point out, however, that the CGE-derived cohort of neocortical and hippocampal interneurons comprises a broad and functionally diverse collection of interneurons types, including VIP-, CCK-, CR-, reelin-, NPY-, and in hippocampus SST-containing cell types (see sect. III).

In vivo recordings revealed that stimulation of medial raphe fibers elicits a rapid and robust modulation of ongoing hippocampal activity (841). Early studies in vitro showed complex responses to exogenously applied serotonin, suggesting that multiple overlapping receptor subtypes may contribute to the observed response. Recordings from CA1 pyramidal cells showed an increased frequency and amplitude of unitary IPSPs, which primarily resulted from a 5-HT$3_A$R-mediated depolarization of select but unidentified s.r. interneurons (954). Indeed, subsequent voltage-clamp recordings from s.r. interneurons revealed a rapid inward current triggered by serotonin application that was G protein independent (773). The current-voltage relationship of this current possessed a region of negative slope conductance reminiscent of that seen at NMDARs, that was insensitive to extracellular $Mg^{2+}$ concentrations (in contrast to NMDAR) but linearized when extracellular $Ca^{2+}$ was reduced. More recently, optogenetic activation of median raphe fibers was shown to rapidly recruit hippocampal interneurons via glutamate/serotonin cotransmission through AMPARs and 5-HT$3_3$Rs, respectively, with high spatial and temporal resolution (1164). These data suggest that unlike other subcortical inputs into the hippocampus and neocortex, the median raphe serotonin projections can trigger a rapid modulation of ongoing activity via ionotropic receptors.

As described in section IIF, a subset of CGE-derived SST-containing O-LM interneurons in CA1 express 5-HT$3_A$Rs (203). The presence of 5-HT$3_A$Rs on these cells endows them with a divergent role from their MGE-derived counterparts in kainate-induced gamma frequency oscillatory activity in vitro (203). CGE-derived O-LM cells exhibit a mean firing frequency probability per gamma cycle of ~0.033, which is significantly lower than that observed in their MGE-derived counterparts (mean firing probability per cycle is ~0.16). Of particular interest, 5HT$3_A$R activation of CGE-derived O-LM cells doubles their firing probability during each gamma cycle without altering their phase preference (203). These data suggest that MGE- and CGE-derived O-LM cells are differentially recruited during hippocampal gamma oscillations in acute slices and that participation of CGE-derived O-LM interneurons in synchronized hippocampal network activity can be rapidly modified by serotonergic tone. This observation is consistent with a report that 5-HT$3_A$R antagonism with ondansetron reduces the recruitment of some hippocampal interneurons in network oscillations recorded in freely moving rats (942).

Much less is known about the expression patterns of metabotropic serotonin receptors on specific interneuron populations. Exogenous application of serotonin hyperpolarizes unidentified hippocampal CA1 interneurons and reduces evoked fast and slow IPSPs onto CA1 pyramidal cells via 5-HT$1_A$Rs (989). Evoked EPSPs onto interneurons of both the CA1 hippocampus and layer I and II entorhinal cortex are similarly reduced by activation of 5-HT$1_A$Rs, suggesting that the reduced inhibition onto principal cells results in part from reduced excitatory drive onto interneurons (988, 989). Paired recordings of EPSPs between CA1 pyramidal neurons and O-LM cells are similarly inhibited by activation of presynaptic 5-HT

receptors (110). $GABA_B$-mediated slow IPSPs (but not $GABA_A$-mediated IPSPs) onto CA3 pyramidal cells are also reduced by exogenous serotonin application via a presynaptic modulation of inhibitory transmitter release (860).

With the use of an $Htr_{2A}$-eGFP mouse line, 5-$HT2_A$Rs were observed to be highly enriched in interneurons localized primarily to the CA1 s.r. and s.l.m. border, with a few additional cells observed in the s.o. of CA1 and CA3 (1226). Activation of pharmacologically isolated 5-$HT2_A$Rs generates a robust inward current and depolarization of CA1 s.r. interneurons (1226), leading to an increased inhibitory drive onto principal cells (1003). The identities of 5-$HT2_A$R expressing interneurons from which the recordings were made are somewhat unclear, but anatomical reconstructions of these cells are consistent with PPA, CCKBC, and SCA morphologies. In situ hybridization studies have also shown 5-$HT1_A$, 5-$HT2_A$, 5-$HT2_C$ receptor mRNA expression in prefrontal cortex interneurons including PV-containing cells (975). 5-$HT5_B$Rs, like 5-$HT2_A$Rs, are most commonly observed in interneurons at the s.r. and s.l.m. border (1000). Anatomical reconstruction of these cells suggests that they are most likely NGFCs or IvCs, capable of showing persistent firing properties (1000, 1001). In situ hybridization analysis of the recently described metabotropic 5-HT6R revealed expression in ~15% of hippocampal and layer I/II neocortical interneurons. Of these, ~50% of 5-$HT3_A$R-positive interneurons expressed 5-HT6R, while negligible levels were observed in PV- and SST-containing interneurons (479).

## XII. OPIOID RECEPTORS

The three opioid receptors mu-, delta- and kappa- belong to the superfamily of G protein-coupled receptors and together with the endogenous opioid peptides play a major role in nociception, learning and memory, anxiety, as well as neuroendocrine and autonomic function.

### A. Mu-Opioid Receptors

Modulation of hippocampal network activity by opioid peptides has been long recognized (228). Early studies in hippocampal slices in vitro demonstrated that enkephalin generally excites the hippocampal network (836) by a mechanism involving a reduction in inhibitory drive (835, 1276). Using blind sharp microelectrode recordings from CA1 inhibitory interneurons, Madison and Nicoll (728) demonstrated that the enkephalin analog, D-Ala-Met-enkephalinamide, hyperpolarized interneurons by increasing a potassium conductance which led to a disinhibition of both pyramidal cells and other interneurons. Subsequent studies demonstrated that mu-opioid receptor activation decreased presynaptic GABA release onto CA3 pyramidal cells by a G protein-mediated mechanism (166). This reduction in GABAergic tone acts to increase network excitability resulting in increased seizure susceptibility and lowered threshold for synaptic plasticity (124, 776, 806).

Mu-opioid receptors are expressed on a small number of discrete inhibitory interneuron subtypes, which include PV-containing and NPY-containing cells (285, 1060) and appear to be absent in CB1R-expressing CCK-containing interneurons (833). Accordingly, electrophysiological studies revealed that mu-opioid receptor activation by the exogenous agonist DAMGO hyperpolarizes the membrane potential and reduces inhibitory transmission between PVBCs and their downstream pyramidal cell targets (1070). The mechanism of mu-receptor modulation of synaptic transmission is consistent with a reduction in presynaptic transmitter release probability (403, 1070). In contrast, unitary connections between CB1R expressing CCK-containing interneurons and CA1 pyramids were largely unaffected (403). Evoked IPSCs onto PVBCs and CCKBCs are also modulated by mu-opioid receptor activation, with transmission onto the former being suppressed to a larger extent (decreased by ~60% compared with ~30%, respectively) (403). Consistent with this observation the feedforward component of inhibition is strongly modulated by mu-opioid receptor activation, whereas the feedback component largely driven by CCK-containing interneurons is largely resistant.

Mu-opioid receptor modulation of presynaptic transmitter release has also been observed at synapses responsible for the $GABA_B$R-mediated inhibitory input onto pyramidal cells. These synapses are dendrite targeting and use N-type $Ca^{2+}$ channels for transmitter release but are insensitive to eCB modulation, implicating IvCs and NGFCs (628, 775). Indeed, direct recordings from IvCs and NGFCs revealed sensitivity to mu-opioid receptor modulation (606). Similar to PVBCs, paired recordings between

synaptically coupled IvCs and CA1 pyramidal cells revealed mu-opioid receptor modulation of presynaptic transmitter release (606). Of particular interest, induction of persistent firing (see sect. IVM for discussion) in IvCs is inhibited by mu-opioid receptor activation (606), and although the exact mechanism of action is unclear, it may be linked to general mu-opioid receptor-mediated hyperpolarization of gap junction connected neurogliaform family cells. Mu-opioid receptor mRNA has also been detected in SST-containing HIPP cells in the dentate gyrus as well as a small number of CR-containing interneurons in the granule cell layer (284). However, the physiological roles played by mu-opioid receptors on these cell types have not been explored.

Ovarian sex steroid hormones modulate mu-opioid receptor expression in select interneuron populations. Elevated levels of estrogens in proestrus females increase mu-opioid receptor trafficking and expression in dentate gyrus PVBCs (1115). Thus the magnitude of mu-opioid receptor modulation of inhibitory networks is likely tuned by fluctuations in steroid hormones.

### B. Delta-Opioid Receptors

Delta-opioid receptors play important roles in anxiety, depression, control of emotional responses, and spatial memory (218, 329, 950). Immunohistochemistry has shown highest delta receptor expression in NPY-containing and a subset of SST-containing interneurons (218). Using a knock-in mouse expressing a functional delta-opioid receptor fused at its carboxy terminal with eGFP mouse, the highest GFP signal was found in the GABAergic axonal fibers terminating throughout the pyramidal cell layer, suggesting presynaptic expression of delta receptors; however, colocalization interneuron neurochemical markers was not studied (941).

Despite the findings in delta-opioid GFP mice, delta receptor expression is generally accepted to be highest on dendrite projecting interneuron subtypes and appears to be complementary to mu-opioid receptor expression (1070). Early electrophysiological studies showed that mu-opioid receptor activation attenuated electrically evoked IPSCs in principal cells, whereas delta-opioid receptor agonists had no effect (711, 1193). Consistent with these early observations, electrophysiological recordings combined with anatomical reconstruction demonstrated that dendrite targeting, BiCs and O-LMs, are hyperpolarized by agonists selective for delta receptors but are largely insensitive to mu-receptor agonists (1070). Thus, rather than regulating perisomatic inhibition and action potential timing in principal cells, delta-opioid receptors are positioned to modulate feedback dendritic inhibitory input to principal cells. Moreover, given the role that O-LM cells play in modulating the influence of temporoammonic inputs onto the distal dendrites of CA1 pyramidal cells (720), it is possible that delta-receptor-mediated inhibition of these cells would act as a gate to minimize their influence on temporoammonic inputs, thus strengthening enthorinal cortex input into the CA1 hippocampus. Like mu-opioid receptors, delta-opioid receptor availability is modulated by ovarian hormones. In NPY-containing interneurons, ovarian hormones present in normal cycling females alter the number of soma containing delta-opioid receptor immunoreactivity in CA1 and CA3 s.o., without influencing the number of axon terminals containing delta-opioid receptors in CA1 s.r. (1211).

### C. Kappa-Opioid Receptors

Significantly less is known about kappa-opioid receptor expression and modulation of inhibitory interneurons. Kappa-opioid receptor immunoreactivity has been observed on subsets of both NPY- and SST-containing interneuron populations (456, 931), reminiscent of the same cell populations expressing delta-opioid receptors (1070). The functional role(s) of kappa-opioid receptors has to date been completely unexplored in specific interneuron populations. However, by analogy to observations for delta-opioid receptors, inhibition of SST- and NPY-containing interneurons by kappa-opioid receptor activation to regulate dendritic inhibition seems plausible.

## XIII. OXYTOCIN RECEPTORS

The neurohypophysial peptide oxytocin is released from axon terminals of the hypothalamo-extrahypophysial pathway to exert a diverse array of actions throughout the central nervous system (140, 141). Light microscopic autoradiography and in situ hybridization approaches have shown high-affinity oxytocin receptors in hippocampus and subiculum that appear to be targeted to nonprincipal cells,

presumably inhibitory interneurons (357, 1136). Early physiological recordings indicated that exogenously applied oxytocin hyperpolarized the membrane potential and increased spontaneous inhibitory input to pyramidal cells while directly exciting unidentified nonpyramidal cells in the CA1 subfield (814). Application of the oxytocin receptor agonist [Thr4, Gly7]-oxytocin (TGOT) was also shown to excite s.p. interneurons, as well as a subset of s.o. cells but failed to excite s.r. interneurons (1263), indicating cellular heterogeneity in oxytocin receptor expression. More recently, a study by Tsien and colleagues (871) demonstrated that TGOT directly increases the firing frequency of anatomically identified CA1 PVBCs. Most remarkably, while this increase in PVBC activity suppresses spontaneous pyramidal cell firing, it also enhances spike fidelity and sharpens spike timing for evoked inputs, thus dramatically improving signal-to-noise in the network. The authors intelligently asked how could this paradoxical increase in basket cell activity and resulting inhibitory tone result in a higher fidelity of principal cell action potential throughput and timing? Using paired recordings they then demonstrated that PVBC unitary IPSCs were reduced by oxytocin receptor activation when the PVBC was allowed to depolarize in response to TGOT, thus shifting the excitation:inhibition balance onto pyramidal cells in the favor of excitation (871). As discussed in section VII, transmission between PVBCs and their downstream targets undergoes profound short-term depression in response to repetitive activation. Owen et al. (871) demonstrated that the TGOT-induced increase in basket cell firing causes a use-dependent depression of the IPSC that is both necessary and sufficient for the enhancement of excitation-spike coupling in pyramidal cells. Finally, the authors demonstrated the generality of this phenomenon by using two other unrelated agents, CCK and channelrhodopsin, to drive increases in fast spiking interneuron action potential activity. Importantly, many studies have demonstrated that particular agents or modulators increase the firing rates of particular subtypes of interneuron and simplistically concluded that such recruitment will ultimately result in an increased inhibitory output that is presumed to silence or reduce the excitability of the particular downstream targets. The study by Owen et al. (871) brings into sharp focus that one has to also consider the downstream temporal dynamics of the resulting inhibition to fully appreciate the outcome of increasing the excitability of a particular interneuron type.

In addition to direct excitation of interneurons, oxytocin appears to play an important role in influencing GABAergic synaptic transmission in fetal neurons during delivery (579). As discussed in section III, GABA has a depolarizing and excitatory action during development and early postnatal life. This depolarizing action of GABA relates to developmental changes in the two cation-chloride cotransporters $Na^+$-$K^+$-$Cl^-$ cotransporter (NKCC1) and $K^+$/$Cl^-$ cotransporter (KCC2). In early development, the high expression of NKCC1 and low expression of KCC2 ensure that cytoplasmic chloride concentrations are high and that under normal conditions, activation of synaptic GABA receptors will trigger a $Cl^-$ efflux and a membrane depolarization (92). Tyzio et al. (1147) observed that while GABA is indeed depolarizing during fetal and early postnatal life, there is a window of ~48–72 h around the period of term (E20-P0) when the proportion of cells excited by GABA decrease. This transient perinatal loss of GABAergic excitation results from an oxytocin-dependent negative shift in the $Cl^-$ reversal potential via a mechanism involving inhibition of NKCC1 cotransporter activity (579, 1147). These observations suggest that one of the roles for the massive release of oxytocin at term and during delivery may be a form of neuroprotection by limiting neural network activity during perinatal hypoxia (579).

## XIV. CHOLECYSTOKININ

Cholecystokinin is one of the most abundant peptides in the mammalian central nervous system and is implicated in a broad range of central functions including feeding/satiety, anxiety, nociception, and learning and memory. Despite such broad participation, surprisingly little is known, beyond the most basic information, about the precise mechanisms and circuit functions of CCK. As described in section II, CCK-containing inhibitory neurons represent a large subpopulation of CGE-derived inhibitory neurons, whose GABAergic synaptic mechanisms have been well studied. However, like most neuropeptide-containing central neurons, it has been extraordinarily difficult to ascertain the mechanism(s) underlying CCK release from these cells and more importantly what CCK does once liberated. In the CNS, the CCK peptide exists primarily as the sulfated 8-amino acid CCK8S, which binds primarily to G protein-coupled CCK2 (or CCKB) receptors, although a few central areas also express the CCK1 receptor (657). Application of exogenous CCK8S to hippocampal neurons in vitro was originally shown to increase action potential-dependent sIPSCs onto CA1 pyramidal cells and DG granule cells (269, 341, 555, 792). This increase in

sIPSCs was blocked by prior application of agatoxin-TK, a blocker of P/Q $Ca^{2+}$ channels, on perisomatic targeting PVBC terminals. Subsequent studies demonstrated a direct CCK-mediated excitation of PVBCs (but not BiCs) via activation of the CCK2 receptors (341). CCK2 receptor activation on PVBCs triggers a pertussis toxin-sensitive pathway coupled to ryanodine receptor-mediated intracellular $Ca^{2+}$ release (658). This stands in marked contrast to the canonical $G_q$-PLC pathway typically associated with CCK2 receptor activation. In paired recordings between PVBCs and CA1 pyramidal cells, CCK had no effect on the unitary IPSP (cf. Ref. 871), this discrepancy is most likely due to the holding of the PVBC at a fixed holding potential in the study of (341). In contrast, in paired recordings between CCKBCs and CA1 pyramidal neurons, exogenous CCK significantly reduced the unitary IPSP by altering presynaptic transmitter release (341). This presynaptic reduction in GABA release was not a consequence of activation of presynaptic CCK receptors but rather by activation of postsynaptic CCK2 receptors on pyramidal cells, which then triggers PLC/DAG lipase-mediated eCB formation and liberation, that results in the activation of a canonical retrograde suppression of GABA release from CCK interneurons via presynaptic CB1R activation (see sect. VIII).

Perhaps the most surprising aspect of this data set is the narrowness of the cellular targets for CCK influence: primarily perisomatic PV- and CB1R-positive, CCK-containing interneurons. Such an arrangement will favor simultaneous excitation of PVBCs but inhibition of release from CCKBCs. Thus CCK acts as a gate to switch between the two modes of perisomatic inhibition to favor tasks that require precision and timing such as oscillatory activity (47, 657). As described above, in addition to targeting perisomatic regions, CCK-containing interneurons also target the proximal and distal dendrites of principal cells as well as targeting other interneurons, suggesting a complex role for CCK in sculpting network dynamics. It is worthwhile to point out that most studies of neuropeptide modulation of central neurons, including CCK, rely primarily on exogenous application of CCK, which will target numerous sites simultaneously, perhaps masking the subtleties of CCK-dependent modulation of circuit function. However, it has proven difficult to determine the conditions necessary to trigger endogenous CCK release, which coupled to local degradation mechanisms make it problematic to study intrinsic release of neuromodulators.

## XV. INTERNEURONS AND NETWORK FUNCTION

Information processing in neuronal networks is critically dependent on the precise synchronization of ensembles of neurons. Interneurons play a key role in coordinating network activity both within local networks and across the relatively long distances that separate different brain regions. The synchronous firing of neurons gives rise to neuronal oscillations, characterized by waves of electrical activity that can be observed in extracellular field recordings or electroencephalograms (EEGs). The first EEGs were reported by Hans Berger in 1929 (94), where he described oscillations below 12 Hz as alpha waves, and those above 12 Hz as beta waves. The convention of naming neuronal oscillations by their frequency band is still followed today and are categorized by their frequency band, such as slow oscillations (<1 Hz), theta oscillations (4–10 Hz), or gamma oscillations (30–90 Hz) (152). The exact frequency bands reported can vary between species; for example, theta oscillations occur at 6–12 Hz in rodents, but slow down to 4–6 Hz in carnivores, and occur at 1–4 Hz in humans (for review, see Ref. 154). Interestingly, recent work found that 7–9 Hz theta oscillations do indeed occur in human hippocampus during real-world navigation, with the slower observed 3- to 4-Hz theta oscillation likely being an experimental artifact from having humans navigating in a virtual reality environment (109). However, while the exact frequency range may vary between species, each oscillation band consistently correlates with different behavioral states and, by controlling the timing of principal cell output, inhibitory interneurons are key to generating these rhythms of the brain (FIGURE 21).

### A. Gamma Oscillations

Gamma oscillations are associated with numerous cognitive functions such as memory and spatial navigation (e.g., Refs. 67, 302, 1189) and correlate with working memory load in humans (500). While gamma oscillations occur in all cortical regions (152), many of the mechanistic insights into their genesis come from hippocampal studies. Early in vivo studies of nonanesthetised rats revealed that gamma oscillations (40–100 Hz) occurred in all hippocampal subfields, correlated with theta oscillations, and had

the highest power in the dentate gyrus (123). Interestingly, this study found that bilateral lesions of the entorhinal cortex attenuated or ablated the oscillation in the dentate gyrus but revealed a slower (25–50 Hz), larger amplitude gamma oscillation occurring in the CA3 to CA1 network (123). This study demonstrated that there are two hippocampal gamma oscillators, one in the dentate gyrus and one in the CA3-CA1 network, with the former requiring input from extrahippocampal regions. A follow-up study of the intrahippocampal oscillator found that gamma oscillations were generated within the recurrent network of CA3 by interactions between pyramidal cells and interneurons, and that gamma oscillations in CA1 were entrained by CA3 pyramidal cells driving the activity of CA1 interneurons (244).

**1. Interneurons and gamma oscillations in CA3** In vivo experiments demonstrated the essential role of interneurons in driving intrahippocampal gamma oscillations, but the precise cellular mechanisms generating the oscillation can be better dissected using in vitro slice preparations. This intrahippocampal gamma oscillation can also be evoked in hippocampal slices through bath application of the cholinomimetic carbachol, where it occurs at a peak frequency of 40 Hz and appears to be generated in CA3 (138). Carbachol-evoked oscillations are remarkably stable over time (occurring on the order of hours), and persistent gamma oscillations can also be observed through bath application of kainate, both in CA1 (1129) and CA3 (332). Brief epochs of gamma oscillations can also be evoked in vitro by electrical stimulation (1200) or by local application of kainate to s.r. in both CA3 (291, 408) or CA1 (238).

The earliest studies of hippocampal gamma oscillations revealed that inhibitory neurotransmission was essential for their generation. Electrical stimulation of CA1 afferents revealed that gamma oscillations were associated with rhythmic barrages of IPSCs and could be blocked by bicuculline (1200). Persistent carbachol-evoked gamma oscillations observed in vitro require both $GABA_A$ and non-NMDA ionotropic glutamate receptors for their genesis (333). In vivo recordings show that pyramidal cells do not fire on every gamma cycle (123, 244, 997), with in vitro slice experiments suggesting that an individual pyramidal cell fires during ~5% of gamma cycles (333). Further in vitro slice studies of persistent gamma oscillations in CA3 confirmed this and reported that PVBCs were strongly phase-locked to the oscillation (453). This study also found that interneuron-selective interneurons in CA3 were strongly phase-locked with the oscillation; morphological reconstructions of these ISIs revealed cells with dendrites restricted to s.o. and the axon targeting both s.o. and s.r (453). Another in vitro study of kainate-evoked gamma oscillations in CA3 confirmed that individual pyramidal cells fired infrequently while PVBCs and BiCs were both strongly phase-locked to the oscillation (408). Subsequent in vitro slice studies strongly indicated that fast-spiking, perisomatic targeting interneurons were essential for generating gamma rhythms in CA3 (740, 865, 866). Two landmark studies using optogenetic control of PV-expressing interneurons confirmed that silencing PV interneurons impaired gamma oscillations, while driving the cells was sufficient to evoke a gamma-frequency oscillation in vivo in various cortical regions (169, 1027).

**2. Other hippocampal gamma oscillators** Although the term gamma oscillation is given to any oscillation occurring between 30 and 90 Hz, it is becoming clear that this broad term encompasses several distinct network rhythms (154, 216). Gamma oscillations are also apparent in CA1 and can be further parsed by peak frequency into two bands [slow (~40 Hz) and fast gamma (~90 Hz) (215)] or into three bands [slow (30–50 Hz), mid-frequency (50–90 Hz), and fast/epsilon (90–150 Hz) (87)]. Slow gamma in CA1 is coherent with CA3 gamma (215) and is strongest in s.r. (87), indicating that it is driven by CA3, while mid-frequency (90 Hz) gamma is coherent with entorhinal gamma (215) and is strongest in s.l.m. (87), indicating that it is driven by the entorhinal cortex. Gamma oscillations generated in CA3 are critically dependent on the interaction between pyramidal cells and PVBCs, as are gamma oscillations in a number of other cortical regions (154), but is this mechanism common to all forms of gamma oscillation?

Theoretically, gamma oscillations can be generated purely through networks of coupled interneurons (interneuron network gamma oscillations, or the ING model) or through reciprocally coupled networks of pyramidal cells and interneurons (pyramidal-interneuron network gamma oscillations, or the PING model) (1201). PING-type oscillations require phasic synaptic excitatory input onto interneurons, while ING-type oscillations can be observed in sparsely connected interneuron networks with just tonic excitatory drive (1132, 1200). In vitro studies of CA3-generated persistent gamma oscillations (332, 333, 408, 1129) show that this gamma rhythm is of the PING type, as is the mid-frequency gamma oscillation observed in isolated slices of medial entorhinal cortex (mEC) (246). It should be noted that, unlike carbachol-induced gamma (333), the kainate-evoked persistent gamma oscillation persists when AMPARs are blocked (332),

showing that both kainate and AMPARs can provide sufficient excitation to generate a gamma rhythm. In CA1, the slow CA3-driven gamma oscillations can be observed using in vitro slices (910). When CA1 is isolated from the rest of the hippocampal network, another gamma oscillation emerges, which is ~10 Hz faster and can be evoked using either carbachol (910) or kainate (786). The carbachol-evoked intrinsic gamma oscillation in CA1 appears also to be a PING-type oscillation with peak pyramidal cell firing slightly preceding peak interneuron firing (910), although no interneuron subtype-specific data were reported in this study.

Craig and colleagues (238) conducted an in vitro survey of the behavior of CA1 interneurons during gamma oscillations, using local application of kainate to evoke brief epochs of gamma oscillation without chronic application of drugs. This experimental paradigm produces a mid-frequency gamma oscillation intrinsically generated in CA1, which is 11 Hz faster but of a lower power than CA3 gamma and, unlike CA3, could still be evoked during optogenetic inhibition of pyramidal cell firing (238), consistent with an ING-type gamma. PVBCs displayed strong, phase-locked firing in CA3, but had a much lower firing frequency in CA1, and exhibited no phase preference. In CA1, they found that MGE-derived BiCs and AACs were strongly phase-locked to the oscillation, as were CGE-derived putative trilaminar cells and back-projecting interneurons (238). Unlike other forms of gamma oscillation studied in vitro, they found that PVBCs were not essential for kainate-evoked CA1 gamma. Similar results can be seen in CA1 in vivo, where PVBCs drive gamma oscillations around s.p. but not in distal s.r. or s.l.m. (637). Indeed, in vivo recordings show that CA1 PVBCs are only weakly modulated by gamma oscillations (1142). In mEC, PVBCs modulate slow NMDAR-dependent, but not mid-frequency NMDAR-independent gamma oscillations (786). Mid-frequency ING-like gamma oscillations can be evoked using local application of extracellular potassium in DG slices, and fast gamma oscillations can be evoked in DG even in the absence of synaptic transmission (1124). Together, these studies reinforce the observation that several qualitatively different gamma oscillations coexist (154) and that PVBCs are often, but not always, a key driver of gamma rhythms. Interestingly, in vivo recordings show that CA1 dendrite-targeting BiCs show the strongest depth of gamma modulation (1142). The preferred in vivo gamma firing phase of identified CA1 interneurons is summarized in FIGURE 22H.

While gamma oscillations are strongly correlated with numerous cognitive tasks such as attention, working memory, and conceptual categorization (302), some authors argue that gamma oscillations serve no functional role beyond homeostatic matching of inhibition in response to increased excitation (784). However, the consensus opinion in the field is that gamma oscillations are essential for neural computation and that they provide a temporal window that allows functionally coupled neurons or ensembles to interact both locally and across long distances (302, 360, 361, 1018). Regardless of whether gamma oscillations are essential to cognition or epiphenomenal, deficits in gamma oscillations correlate with deficits in interneuron and circuit function seen in many pathological conditions (670, 1151). Thus gamma oscillations provide a useful assay of network function that can be carried out in vitro, which can reliably predict deficits in behavioral tasks.

### B. Sharp Wave-Ripple Oscillations

Hippocampal sharp wave-ripples (SWRs) are irregular, synchronous bursts found in the hippocampus, which occur as slow sharp waves (0.1–3 Hz, most prominent in s.r.) and associated ripples (~200 Hz). SWRs occur most frequently during slow-wave sleep, but can also be observed during periods of immobility in freely moving animals (149, 848). Early work found that SWRs were associated with population bursts of pyramidal cells along with increased firing of interneurons and dentate granule cells (149). The first in vivo studies supported the notion that SWRs generally initiate from a population burst of CA3 pyramidal cells, which then triggers a subsequent burst in CA1 (243); it seems that individual ripples do not propagate to CA1 but that a burst of activity in CA3 provides sufficient excitation to locally generate a ripple in CA1 (118, 1064). A recent study confirmed that SWRs occur in CA3 before "spreading" to CA1, but found that pyramidal cells in CA2 became active before synchronous firing in CA3, stongly implying that CA2 is the site of SWR generation in vivo, especially during awake states (861). In CA1, neurons that fire together during exploratory behavior also coactivate in SWRs occurring during periods of slow-wave sleep following the behavioral task (851), suggesting that SWRs during sleep represent a reactivation, and thus consolidation, of waking memories (850). Blocking SWR generation in CA3 reduces the incidence of SWRs seen in CA1 and impairs consolidation of memory (823).

Early studies of SWRs revealed that interneurons were active during this oscillation (149), but the first interneuron subtype-specific information came from elegant in vivo juxtacellular recordings in anesthetized rats spearheaded by Peter Somogyi, Thomas Klausberger, and colleagues. Of the dendrite targeting interneurons, O-LM cells (582), and CCK-expressing PPA interneurons (584) are silent while PV/SOM-expressing BiCs (583) fire during SWRs. Of the perisomatic-targeting interneurons, AACs are silent during SWRs (582) while PVBCs are very active (582, 584); CCKBCs do not display a homogeneous firing pattern during SWRs, with some becoming more active and others become less (584). These in vivo experiments in anesthetized animals reveal that pyramidal cells, PVBCs, and BiCs are the most active during SWRs (586). Later work in unanesthetized animals (FIGURE 22, A–F) confirmed that PVBCs are very active during SWRs (635, 1161) but additionaly that O-LM cells do fire during SWRs in awake states (1161). IvCs do not seem to participate in SWRs (366, 1081).

While in vivo juxtacellular recordings provide the gold standard for observing interneuron behavior in network activity, in vitro models provide a complementary system that allows manipulation of neural circuitry. Like gamma oscillations, SWRs can be observed in vitro in CA3 in interface conditions (609), or in submerged conditions when adequately oxygenated (450). SWRs can originate from any CA3 subfield, although they are most likely to begin in CA3b (301). In CA3, generation of SWRs depends on both AMPA and $GABA_A$ receptors, with only a small number of pyramidal cells firing during an individual SWR (301, 451). PVBCs greatly increase their firing during SWRs (451) and, remarkably, stimulating a single PVBC is sufficient to generate a SWR in vitro (301). Of the other interneuron types in CA3, IvCs are silent but most other interneuron types fire, with no overall significant difference in firing rate between perisomatic targeting interneurons (PVBCs, AACs, and CCKBCs) and dendritic targeting cells (O-LM cells, s.o.-s.o. cells, s.o.-s.r. cells, and s.r. cells) (451). During SWRs, the predominant synaptic input to pyramidal cells is inhibitory while the dominant input to all firing interneurons is excitatory (451). Perisomatic inhibition via PVBCs is one of the main sources of the large extracellular field signal seen in s.r. during SWRs (451).

For SWRs generated in CA1, pyramidal cell activity is also essential both in vitro (56) and in vivo (1050). The firing of CA1 perisomatic targeting interneurons is phase-locked to SWRs in vitro (56), and local $GABA_A$ receptor-mediated inhibition is critical for SWR generation. Optogenetic activation of pyramidal cells can induce a SWR in vivo, and while activation of PV-containing interneurons does not generate a ripple, they can pace the rate of ensemble firing (1050). Interestingly, while O-LM cells are silent during SWRs in CA3 (582), they are recruited into CA1 SWRs in vivo (879), so it seems that similar, but not identical, mechanisms drive the generation of SWRs in CA3 and CA1.

### C. Slow Oscillations

In the hippocampus, SWRs are the prominent oscillation associated with slow-wave sleep and memory consolidation. In cortical areas, including the entorhinal cortex, the dominant network rhythm during slow-wave sleep is the slow oscillation. During the slow oscillation, cortical neurons display synchronous bursts of depolarization (Up states) punctuated by periods of relative quiescence (Down states) and oscillate between up and down states at frequencies of <1 Hz (1054). Cortical up and down states modulate SWR activity during slow-wave sleep (73, 445, 532, 1009, 1021), and the slow oscillation is ubiquitous to all cortical regions. Up states can initiate in any layer in the cortex, likely due to spontaneous synaptic events (192), and although slow oscillations can be generated within the cortex alone (1103), the thalamus is also important for their generation in vivo (242). As might be expected for an oscillation associated with sleep, in vivo activation of cholinergic neurons in the medial septum strongly reduces the power of neocortical slow oscillations (1158).

Many mechanistic insights into the cellular circuitry that generates up and down states have come from in vitro slice experiments, where the oscillation can be observed using "in vivo-like" artificial cerebrospinal fluid containing low concentrations of calcium and magnesium (974). Up states are sustained through a balance of recurrent fast ionotropic excitatory and inhibitory neurotransmission, where inhibitory conductances dynamically scale to match excitation, both in vitro (219, 1007) and in vivo (446). Slow $GABA_B$R-mediated inhibition is also important for terminating up states in vitro (738), with postsynaptic $GABA_B$Rs needed for afferent-evoked termination of up states (236); although this mechanism has yet to be confirmed in vivo, a number of converging lines of evidence suggest that it should exist (237).

During up states, principal cells receive strong inhibitory conductances in ferret prefrontal cortex (1007), rat mEC (738), and mouse barrel cortex (831). PVBCs have the highest firing rate of any interneuron subtype during up states in both barrel cortex and mEC and receive more excitatory than inhibitory conductances (831). In barrel cortex, SST-expressing interneurons are moderately active during up states in barrel cortex (315, 831), where they regulate the excitability of pyramidal cells (830), but fire only sparsely in mEC (831, 1080). Similarly, VIP-expressing cells are active during up states in the barrel cortex (831), although they do not affect pyramidal cell firing (830). Unlike in the barrel cortex, VIP-expressing interneurons are almost completely silent during mEC up states, while NPY-expressing interneurons are rarely active during cortical up states in either mEC or barrel cortex (831, 1080). The role of ionotropic glutamate receptors in sustaining up states is also divergent between barrel cortex and mEC, with NMDAR important for the former, while kainate receptors are important in the latter (273). While the slow oscillation is common to all cortical regions, these studies advise caution when trying to make generalizations about interneuron function during network states. Given the unusual circuitry of the entorhinal cortex when compared with other cortical regions (163), it is perhaps not surprising that interneuron behavior during network activity is different.

In vivo recordings show that, in PFC, pyramidal cells and PVBCs fire rapidly at the beginning of up states, while AACs fire more than 200 ms after their onset, at around half the frequency of basket cells (760). Similarly, PV-containing interneurons are also very active during up states in both barrel (392) and visual (915) cortices, with SST cells also participating in slow oscillations in vivo (915). Earlier in vivo studies also reported that PVBCs are very active during up states in ferret prefrontal cortex (446). Deleting GAD67 from PV-containing interneurons leads to shorter up states with more multiunit firing, while deleting GAD67 from SST-expressing interneurons has the opposite effect (615), supporting in vitro observations that these two groups of interneurons are likely important for controlling excitation during up states.

### D. Theta Oscillations

The hippocampal theta oscillation (4–10 Hz) is apparent during voluntary movements and REM sleep, where the oscillation modulates the timing of action potentials (848, 936, 1159). Gamma oscillations are often nested within theta oscillations in vivo, such that the amplitude of the gamma oscillation varies in phase with the theta rhythm (153). Indeed, optogenetic stimulation of CA1 pyramidal cells at theta frequencies is sufficient to evoke gamma rhythms in vitro (146). In vivo, theta oscillations are most regular and have the highest amplitude in CA1 s.l.m., require glutamatergic input from the entorhinal cortex and cholinergic input from the medial septum, and can also be generated in CA3 (reviewed in Ref. 150). However, in vitro experiments using isolated whole hippocampus preparations show that CA1 can intrinsically generate spontaneous theta oscillations without the application of drugs (429). Surprisingly, the same group also found that the subiculum can generate theta oscillations that "reverse propagate" through CA1 to entrain network rhythms in CA3 (526).

Excitatory pyramidal cells make an important contribution to generating theta oscillations in vivo, with both recurrent connectivity and intrinsic membrane oscillations playing a role (150). However, interneurons also appear to be critical (153), and a single PVBC can phase-lock the firing of CA1 pyramidal cells at theta frequencies (210). BiCs and PVBCs are both phase-locked to CA1 theta oscillations, as are AACs and O-LM cells (582, 583). IvCs fire sparsely during theta oscillations but are phase-locked to the trough (366), and modulate their firing rate in response to the frequency of the theta oscillation (635). CCK-expressing interneurons, although representing a morphologically diverse group of neurons, seem to have a relatively homogeneous, but similarly phase-locked, firing behavior during theta oscillations in CA1 (584, 1142). However, in CA3, CCK-expressing interneurons display divergent behaviors with CCKBCs- and dendrite targeting-cells firing at the peak, and PPA interneurons firing at the trough, of the CA1 theta oscillation (638). Inhibitory input onto PV-containing interneurons is essential for the coupling of gamma and theta oscillations in CA1; deleting $GABA_A$ receptors from PV-containing interneurons also greatly reduces the amplitude of CA1 theta oscillations but has no effect on gamma oscillations (1222). More direct evidence for PV-containing interneuron involvement in the generation of theta oscillations come from optogenetic experiments, which show that PV-containing interneurons can entrain hippocampal networks more effectively than pyramidal cells to resonate at theta frequencies in

vivo (1049). Inhibiting PV-containing interneurons strongly impairs intrinsically generated CA1 theta oscillations in whole hippocampal preparations in vitro, while inhibiting SST interneurons has only a modest effect (31). The preferred in vivo theta firing phase of identified CA1 interneurons is summarized in FIGURE 22G.

While we tend to think of transmission through the hippocampus as being a unidirectional flow of excitatory projections, the subiculum-generated theta oscillation can propagate "backward" through the hippocampus via inhibitory mechanisms, with optogenetic activation of subicular PV-containing interneurons sufficient to drive network activity in CA3 (526). This result shouldn't be too surprising, given that in vivo labeling studies describe interneurons in CA1 that project to both CA3 and the subiculum, and which show firing phase-locked with the theta rhythm and SWRs (536, 1014). At least some of these back-projecting interneurons are CGE-derived and also participate in network rhythms in vitro (238). The spike timing of pyramidal cell firing relative to the phase of the theta rhythm is believed to encode spatially-relevant information: as an animal progresses through the place field for a particular pyramidal cell, the cell will fire at progressively earlier points in the theta cycle, a phenomenon that is termed "phase precession" (849). This was initially assumed to be a feature unique to pyramidal cells, but later studies demonstrated that interneurons in CA1 also display phase-precession (297), implying that interneurons also have an important role in information processing.

So far, we have considered the role of interneurons in shaping neuronal oscillations, which is a key aspect of how interneurons behave and influence network function. We will now broaden our focus to consider how interneurons regulate the development of neural circuits, and how different interneuron types can influence network function in the context of behavior.

### E. Interneuron Broad Subtypes and Behavior

The advent of optogenetic (266) and pharmacogenetic (1153) tools, combined with interneuron-specific Cre driver lines (1096), means that it is now possible to study the effects of selectively manipulating identified groups of interneurons in vivo on circuit function and behavior. For in vivo experiments, interneurons are often parsed into three groups that, in the cortex at least, are nonoverlapping: PV containing, SST containing, or VIP/5-$HT3_A$R expressing (966, 1237). In the hippocampus, this grouping does not quite hold, as some interneurons express both SST and 5HT3a receptors (e.g., subset of O-LM cells) and some interneurons express both PV- and SST (e.g., BiCs) (74, 203, 1138). Two recent reviews discuss how these broad interneuron subtypes alter their activity during behavior and how neuromodulators affect their activity in vivo (1197), and discuss the function of interneurons in intact circuits (956). Instead of recapitulating much of the content of these reviews, we will briefly discuss the consequences of manipulating interneuron activity during hippocampus-dependent behavioral tasks.

Global reductions in excitatory input onto PV-containing interneurons impair performance in cognitive functions dependent on the hippocampus such as spatial working memory (365, 886) without affecting reference memory (365). Directly inhibiting synaptic release from PV-containing interneurons locally in CA1 confirms that PV-containing interneurons in this region are essential for spatial working memory but do not contribute to reference memory (818). Recent evidence shows that hippocampal PVBCs can be further subdivided by their birth date during embryogenesis, with each subtype having different roles in learning: early-born PVBCs contribute to learning associations while late-born PVBCs contribute to acquiring new knowledge (279). PV-containing interneurons are also important for maintaining memory, as mice with enhanced PV-containing interneuron function show reduced extinction of fear memory in behavioral tasks, as well as increased frequency of SWRs in hippocampal slices (158). However, PV-containing interneurons in CA1 are not required for memory acquisition in contextual fear conditioning (CFC) tasks, which instead is dependent on SST-expressing interneurons in s.o. that target s.l.m. (702). During CFC acquisition, these SST interneurons (presumably O-LM cells) become activated by cholinergic inputs from the medial septum and seem to block nonsalient sensory information arriving from glutamatergic entorhinal projections onto the distal dendrites of CA1 pyramidal cells (702). The entorhinal cortex also sends inhibitory projections to the hippocampus (781), and inhibitory projections from lateral entorhinal cortex (LEC) are important for efficient learning of context in CFC and novel object recognition tasks, where they inhibit the activity of CA1 s.r. and s.l.m. CCK-expressing interneurons to increase excitation of pyramidal cells by disinhibition (69). Interestingly, LEC inhibitory projections to CA1 were

not required for either hippocampus-dependent learning task, but blocking their activity caused overgeneralization of contextual cues (69). Additionally, SST-expressing interneurons in the dentate gyrus control which granule cells become incorporated into the ensemble that encodes a memory trace in CFC, while PV-containing interneurons are not involved in this process (1051).

In addition to memory, one of the other main functions attributed to the hippocampus is spatial navigation (847). Pyramidal cells are well-known to be place cells, so are most associated with the encoding of spatially-relevant information, but emerging evidence suggests that interneurons also have an important function in navigation (reviewed in Refs. 239, 407). Interneurons also show discrete place fields (1207), which can be inverted relative to pyramidal cells (462), implying that the interneurons are not just driven by principal cells but can actively shape place fields through disinhibitory mechanisms. The latter study did not unequivocally identify the interneurons involved, but their firing properties and theta phase preference implied that they were perisomatic-targeting interneurons (462). Loss of gap junctions between interneurons is sufficient to interfere with short-term spatial memory and the relative firing of place cells relative to the theta oscillation (24). Optogenetic silencing shows that PV-containing interneurons control the spike timing of place cells relative to the theta oscillation and that SST interneurons control the firing rate of place cells (958), implying different functions in the coding of spatial information. Glutamatergic projections from the medial septum to interneurons located in the alveus/s.o. are also important for entraining place cell firing to the theta oscillation during locomotion (368). Interestingly, evidence suggests that while interneurons are important for controlling principal cell firing within their place field, inhibitory interneurons appear not to affect the overall spatial scale of place fields (513, 958), with evidence also suggesting that PV-containing interneurons do not contribute to grid formation in mEC (134).

Hippocampal interneurons play an important role in controlling network rhythms and in cognitive processes such as memory and spatial navigation, especially MGE-derived interneurons such as those expressing PV and SST. Indeed, it is hard not to assume that PVBCs do all the heavy lifting in terms of network function, given how much research focuses on them. While these perisomatic targeting interneurons are clearly essential to many processes, questions remain over what role the other subtypes play in network function, especially CGE-derived interneurons. Identifying how CCK-expressing interneurons modulate behavior will be particularly challenging using genetic targeting approaches, as interneurons from this broad subtype display remarkably diverse firing patterns in vivo (FIGURE 23). Future experiments, combined with more specific genetic tools to improve subtype-specific selectivity, should help address these questions.

## XVI. INTERNEURONS AND NEURAL CIRCUIT DISORDERS

Considering the critical role that interneurons have in controlling neuronal network function, it should not come as a surprise that dysfunctional inhibitory neurotransmission has been implicated in numerous neurological and psychiatric disorders. From neurodegenerative conditions like Alzheimer's disease through to psychiatric disorders such as schizophrenia, disruptions in the function, or a specific loss of, inhibitory interneurons appears to underlie at least some of the cognitive impairments associated with these conditions. In this section, we will discuss pathologies affecting interneurons by parsing disorders into three broad groups: developmental disorders (such as autism), neurological disorders (such as epilepsy, stroke, or dementia), or psychiatric disorders (such as major depression). However, it should be borne in mind that some disorders resist such a simple categorization. The most obvious example is schizophrenia, which is a complex psychiatric disorder that clearly has a developmental component, but where environmental factors also contribute to its etiology.

### A. Developmental Disorders of Interneuron Circuits

One of the most sensitive periods for the developing brain is during embryogenesis and early postnatal development, when perturbations during phases of rapid neuronal proliferation and migration can have profound consequences for the developing brain. Glutamatergic neurons undergo radial migration during development, and disruption of this process has been associated with a number of human conditions such as lissencephaly and periventricular heterotopia (402). Similarly, disruptions to interneuron development can cause severe congenital brain injury. In addition to functioning as a neurotransmitter, GABA is also an

important neurotrophic signaling molecule in the developing brain, acting through both inotropic $GABA_A$ and metabotropic $GABA_B$Rs (373), so disruptions in GABAergic signaling can severely affect brain development. This is highlighted by conditions such as fetal alcohol syndrome, where prenatal exposure to alcohol can cause abnormal gross morphology of the brain and intellectual disability (953); animal models show that early exposure to ethanol disrupts the tangential migration of MGE-derived interneurons by increasing GABA concentrations in the embryonic brain (248), and can cause shrinkage of the dendrites of PV-containing interneurons (259). Antiepileptic drugs (AEDs) are also known to be teratogens that increase the likelihood of neurological problems, with valproate being one of the AEDs most likely to cause fetal anticonvulsant syndrome (895). Animal models suggest that AEDs that increase concentrations of GABA in the developing brain are more likely to cause neurological defects through the mechanisms of impaired migration and cell death (737). Numerous other genes and trophic factors can affect interneuron migration (see sect. III). One such gene is X-linked aristaless homeobox gene (ARX), mutations in which cause several neurological syndromes in humans (685). While ARX is most associated with migration of glutamatergic neurons, it also controls interneuron migration, and interneuron-specific deletion of ARX causes a developmental epilepsy phenotype in mice resembling that observed in heterozygous human carriers of ARX mutations (753).

**1. Autism and related disorders** The term Autism Spectrum Disorder (ASD) is given to a wide range of neurodevelopmental disorders of complex or unknown etiology, but which share a number of common features including an onset in the early developmental period, impaired social interaction and communication, and stereotyped or repetitive behaviors; these features can vary in the degree of severity (693). Fragile X syndrome and Rett syndrome both cause autistic phenotypes, but they are often not considered ASDs (1). Many of those with Fragile X syndrome who display autistic-like phenotypes do not meet the DSM criteria for ASD (133), and Rett syndrome was removed from the ASD category in DSM-V (1182). The pathophysiology of ASD is believed to involve perturbations in synaptogenesis and synaptic pruning during critical developmental periods, which disrupt the assembly and function of neural circuits and lead to alterations in excitatory-inhibitory balance; many of those with ASD exhibit seizures and abnormal EEG activity (120, 962). Genome-wide association studies have found that ASD has a strong genetic link (520), with recent work suggesting that a large number of ASD cases are caused by de novo mutations in genes that are highly expressed in the brain during embryogenesis (521). Several genes acting on the mTOR pathway, such as NF1, Tsc1/Tsc2, and PTEN, have been implicated in ASD, as have mutations in the NRXN-NLGN-SHANK pathway (120, 962). The brains of those with ASD tend to be larger than normal, and although they frequently have more neurons, the dendritic arbors of those neurons are often less complex (reviewed in Ref. 693).

Animal models carrying mutations or deletions of genes implicated in ASD have provided valuable insights into circuit-level disruptions in ASD. For example, deleting Tsc1 from CA1 pyramidal cells increases mTOR activity and causes a reduction in inhibitory input, leading to hyperexcitability in the network (70). Similarly, selectively deleting Tsc1 from MGE interneurons also increases excitability in hippocampal networks, due to both a loss of interneurons and disrupted migration during development (362). EphA7, a receptor tyrosine kinase, is essential for stabilizing inhibitory synapses from PVBCs onto dentate granule cells, through mTOR-dependent mechanisms; knocking down EphA7 activity in adults is sufficient to impair learning (101). Mutations in EphA7 and EphA3 have been linked to ASD in humans, and mice lacking the ligands for these receptors also display behavioral deficits consistent with ASD (1223). Mutations in the SHANK family of genes are also strongly associated with ASD (534). Shank1 is highly expressed in PV-containing interneurons and regulates their excitatory input; mice lacking Shank1 show reduced basal firing of hippocampal PV-containing interneurons and an excitatory shift in excitation/inhibition balance (742). Recent evidence suggests that Shank1 mice have an altered excitation/inhibition balance because of a loss of the PV protein itself, as opposed to a loss of neurons (327). Mice lacking CNTNAP2, another gene associated with ASD, show hyperexcitability, impaired neuron migration, and a loss of NPY-, PV-, and CR-expressing interneurons, along with behavioral deficits including impaired social interactions, stereotypic movements, behavioral inflexibility, and hyperactivity (892). Hippocampal slices from mice lacking CNTNAP2 show normal excitatory neurotransmission; however, CA1 pyramidal cells show deficits in perisomatic, but not dendritic, evoked IPSCs (544).

Both Fragile X syndrome and Rett syndrome are associated with impaired inhibitory function, with each caused by a single mutant gene (FMR1 and MECP2, respectively), which leads to circuit dysfunction due to impaired excitation/inhibition balance (387). Given that both syndromes are caused by a mutation in a single gene, they can be reliably modeled using transgenic mice. Most of those with Fragile X syndrome show a degree of developmental delay or intellectual disability, particularly in short-term memory and executive function (385, 458), and up to 60% of Fragile X syndrome cases show some autistic features (133). Mouse models show that loss of FMR1 leads to reductions in tonic but not phasic GABAergic inhibition onto pyramidal cells, implying a loss of extrasynaptic GABA receptors (247). FMR1 knockout mice also show reduced excitatory input onto fast-spiking interneurons but increased inhibitory input onto SST-expressing interneurons (396). The net effect at the network level is hyperexcitability, which is apparent through prolonged Up states that show impaired synchrony of IPSCs (396). Studies on Drosophila show that the protein encoded by FMR1 differently regulates intracellular calcium signaling in interneurons and excitatory cells during a critical developmental period that is essential for synaptogenesis and achieving the appropriate excitation/inhibition balance (278). As may be expected with a disrupted excitation/inhibition balance, those with Fragile X syndrome have an increased risk of epilepsy (385).

Rett sydrome is caused by mutations in the X-linked gene MECP2 that cause a loss of function in the protein MeCP2 and is characterized by normal development up until 18 mo of age, followed by a gradual loss of language and motor skills, along with the development of microcephaly, autistic features, seizures, and ataxia (32). Mouse models of Rett syndrome show that cortical networks display altered excitation/inhibition balance, with reduced excitation in both cortical (254) and hippocampal (1267) networks. Principal cells in MECP2 knockout mice do not show a reduction in spontaneous inhibitory inputs (254), but electrical stimulation in CA3 reveals a hyperexcitable phenotype as it evokes spontaneous sharp-wave like events in knockout, but not wild-type, mice (1267). The onset of hippocampal hyperexcitability in MECP2 knockout mice occurs in early adulthood and correlates with the onset of Rett Syndrome symptoms (156). Hyperexcitability suggests that interneuron-specific deficits may occur in Rett syndrome. This was confirmed by the finding that selectively deleting MECP2 from inhibitory interneurons recapitulates many features of Rett syndrome including impaired motor function and autism-like behaviors, as well as reduced GABA release and hyperexcitability in slices (190). PVBCs in CA3 of MECP2 knockout mice show reduced excitatory input, which points towards a failure in recruitment of inhibition being the cause of hyperexcitability in Rett syndrome (157). Compared with glutamatergic cells and SST-expressing interneurons, MeCP2 is highly expressed in cortical PV- and calretinin-containing interneurons (1105), and biochemical fractionation experiments show that MeCP2 is found in the postsynaptic domain (3). MeCP2 is phosphorylated in neurons in an activity-dependent manner, and this phosphorylation regulates dendritic growth and spine maturation (1274). These lines of evidence support the hypothesis that the cognitive deficits in Rett syndrome are, at least in part, caused by a failure in maturation of excitatory synapses onto inhibitory interneurons, particularly PVBCs. This is supported by recent evidence showing that deleting MECP2 from PV-containing interneurons is sufficient to induce the same circuit-level deficits in visual cortex that occur in a global MECP2 knockout mouse (59).

In summary, while ASD and disorders such as Fragile X syndrome and Rett syndrome each have different underlying genetic causes, it seems that these multiple developmental pathways converge upon similar mechanisms of disrupted inhibitory interneuron function. Studying the commonalities between these disorders may lead to greater understanding both of the pathological changes occurring in inhibitory circuits and how these circuits relate to behavior in healthy, physiological conditions.

**2. Schizophrenia** Schizophrenia is a complex psychiatric disorder or spectrum of disorders that generally has an onset in early adulthood and is associated with psychosis and hallucinations (positive symptoms), as well as loss of motivation, social withdrawal, cognitive impairments (negative symptoms), and affective dysregulation (where the patient experiences manic and depressive episodes). Although schizophrenia has a very high heritability (80%), the disorder does not have a single genetic cause, but rather appears to require further environmental factors to precipitate the illness in those with a genetic predisposition (1157). Numerous genes have been proposed to have a strong role in causing schizophrenia, including DISC1 (791), Neuregulin1 (1052), and COMT (295), but no significant linkage of historical schizophrenia candidate genes has emerged from large genome-wide association studies (318). The genetics of schizophrenia remain highly contentious. Recent insights from rare but highly penetrant mutations suggest

that changes in levels of gene expression or gene dose, as opposed to mutations in individual genes, can have a causal role in schizophrenia. Variations in the copy number of genes (CNVs) are widespread in normal genomes and can be caused by de novo microdeletions or duplications of small chromosomal regions. It is becoming clear that multiple CNVs can confer a very high risk for disorders such as schizophrenia or autism (735). For example, up to one-third of those carrying microdeletions at the 22q11.2 region develop schizophrenia or schizoaffective disorder (reviewed in Ref. 551). CNVs at both the 22q11.2 and 16p11.2 loci confer a very high risk of both ASD and schizophrenia (286, 496, 551, 1078), which strongly implies that common developmental mechanisms underlie the pathology in at least some forms of these disorders. For example, the regulation of interneuron migration by Cxcr4 is disrupted in 22q11.2 deletion syndrome (780), and this gene is also involved in the correct targeting of thalamocortical axons (2), so this provides at least one mechanism that could underlie the etiology of both ASD and schizophrenia. While the causes of schizophrenia remain controversial, a wealth of evidence points towards deficits in neural circuits and interneuron function as being key factors in the pathophysiology of the disorder (670, 683, 745).

Reductions in CB levels in schizophrenic post-mortem brains have been reported for prefrontal cortex (PFC) (77), anterior cingulate cortex (ACC) (232), and planum temporale (187). Postmortem studies of PV expression in schizophrenic patients are more controversial, with studies showing either decreases (77) or no change (1216) for PFC, no changes being reported in ACC (232), but with large decreases in PV levels reported for the hippocampus (1272) (FIGURE 24, A–D). These differences could be due to differences in methodology or medication of patients, or may suggest that schizophrenia-related changes to interneurons are restricted to specific circuits. Interestingly, rearing rats in social isolation from weaning is sufficient to elicit behavioral changes reminiscent of schizophrenia and leads to reductions in hippocampal levels of PV and CB (468), raising questions about the causal relationship between neurochemical changes and behavioral symptoms in schizophrenia. Although the results of post-mortem studies vary in the detail of interneuron types affected, there are clear overall deficits in inhibitory interneurons: one of the most consistent findings in post-mortem brains of schizophrenics is a reduction in prefrontal expression of GAD67 (but not GAD65), as well as lower levels of CB and reelin (reviewed in Ref. 588). Functional studies of schizophrenic patients also point to clear deficits in circuits involving interneurons, with decreases in gamma oscillation power and synchrony reported in many studies of schizophrenia, including those carried out in unmedicated patients and nonschizophrenic first-order relatives (reviewed in Ref. 1209).

A key outstanding unknown in the pathophysiology of schizophrenia is the relationship between the observed changes in interneuron numbers to and dysfunction in neural circuits. At the circuit level, schizophrenic patients consistently show deficits in gamma oscillations (reviewed in Refs. 683, 745), consistent with deficits in PV-containing interneuron function. Furthermore, numerous studies report that schizophrenic patients have impaired synchrony between the hippocampus and prefrontal cortex, both at rest and during working memory tasks, and the degree of impairment correlates with the severity of some symptoms (reviewed in Ref. 412). Hyperactivity in the dopaminergic system was initially believed to be an underlying causal factor in schizophrenia as drugs that activate this system mimic positive symptoms of schizophrenia, but more recent theories suggest that impaired glutamatergic neurotransmission (NMDA hypofunction model) is causative because drugs such as phencyclidine, which are NMDAR antagonists, reproduce both positive and negative symptoms in humans (683).

Disruption of NMDAR function specifically in PV-containing interneurons has been suggested as a causal factor in schizophrenia. Deleting GluN1 from a mixed population of neurons (around 70% of which express PV) early in development causes schizophrenia-related behaviors, including hyperactivity and impaired social memory, spatial working memory, and prepulse inhibition (82). However, this model also deleted GluN1 from NPY-expressing interneurons and a small number of pyramidal cells, and deficits were only observed if the deletion occurred early in development, as opposed to in adult mice (82) (FIGURE 24, E–G). Another study where GluN1 was deleted specifically from PV-containing interneurons also found impairments in neural synchrony and spatial working memory (599). However, additional studies report that mice lacking NMDARs in PV-containing cells show only modest impairments (170) or are indistinguishable from controls (103, 155, 979) in tests of working memory and other behaviors relevant to schizophrenia. One of the main arguments in favor of a PV-containing interneuron-specific

deficit in NMDAR function is the finding that, unlike wild-type controls, mice lacking NMDARs in these interneurons do not show increased hyperlocomotion when exposed to the NMDAR antagonist MK801 (82, 170). However, more recent work has shown that mice with PV-specific deletions of GluN1 are actually more sensitive to the effects of MK801, compared with wild-type control. MK801 induces stereotyped behaviors and catalepsy in these mice (FIGURE 24, H–J), which confounds experimental measures of hyperlocomotive behavior, as well as impairments in working memory and large amplitudes in delta oscillations in PFC (155). This later study presents evidence against the hypothesis that a PV-containing interneuron-specific dysfunction of NMDARs underlies schizophrenia-related behavioral deficits, but does support the model that NMDARs on other neurons are important to the pathophysiology. Indeed, PV-containing interneurons show very small NMDA currents relative to other interneuron types (763). The studies showing more modest or no behavioral deficits used the PV promoter to drive deletion of NMDARs (103, 155, 170, 979), so NMDARs would function in these neurons during early postnatal development, while the report showing the strongest effect was when NMDARs were deleted from multiple cell types early in development (82). Together, these data suggest that dysfunction in NMDAR signaling during development is more likely than a mature PV-containing interneuron specific deficit in NMDAR function to cause schizophrenia-related behavioral deficits.

### B. Neurological Disorders Involving Interneuron Function

In addition to developmental disorders such as ASD, the pathophysiology of myriad neurological conditions, from epilepsy to Alzheimer's disease, involves dysfunction of interneuron function. Indeed, even diseases not commonly considered neurological diseases can affect interneuron function. For example, human immunodeficiency virus (HIV) is most commonly associated with the immune system, but some patients also develop HIV-associated neurocognitive disorders (41, 767). This syndrome is associated with hippocampal pathology, and expression of an HIV protein, HIV-1 Tat, in mice causes impaired cognitive function and a selective loss of several MGE-derived interneurons, including those expressing PV, SST, and nNOS (750). In addition to HIV, infection by several other neurotropic viruses, as well as the associated inflammatory immune response, can lead to neurological pathology (708); herpes simplex virus 1 preferentially targets the hippocampus, and infection increases hippocampal excitability and the risk of seizures (1220). Maternal infection with influenza or other viruses during pregnancy is believed to increase the risk of schizophrenia in offspring (111), with mouse models showing similar deficits in schizophrenia-related behaviors and reduced expression of mGluR2 and 5-HT$2_A$ receptors (804).

**1. Epilepsy** Epilepsy is a broad term applied to neurological conditions in which the patient suffers from a recurrence of epileptic seizures (334), which can vary from almost undetectable brief absence seizures to long tonic-clonic seizures, but always involve abnormal rhythmic firing of large ensembles of neurons. Epilepsy can be caused by acute traumas such as head injury or stroke, or can occur due to genetic mutations and/or as a comorbidity in other neurodevelopmental disorders (188). While AEDs can control seizures in many patients, they are associated with a range of adverse effects, and up to 35% of patients do not respond to treatment (987). Numerous animal models of epilepsy exist, and commonly used models include kindling via repeated electrical stimulation, or through use of excitotoxic agents such as systemic injection of pilocarpine or intrahippocampal injection of kainic acid; in all cases, animals develop spontaneous recurrent seizures after a latency period (696). While these models do have limitations (e.g., Refs. 436, 697), they have provided useful insights into the circuit mechanisms underlying seizure genesis. Hippocampal atrophy, especially in CA1, is a common feature in human temporal lobe epilepsy patients (53, 743) and animal models confirm that the dentate gyrus and CA1 are the most vulnerable regions (356).

In a rat kindling model, development of spontaneous seizures was associated with a loss of CCK-expressing interneurons in the dentate gyrus (981), and a rat pilocarpine model reported a loss of interneurons expressing either SST or PV in CA1 s.o. (276). Interestingly, this latter study found no loss of interneurons that expressed both SST and PV, or SST and CB, and found no significant loss of interneurons in other layers of CA1 (276). Another study, using pilocarpine in mice, found that animals displaying recurrent seizures had a loss of inhibition from CCKBCs onto CA1 pyramidal cells, but that perisomatic inhibition from PVBCs remained intact (1225). In contrast to this pilocarpine model, a study

using intrahippocampal injection of kainic acid found a loss of PV-expressing interneurons that extended beyond the injection site, along with ectopic expression of NPY (759). Interneuron activity also changes in response to epileptogenesis: hippocampal expression of NRG1 increases after electrical stimulation or dosing of pilocarpine and intracerebral infusion of NRG1 delays the onset of seizures (1087). Furthermore, inhibiting endogenous NRG1 or deleting its receptor, ErbB4, from PV-containing interneurons alone is sufficient to exacerbate epileptogenesis in both kindling and pilocarpine models (1087) (FIGURE 25, A–J). A separate study found that NRG1 acts to make PVBCs more excitable by reducing the activity of Kv1.1 and lowering action potential threshold, and this study also found that deleting ErbB4 from PV-containing interneurons increased susceptibility to epilepsy in the pilocarpine model (674) (FIGURE 25, K–N).

Inhibitory neurotransmission also influences the spread of an ictal event through cortical networks, with in vitro slice models showing that feedforward inhibition acts as a "brake" to slow down the spread of ictal events (1135). Neurons in cortical areas adjacent to ictal regions display large barrages of inhibitory events that become excitatory as the ictal event invades that region, with the transition to ictal activity being marked by a large increase in coherence between cells (984). Extracellular recordings from human epileptic patients show a similar EEG pattern to these in vitro models, implying that similar mechanisms may underlie ictal spread in humans (984). Changes in chloride reversal potential due to intracellular $Cl^-$ accumulations may underlie seizure propagation, by switching $GABA_A$ receptor-mediated events from inhibitory to depolarizing and helping drive runaway excitation. Pyramidal cells have been shown to accumulate chloride at the start of a seizure (679), and excitatory GABAergic events driven by PV-containing interneurons onto CA1 pyramidal cells are apparent at the end of epileptiform discharges in in vitro slice models (369). Blockade of KCC2 is sufficient to induce seizure-like activity in hippocampal networks, both in vitro and in vivo (1022), and optogenetic perturbation of intracellular chloride levels can alter the propagation of epileptiform activity (15, 16). Activation of potassium currents by adenosine receptors (A1Rs) can also affect $GABA_A$ receptor-mediated currents in in vitro models of epileptiform activity (518). A1R-dependent activation of potassium channels increases the cell's membrane conductance and acts as a shunting effect on $GABA_AR$ currents to limit the spread of seizure activity. Altogether, these studies show that interneurons are important both in the pathophysiology of epilepsy and in regulating homeostatic responses to hyperexcitability and suggest possible circuit mechanisms that could be targeted to provide more specific treatments for the disorder.

**2. Traumatic brain injury** Traumatic brain injury (TBI) occurs when the brain is damaged by an external force and is associated with two phases: the primary injury and a secondary phase associated with continuing damage and loss of neurons that develops in the days after the injury (717). The secondary injury is caused by several factors, including inflammatory, excitotoxic, and oxidative stresses, caused in part by excessive calcium entry through ionotropic glutamate receptors (1061). The time course of the secondary injury can be very long: in human patients, an initial loss of hippocampal pyramidal cells can be seen in both CA1 and CA3 within 1 wk of TBI, with CA1 but not CA3 progressively showing further cell death 6 mo after the initial injury (764). Animal models of TBI show that inhibitory circuits are also affected. Excitatory neurotransmission increases in injured cortex, and spontaneous inhibitory neurotransmission decreases, and these functional deficits are associated with a selective loss of PV- and SST-expressing interneurons (164). Similarly, reduced inhibitory input to dentate gyrus granule cells occurs after TBI (1122) even though excitatory input to hilar interneurons increases (512), suggesting that compensatory changes in inhibitory circuits occur in response to the injury. Interestingly, TBI to the neocortex is associated with a loss of DG CCK- and PV-containing interneurons, but only in the hilus and not in the granular layer, with no obvious change apparent in CA1 (1122). Even mild TBI is sufficient to reduce the amplitude and frequency of spontaneous IPSCs onto CA1 pyramidal cells, and while no overall loss of neurons occurs, there is also a reduction in GAD67 immunoreactivity apparent 7 days after the injury (28).

**3. Ischemia** Ischemic injury to the brain is associated with a similar pattern of hippocampal damage to that seen in temporal lobe epilepsy in both humans (903) and animal models (580), with a loss of neurons occurring after a delay, particularly in CA1. Immediately after injury, CA1 appears normal, but pyramidal cells gradually die over the next 4 days (580). In addition to excitatory cells, SST- and NPY-expressing interneurons are lost from the hilus in the days following ischemic injury (97). In contrast to pyramidal

cells, the total number of interneurons does not change in CA1 following ischemic injury, but the expression of SST and NPY does decrease, implying functional changes in the interneurons (97). Overall, interneurons are significantly more resistant to hypoxic/ischemic injury than glutamatergic cells (346, 985), perhaps due to differential expression of hypoxia-inducible factor 1α (932). In addition to cell death, ischemic injury is also associated with increased neurogenesis. In rats, ischemic injury induces neurogenesis in the neonatal striatum, with CR-expressing interneurons being born (1248). Newborn interneurons following ischemic injury can also been seen in the neocortex in adults, where proliferating progenitor cells form interneurons expressing NPY, SST, and CR (but not PV) in layer 1 of rat primary somatosensory cortex (853). Although there are no reports of proliferating interneuron progenitors in the hippocampus, ischemic injury in the hippocampus increases proliferation of neuronal progenitors destined to become adult-born granule cells (1240), and interestingly, activity-dependent differentiation of these progenitors appears to be driven by depolarizing GABAergic inputs from hippocampal interneurons (1126). Similarly, after ischemic injury, neuronal progenitors infiltrate CA1 from the periventricular region and become pyramidal cells that functionally integrate into the hippocampal network (824).

**4. Alzheimer's disease** Alzheimer's disease (AD) is a neurodegenerative disorder where patients experience a progressive loss of memory and cognitive function. AD is associated with extracellular deposits of β-amyloid (Aβ) plaques and intracellular accumulations of neurofibrillary tangles of hyperphosphorylated tau protein in a number of structures associated with memory, including the hippocampus and entorhinal cortex (122). A wide variety of animal models of AD exist, most of which involve overexpressing forms of human amyloid precursor protein (APP, the protein from which Aβ is cleaved) and/or mutant tau that are found in familial forms of AD (298). Some AD models also involve coexpression with mutant forms of presenilin 1 or 2 (PS1 or PS2), and some use triple transgenic animals that express mutant Aβ, tau, and PS1 (298).

Human AD patients show an increased risk of epileptic seizures (877), and mouse models that overexpress human forms of APP reveal increases in the intrinsic excitability of neurons, through decreased $Na^+$ currents in both CA1 pyramidal cells (128) and interneurons (1170) which lead to circuit disruption and a generalized increase in network excitability. Mice overexpressing APP show significant reductions in the voltage-gated sodium channel Nav1.1, as do human AD patients, and Nav1.1 expression is mostly restricted to PV-containing interneurons in both mice (1170) and humans (1188). The APP mice displayed impaired inhibitory function and gamma oscillations, as well as cognitive deficits, and these deficits could be reversed by overexpressing Nav1.1 (1170). Mice overexpressing APP/PS1 show a significant loss of both SST- and NPY-containing interneurons early in the disease progression, at 4 and 6 mo, respectively, but with no associated loss in the number PV-containing interneurons (934). APP/PS1 mice also show an early loss of CR-positive interneurons, with significant reductions in both CA1 and CA3 by 4 mo (55). A recent study using APP/PS1 mice found a progressive loss of axon in s.l.m., and in vivo calcium imaging reveals O-LM cell-specific deficits in activation during fear conditioning (986). Mice overexpressing mutant tau also display cognitive deficits that are associated with a loss of hippocampal interneurons expressing SST and PV (669). A study using mice carrying the human AD risk gene apolipoprotein E4 (ApoE4) also reported significant losses of SST interneurons, but from the DG and not CA1, which was associated with impaired spatial learning on the Morris water maze (37). At least three mechanistically independent mouse models of AD show a loss of SST interneurons, so targeting this cell type may prove a fruitful strategy for future treatment of AD. Improving inhibitory neurotransmission alone may be sufficient to improve function, as the ApoE4 study reported that daily treatment with the $GABA_A$ receptor agonist pentobarbital for 4 wk was sufficient to rescue deficits in learning and memory (37). Deleting nitric oxide synthase2 (NOS2) from APP mice greatly exacerbates AD pathology, leading to extensive neuron loss, particularly NPY-expressing interneurons in the hippocampus (1206), so these neurons may also provide a fruitful therapeutic target.

## C. Interneurons and Psychiatric Disease

So far, we have considered the role that interneurons play in the pathophysiology of developmental and neurological disorders. In this section, we will consider how hippocampal interneuron function in neuronal circuits is affected by psychiatric conditions such as mood disorders (e.g., major depression and bipolar disorder), as well as conditions such as anxiety disorders, post-traumatic stress disorder (PTSD), and

addiction. Psychiatric illnesses are widespread, affecting one in five adults annually, placing a significant burden both on individuals and healthcare systems. Major depression, anxiety disorders, and stress disorders such as PTSD are frequently comorbid, with chronic activation of the stress response via the hypothalamic-pituitary-adrenal axis possibly having a causal role in depression (127, 400, 414).

**1. Mood disorders** A substantial body of evidence is accumulating in support of the hypothesis that dysfunction of the GABAergic system underlies major depressive disorder (reviewed in Ref. 712). At the anatomical level, human patients with major depression show a reduction in hippocampal volume (127, 1002), and stress also reduces hippocampal volume in mice (249). However, recent work in primates shows that depression-induced changes in hippocampal volume are due to loss of glia and not neurons (1208). Bipolar disorder is not usually associated with a reduction in hippocampal volume, but a recent meta-analysis concluded that this is due to neuroprotective effects of lithium treatment and found that untreated bipolar patients do show reduced hippocampal volume when compared with treated patients and controls (448). Interneurons are also affected in mood disorders: a post-mortem study comparing brains of patients with schizophrenia, bipolar disorder, and major depression found that all three groups displayed significant reductions in hippocampal reelin levels but, unlike bipolar disorder or schizophrenia, depression was not associated with a reduction in levels of PV or GAD67 (1116). A later post-mortem study of human bipolar disorder patients found that, while there was no overall change in number of neurons in hippocampus, there was a reduction in volume of nonpyramidal layers along with reduced numbers of SST- and PV-containing interneurons, and reduced mRNA for SST, PV and GAD1 (596). These post-mortem studies suggest that, in the hippocampus at least, the pathophysiology of bipolar disorder is more similar to schizophrenia than major depression. While the lack of animal models of bipolar disorder prevent detailed study of interneuron function in the hippocampus in this disorder (832), evidence gathered from human studies suggests that the hippocampus is an important region in bipolar disorder (reviewed in Ref. 358).

Unlike bipolar disorder, robust models of depression do exist in rodents, which use chronic stress to induce depressive-like symptoms in rodents that respond only to chronic and not acute treatment with antidepressant medications (832). Given the links between stress and major depression (127, 400, 414), we will consider these models in the next section. Additionally, some transgenic mouse strains also show depressive behavior. Mice carrying a mutated form of DISC1, which is associated with mental illness in Scotland, show depressive-like behavior and impaired PVBC function, along with impaired theta and gamma oscillations in CA1 (978). Humans with a loss-of-function mutation in the CYP2C19 isoform of cytochrome P-450 have a lower incidence of depressive symptoms (1016), and expressing the human CYP2C19 isoform in mice causes depressive behavior, reduced hippocampal volume, and fewer interneurons immunoreactive for PV or double-cortin (897). Interestingly, experimental diabetes also induces a depressive phenotype in mice linked to reduced hippocampal neurogenesis, and these deficits are reversed with insulin (493).

**2. Anxiety disorders, stress, and PTSD** Anxiety disorders are the most prevalent mental health condition, experienced by one in nine people, with symptoms including excessive fear, anxiety, or avoidance of perceived environmental threats such as social interaction or unfamiliar surroundings (240). Disturbances in GABAergic neurotransmission, especially in the amygdala, are believed to underlie much of the pathology of anxiety disorders, as GABAergic agonists and allosteric modulators are anxiolytic (845). In addition to the amygdala, the ventral hippocampus also plays an important role in anxiety (62). Stress responses are modulated via the hypothalamic-pituitary-adrenal axis, through release of glucocorticoids from the adrenal cortex, and negative feedback from the hippocampus plays an important role in terminating the stress response (1025). Impaired feedback from the hippocampus to the hypothalamic-pituitary-adrenal axis and amygdala has been implicated in anxiety disorders and PTSD (reviewed in Refs. 126, 527, 1006).

Chronic stress reduces the number of neurons that are PV-immunoreactive in the dentate gyrus and CA3 in the tree shrew hippocampus, and these reductions can be prevented by fluoxetine or treatment with antagonists for substance P (NK1) receptors (250). In rats, acute and chronic stress both increase the frequency but not amplitude of spontaneous IPSCs onto CA1 pyramidal cells via glucocorticoid receptors activating mechanisms that appear to involve both CCK- and PV-containing interneurons (505). This study also found a decrease in PV immunoreactivity across all hippocampal subfields, but without a change in

CCK immunoreactivity (505). Further evidence of a role of PV-containing interneurons in regulating the stress response comes from the observation that pharmacogenetic activation of PV-containing interneurons specifically in the dentate gyrus has an anxiolytic effect, without affecting locomotor or depression-related behaviors (1279).

In humans, reduced levels of NPY are associated with PTSD while soldiers with high NPY plasma levels are resilient to stress (reviewed in Ref. 971), and stress also leads to reductions in hippocampal NPY levels in animal models (213, 675). A recent study examined the effects of chronic mild stress on different interneuron populations in rat hippocampus, where they could parse rats into groups that displayed anhedonic (depressive) behavior and those that were resilient. They found similar reductions in PV and NPY immunoreactivity for both anhedonic and resilient groups in all subfields, while reductions in SST and CR immunoreactivity were much more pronounced in the anhedonic group than resilient group, particularly in CA1; no change in CCK or CB immunoreactivity was observed (251). This suggests that, in addition to PV and NPY, studying the activity of hippocampal SST and CR-expressing interneurons in anxiety models may provide further insights to the circuit mechanisms associated with pathological change.

**3. Addiction** While the dopaminergic system is one of the key brain regions implicated in addiction, circuit-level changes in the hippocampus also play an important role (reviewed in Refs. 174, 598). Stimulation of the hippocampus at theta frequency is sufficient to reinstate cocaine-seeking behavior in rats after extinction of self-administration, suggesting a possible role for hippocampal activity in relapse (1178). Blocking mGluR1 receptors within the dorsal hippocampus can suppress reinstatement of cocaine-seeking behavior in rats (1228), although the authors could not determine whether the affected receptors were on glutamatergic or GABAergic neurons. In vivo rat studies show that nicotine induces LTP in dentate granule cells, but that this LTP is preceded by reduced local circuit GABAergic inhibition onto granule cells, making them more responsive to perforant path inputs and possibly reinforcing drug-associated memories (1271). Few studies have examined changes to hippocampal interneurons in addiction, but recent work comparing gene expression in the hippocampi of cocaine or alcohol-addicted humans to alcohol-preferring rats found that all three groups displayed reductions in $GABA_{B1}R$ mRNA expression, as well as changes in other genes related to GABAergic neurotransmission (303). This reduction in $GABA_BR$ expression is interesting in the light of evidence suggesting that activation of $GABA_BRs$ may provide a useful treatment for addiction in humans (reviewed in Ref. 1144). Therefore, we suggest that further study of the role of GABAergic interneurons, in a subtype-specific manner, may provide new insights into circuit-based treatments for addiction.

In this section, we have reviewed the role that hippocampal interneurons have in the pathophysiology of developmental, neurological, and psychiatric disorders. While PV-expressing interneurons have received much attention (understandable, given the lead role that PVBCs have in rhythm generation), it is clear that dysfunction in other interneuron subtypes also occurs in numerous disorders of the brain. With the exception of ASD, many studies on interneurons and disease focus on changes in immunoreactivity for interneuron markers. However, plasticity in interneurons, both synaptic and structural, is an important aspect of their function within circuits (63, 618, 820), so it is important for researchers to consider also disease-related morphological changes that could cause changes in interneuron function without affecting the overall number of cells. In the next section, we will discuss the therapeutic potential of circuit-based strategies that specifically target interneurons.

## D. Therapeutic Potential of Interneurons

The early observation that application of penicillin to the surface of the exposed cortex precipitates electrographic seizures led to a rapid appreciation that erosion of GABAergic control has dire consequences for cortical circuit function. The corollary of this however is that augmentation of GABAergic influence (e.g., pharmacological use of benzodiazepines, closed loop, or deep brain stimulation) or frank replenishment of lost inhibitory interneurons to damaged or compromised circuits might rescue or limit runaway excitation. The concept that GABAergic inhibitory interneurons provide an essential brake on cellular and circuit excitability has existed for over 50 years. In recent years, demonstrations of finely tuned excitatory/inhibitory balances within virtually all cortical circuits has refined our thinking about the nature of GABAergic inhibitory control (522). Indeed, a matched

excitatory/inhibitory ratio, or a controlled temporal or spatial shift in their relative dynamics during trains of activity, enables proper cortical and hippocampal function. This underscores the concept that proper cortical circuit function requires both appropriate timing and magnitude of inhibitory input and that even small changes in the level of inhibitory control can have significant consequences for the nature and function of the circuit.

**1. Brain stimulation and closed loop optogenetics** The hypothesis that a compromised excitatory/inhibitory balance may underlie a multitude of neural circuit disorders has caught the attention of many researchers and importantly suggests that restoring this balance may be a tractable therapeutic strategy. This imbalance may result from an erosion or loss of interneuron circuit efficacy and has led to the suggestion that brain stimulation strategies that preferentially drive the remaining inhibitory circuit could be used as tractable treatment strategy. Indeed, brain stimulation is increasingly used in patients with intractable epilepsy to provide palliative care and improve quality of life. Strategies that stimulate either vagus nerve to activate brain stem nuclei, or stimulation of targeted network hubs either within or outside of the seizure focus are becoming routinely explored as alternative strategies for seizure control often combined with pharmacological strategies (992). Although the precise mechansims underlying their effectiveness are largely unexplored, it is hypothesized that these strategies work by preferentially activating inhibitory circuits and the consequent desynchronization of network activity (992).

Brain implanted devices and in particularly the use of closed loop feedback strategies have received considerable attention in the last few years (45, 604). Closed loop strategies rely on feedback between the output and input signals of an implanted device, which then rapidly reacts to influence an actuator that then delivers an appropriate subsequent intervention. To be effective closed loop systems must detect ongoing neural circuit activity, recognize and extract the "aberrant" signal, which is then fedback and used to rapidly activate "corrective" patterned activity to the target neurons, ideally converting pathological signals into physiological patterned activity. Although at this time closed loop systems have only limited clinical applications (particularly in movement disorders and epilepsy), their utility has been convincingly explored in a number of animal models. Ivan Soltesz and colleagues (603, 605) used an "on-demand" optogenetic closed loop approach to control temporal lobe seizures in a mouse model of epilepsy. Using a tunable, closed loop seizure detection program, which then feedbacks to trigger light delivery, they could arrest seizure activity by either optically inhibiting excitatory principal cells using halorhodopsin, or by activating PV-containing interneurons using channelrhodopsin. That seizure control was effective when only a small (~5%) population of interneurons were light-activated suggests that a cell type approach to neural ciruit disorders represent a viable strategy for tackling neural circuit disorders.

**2. Tissue grafts, transplantation, and stem cell strategies** Early approaches to implant fetal tissue grafts containing GABAergic neurons to limit electrographic seizure events had limited success (330, 698). While the transplanted cells often survived, they typically remained close to the transplantation site, and only limited evidence suggested that they made functional connections in a manner that would appropriately contain electrographic events. Similarly, transplanted genetically engineered cells or cell lines that were selective for "GABA secreting" cells also offered only marginal anticonvulsant potential (394, 1101). However, observations that inhibitory neurons could be harvested from the embryonic ganglionic eminences and subsequently successfully transplanted into the developing cortex (29, 71, 829, 1202) offered the first promise that such a manipulation could be used to correct damaged or compromised circuits. These transplanted cells not only survive transplantation, they also migrate considerable distances and integrate into functional circuits where they establish and receive appropriate synaptic connections with host pyramidal cells (71). However, its has been noted that targeting of transplanted inhibitory cells to host interneuron subtypes (and other GFP-transplanted interneurons) was limited, and it is uncertain whether appropriate connections are made between ganglionic eminence derived interneurons and other interneurons (61, 511; for review, see Refs. 510).

Clear evidence of inhibitory interneuron transplantation as a potential therapeutic strategy for electrographic seizure activity came from two landmark studies (61, 511; for review, see Ref. 510). Using a mouse lacking the voltage-gated potassium channel subunit Kv1.1, a model of congenital epilepsy, Baraban et al. (61) transplanted MGE-derived interneurons into neocortex at postnatal day 2. Approximately 1 mo later, mice receiving grafts showed an ~90% reduction in spontaneous seizure incidence, consistent with the observed increase of inhibitory tone onto glutamatergic principal cells. In a

second study using the pilocarpine model of epilepsy, MGE-derived cells were transplanted once spontaneous seizures had been established. Again mice receiving MGE-derived interneuron transplants showed a remarkable 90% reduction in seizure incidence 60 or more days after receiving transplantation (511). Numerous subsequent studies have also reported amelioration of a number of behavioral and circuit deficits following MGE-derived interneuron transplantation including animal models of stroke (252), AD (1108), schizophrenia (399, 1090), spinal cord injury and neuropathic pain (125, 306), Parkinson's disease (758), and fear erasure (1247). In a mouse model of AD-induced learning and memory deficits, knock-in of apoE4 with or without Aβ accumulation results in hippocampal hyperactivity and a concomitant loss of hilar GABAergic interneurons (328, 673). Transplantation of mouse MGE-derived inhibitory interneuron progenitors into the hilar region restores normal learning and memory in both apoE4 knock-in mice and apoE4 mice expressing amyloid precursor protein (1108).

Taken together, these studies all underscore the importance of appropriate excitation:inhibition balance for correct circuit function. However, the actual consequences of interneuron transplant have not been studied at the circuit level much beyond monitoring the frequency of spontaneous IPSCs. All of these studies exploit the ability of MGE-derived precursor interneurons to survive and integrate into the target circuit. However, it is unclear what aspect of interneuron function is critical for the apparent reversal of all of these diverse circuit disorders. What trophic and environmental factors influence the extent of interneuron migration away from the transplantation site? Do these cells make appropriate cell surface domain specific synaptic contacts or do they form random contacts with their principal cell targets? Is temporal phasic structure in their inhibitory synaptic output important or is an increased generalized inhibitory tone sufficient? MGE-derived cells are a mixed population of diverse interneuron subclasses; are particular subtypes (i.e., PVBCs) better than others in the success of such transplantation studies? Obviously many questions remain regarding exactly what features of the transplanted cells are critically important once they enter their target tissue, and our ability to improve on and exploit these features can only add to the potential for their future use in treatment strategies for neural circuit disorders.

All of the above studies have relied on transplanted GABAergic interneurons harvested from fetal ganglionic eminences and transplanted into the relevant murine host site. In order for this to be a tractable approach in human therapeutic strategies, tissue would have to be similarly extracted from fetal human tissue, which would seem to be an unlikely scenario at this time. However, several alternative strategies exist. Ye et al. (1249) demonstrated that in vivo lineage reprogramming of mouse cortical excitatory projection neurons dictated the degree of inhibitory innervation. Reprogramming layer 2/3 callosal projection neurons into Fezf2-induced corticofugal projection neurons results in an increased innervation by PVBCs (1249). These induced corticofugal projection neurons not only took on the molecular identity of the endogenous cells, they were able to influence the nature of the inhibitory connectivity that they received, providing a clue that cell type specificity could be used to rewire damaged tissue and circuits.

A second and more promising approach has been to differentiate embryonic stem cells into inhibitory interneuron populations. Although cortical interneurons can be generically produced from stem cells, the lack of understanding of specific transcriptional programs has hampered the generation of specific interneuron subpopulaitons. Au et al. (50) utilized the directed differentiation of stem cells into specific subpopulations of cortical interneurons. With the use of transient expression of Nkx2–1 and Dlx2, two factors required for the generation of inhibitory interneurons, they successfully improved the differentiation efficiency and generation of cell type specificity. They then extended this approach to establish a "modular system" that allowed additional transcription factors to be introduced. Using this approach, they then identified Lmo3 and Pou3f4 as genes that augment the differentiation and/or subtype specificity of inhibitory interneurons (50). A second paradigm shifting study by Maroof et al. (752) similarly exploited the known genetics of cortical interneurons to manipulate the timing of sonic hedgehog activation in an NKX2.1:GFP human embryonic stem cell reporter line to produce enriched populations of PV- and SOM-expressing inhibitory interneurons.

Using rat embryonic stem cells in vitro, Donegan et al. (281) generated enriched populations of either PV-containing or SST-containing interneurons and transplanted them into the hippocampus of a rodent methylazoxymethanol model of schizophrenia. Both interneuron types successfully integrated into the surrounding tissue and circuitry to reduce hippocampal hyperactivity and correct aberrant dopaminergic neuron activity with PV-containing cell transplants (but not SST-containing) reversing social interaction

deficits and extradimensional set shifting behavior. In a second rather beautiful study, Fandel et al. (314) transplanted "MGE-like interneurons" derived from human embryonic stem cells into mice harboring spinal cord injury. These transplanted cells survive extended periods of time, differentiate into GABAergic inhibitory interneurons, and fully integrate into the host spinal cord to alleviate pain-related symptoms and ameliorate bladder dysfunction which arises from excessive glutamatergic activity and GABAergic hypofunction (314). Importantly, these cells both receive and make appropriate synaptic contacts with the local circuitry. A major concern for the use of embryonic stem cells is the potential for tumor formation arising from pluripotent cells in the transplant. In the study by Fandel et al. (314), they observed that the vast majority of cells differentiated into interneurons (CR-, CB-, SST-, and PV-containing cell types) with only a small percentage of cells acquiring oligodendrocyte phenotype. Importantly, they found no evidence for tumors in any of their grafts. Going forward such a strategy will undoubtedly be of importance not only in treating spinal cord injury but also manipulating damaged central circuits.

## XVII. SUMMARY

As can be seen from the topics covered in this broad review of hippocampal inhibitory interneurons, we have learned much about the myriad roles played by these cells over the last few decades. However, while our understanding of their cellular physiology and circuit roles played by some cells is extensive, in particular the parvalbumin-containing FSBCs, research into many other interneuron types has languished or we have only rudimentary insight into their basic properties and roles in the cortical circuit. Of course, the emergence and development of new techniques and mouse lines will hopefully facilitate their study in greater depth, and we hope that by highlighting here what is known and what is not that this will shine a necessary light onto these cells so that a more complete understanding of all interneuron types can be achieved.

Over the course of writing this review, many "holes" in our understanding became apparent to us. The most general, yet critical, of these is our lack of confident resolution of the number and types of interneurons that populate the hippocampal formation. The emergence of new tools and genetic approaches has allowed us to parse cells types into ever increasing numbers. There is no reason to doubt that as we come to greater understand the genetic programs that drive interneuron development that these numbers will continue to grow. However, from a pragmatic point of view, we need to adopt strategies that allow us to better understand the roles played by these cells and to ask whether small differences in anatomy, physiology, or protein expression that split interneurons into ever increasing silos truly aid our understanding of their roles. Tools such as the Allen Cell Type Database and neuroelectro.org, which take an agnostic approach to cell feature classification, will greatly facilitate our extraction of the true identity, nature, and roles played by this important cell class. It is important that we as a field continue to explore the properties of channels and receptors of the lesser-studied cell types and when possible make the data available in public databases. The converse of this argument is the unnecessary oversimplification of cell types when using transgenic mouse lines for elimination, overexpression, or optogenetic experiments. In many cases, many of these mouse lines do not report activity in a single interneuron population. For example, using a PV-cre or equivalent line impacts not only FSBCs, but also AACs and BiCs, confounding clean interpretations of the roles played by specific subpopulations. The literature is littered with these kinds of erroneous interpretations, and we urge care and caution when designing experimental strategies and interpreting data from such lines.

A second, critical open question is whether every hippocampal principal cell is innervated by every interneuron subtype? With more than 20 types of interneuron in the CA1 hippocampus alone, is it reasonable to expect that they will all target the same principal cell or do specialized subcircuits exist within this subfield? It is becoming clear that multiple distinct pyramidal cells exist, that project to differing target areas outside of the hippocampal formation. It is not unreasonable to consider that each of these distinct projection neuron types will have its own repertoire of inhibitory cells innervating it. This would suggest that numerous interdigitated parallel circuits exist within the CA1 hippocampus, which could receive common or unique patterns of interneuron innervation, significantly reducing the number of inhibitory interneuron types that innervate a particular population of cells.

In our opinion, one of the single most important successes over the last decade has been to attract developmental cell biologists to this field of research. From their work we have learned much about the genetic and transcription regulation and determination of cortical and hippocampal inhibitory interneurons. This has not only informed a greater understanding of the roles played by interneuron subtypes, but it has facilitated development of numerous mouse lines permitting manipulation of relevant genes. However, many fundamental questions remain. What temporal and spatial rules determine whether an MGE-derived interneuron will adopt a PV-containing or SST-containing fate or any cell subtype for that matter? Are interneurons generated in a stochastic manner, dictated by simultaneous regulation of multiple genes and transcription factors? If so, what and when is the tipping point for dictating cell identity and fate? What roles do the differing migratory streams play, and what determines when an interneuron will choose to leave and enter the cortex or carry on towards hippocampus? What is the true nature of clonal cell lineages and what dictates their ultimate positional destination in the nascent cortical and hippocampal circuit and beyond? Can cell duplication during evolution explain why there are so many similar cell types? We now know that the MGE and the CGE give rise to distinct basket cells, O-LM cells, bistratified cells, and NGFCs that share many anatomical and physiological features and differ in expression of only a small number of mRNAs and protein. Consideration of the evolution and development of both the hippocampus and cortex could shed light onto this question.

In the last few years there has been an extraordinary proliferation of papers that indict interneurons in a number of neural circuit disorders. In hindsight, this is of course not particularly surprising given the multiple roles interneurons play in shaping and coordinating network activity. Small perturbations in cell and circuit excitability likely have major consequences for network function. We are encouraged by the burgeoning number of cell transplantation, grafts, stem cells, and optogenetic papers that point toward a tenable strategy for therapeutic intervention and consider this to be a major beacon for future research that will attract new investigators and pharmaceutical companies to this field of research. We also hope that these approaches will usher in a new epoch where studies in human inhibitory interneurons will be commonplace, since it is likely that many secrets are harbored in the human interneuron population.

Finally, from a personal standpoint, it is almost 30 years since the senior author of this review made his first electrophysiological recordings from hippocampal inhibitory interneurons. I can still remember the jubilation in Dr. Ray Dingledine's laboratory at that time as we began to explore this new frontier. These early, tentative steps took my research life down the path of inhibitory interneurons for better or for worse, and I would urge any young scientist reading this review who is remotely interested in this field to jump in with both feet and have fun doing so because we still have much to learn!

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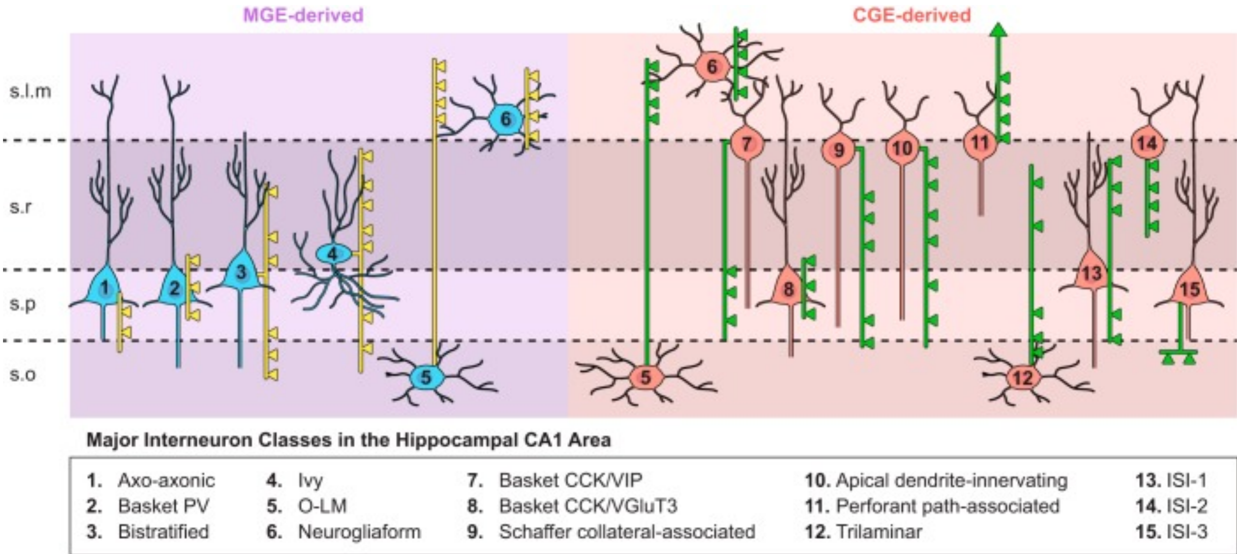
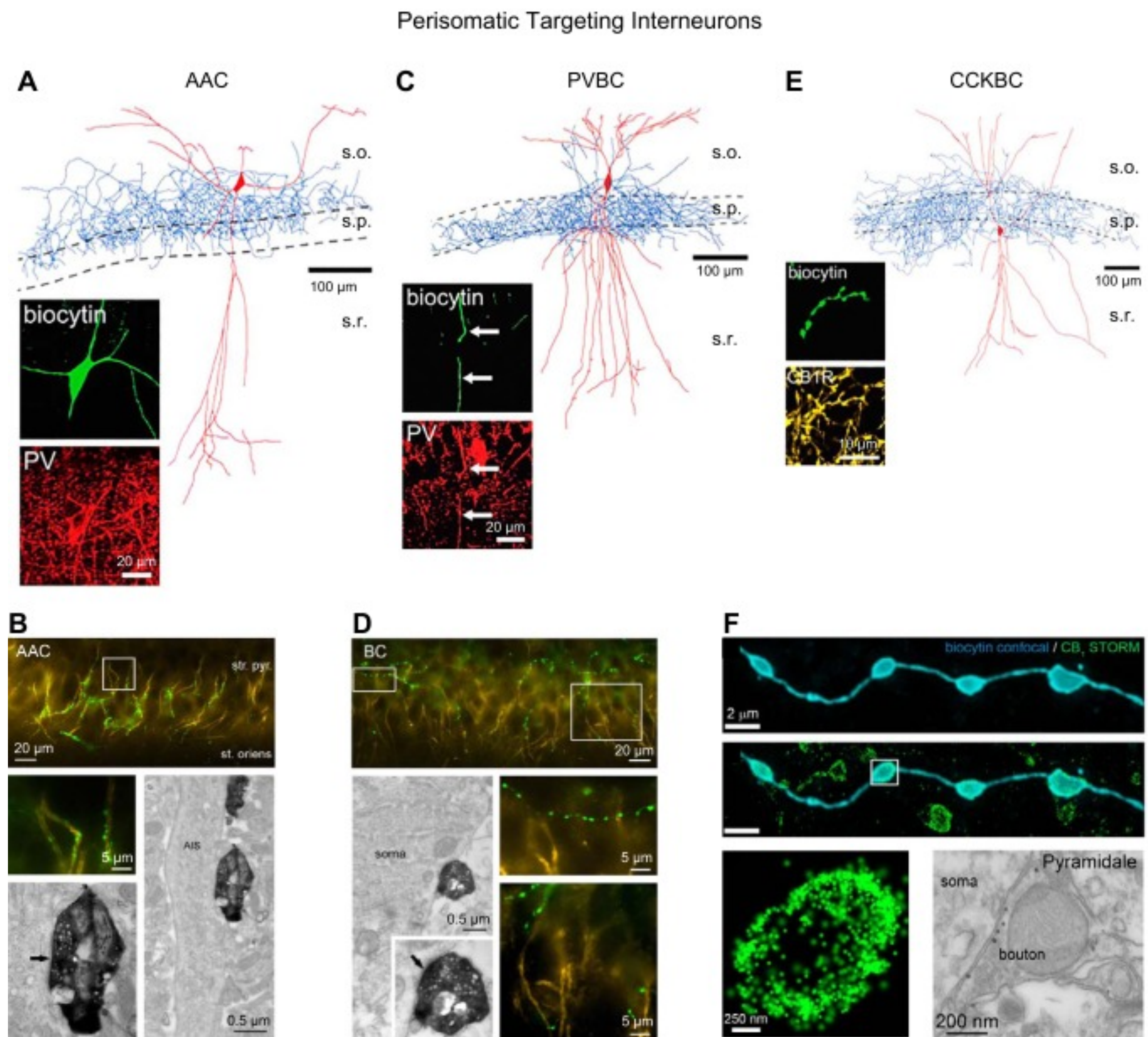
## Figures and Tables

## FIGURE 1.




Schematic representation of hippocampal interneuron subtypes highlighted in this review. Interneuron subtypes are parsed according to origin within the medial ganglionic eminence (MGE) or caudal ganglionic eminence (CGE). Cells with dual origins are represented in both cohorts. Somato-dendritic profiles are represented in uniform color (blue for MGE, red for CGE). Thinner axon trajectories are illustrated in yellow (MGE-derived cells) and green (CGE-derived cells) with boutons (triangles) illustrating the dominantly targeted domains of CA1 pyramidal cells innervated by each interneuron subtype.

## FIGURE 2.

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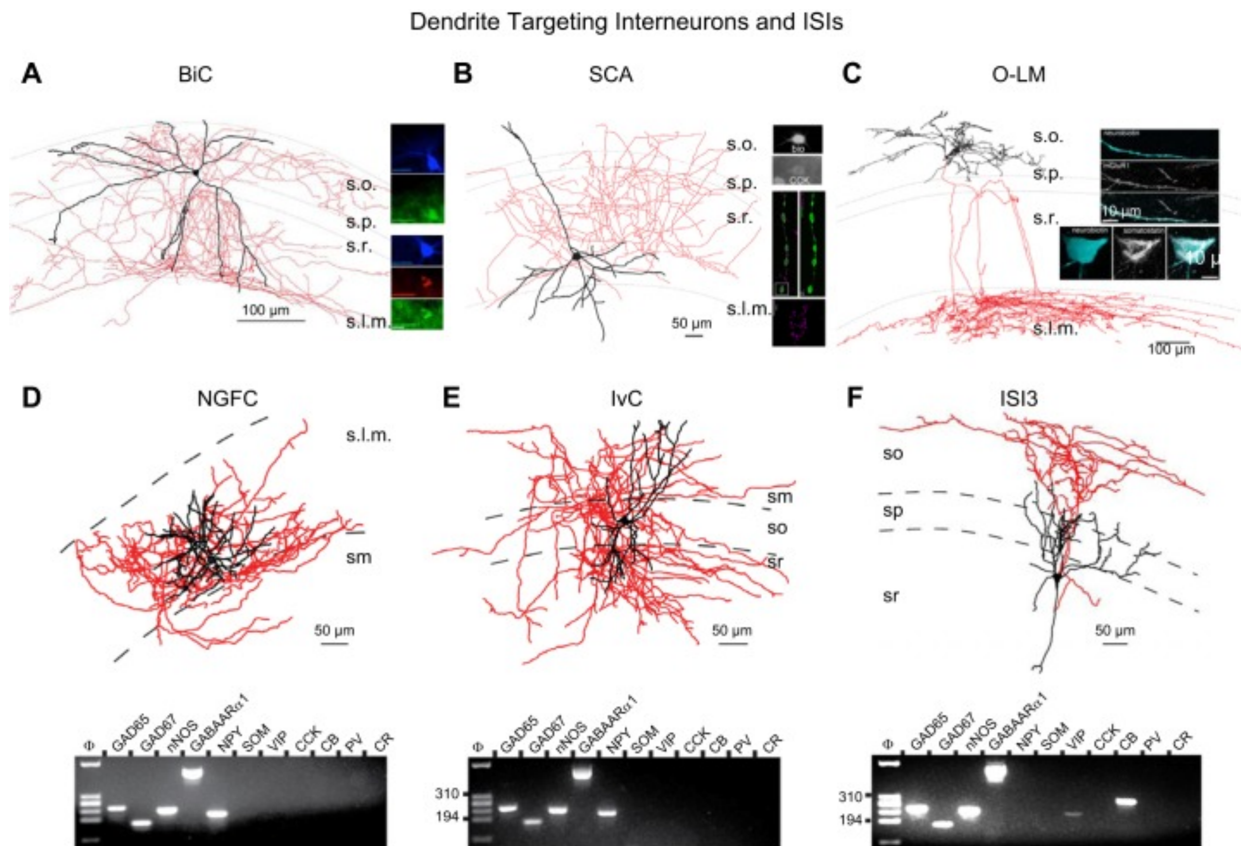
Perisomatic targeting interneurons. A: morphological reconstruction of a representative axo-axonic cell (AAC). Inset shows that the dye-filled AAC is immunopositive for parvalbumin (PV). B: immunohistochemistry and electron microscopy images illustrating that the cartridges and axon terminals of a dye filled AAC (green) target ankyrin G-positive (yellow) axon initial segments (AISs) of principal cells. C: morphological reconstruction of a representative PVBC with inset confirming PV immunoreactivity within a dendritic segment of the dye filled PVBC. D: immunohistochemistry and electron microscopy images illustrating that PVBC terminals (green) target principal cell somas and avoid ankyrin G-positive AISs. E: morphological reconstruction of a representative CCKBC with inset showing CB1R immunolabeling within a segment of dye filled axon. F: superresolution STORM imaging illustrates intense CB1R immunolabeling of dye-filled CCKBC terminals. Also shown is an electron micrograph highlighting CB1R expression in perisomatic targeting GABAergic terminals. [Reconstructions with inset immunohistochemistry presented in A, C, and E are modified with permission from Nissen et al. (838) and Journal of Neuroscience. Images B and D are modified with permission from Gulyás et al. (443) and Journal of Neuroscience. STORM images in F were kindly provided by Dr. Katona while the electron micrograph was modified with permission from Dudok et al. (289) and Nature Neuroscience.]

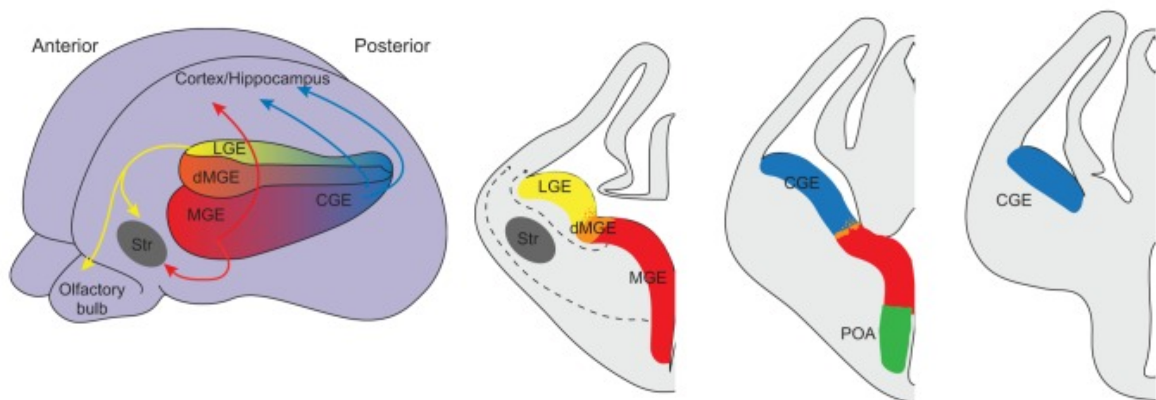
## FIGURE 3.



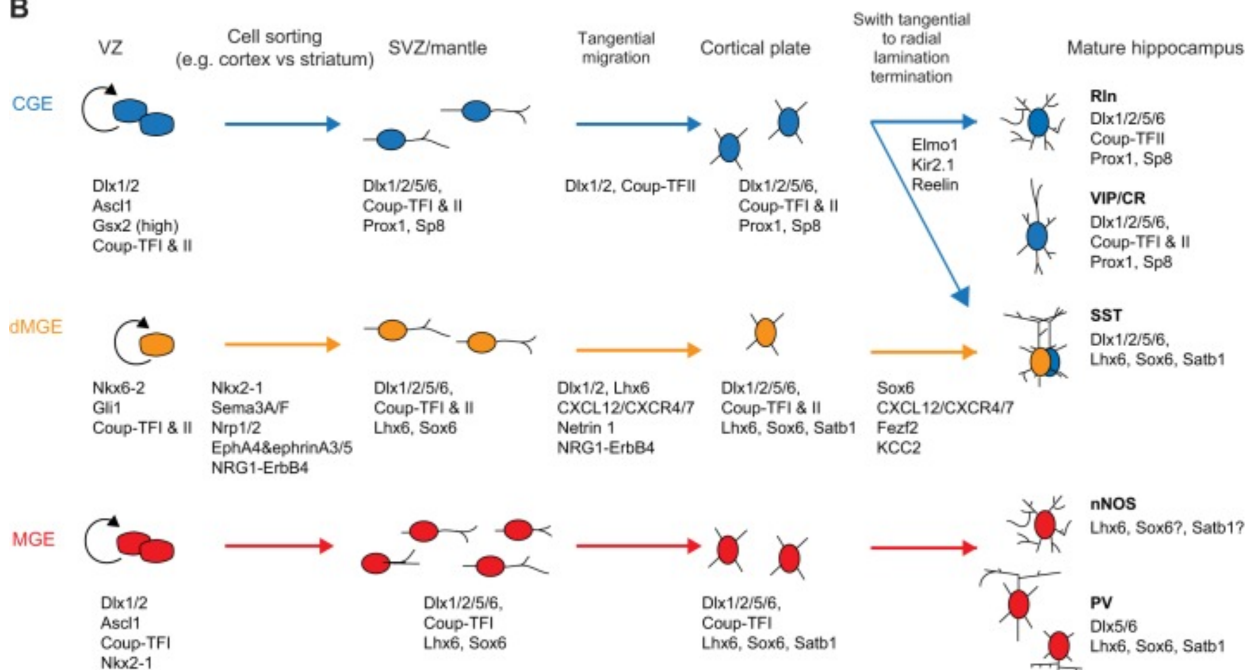

Dendrite targeting interneurons and interneuron selective interneurons (ISIs). A: morphological reconstruction of a representative bistratified cell (BiC). At right, the reconstructed cell is illustrated to be immunopositive for SST and NPY while a different BiC highlights PV expression in this interneuron subtype. B: morphological reconstruction of a representative SCA with top inset showing that the cell is CCK immunopositive. Also shown at right (bottom) are STORM images illustrating strong CB1R immunolabeling within terminals of a separate dendrite targeting CCK interneuron. [Bottom right panel modified with permission from Dudok et al. (289).] C: morphological reconstruction of a representative O-LM with insets illustrating SST and mGluR1α immunoreactivity in the soma and along a dendritic segment, respectively. D–F: morphological reconstructions of representative NGFC (D), IvC (E), and ISI3 (F) cells along with single cell RT-PCR profiles probing for mRNA expression of the indicated markers. [A modified with permission from Klausberger et al. (583) and Nature Neuroscience. B modified with permission from Lee et al. (654) and Journal of Neuroscience. C modified with permission from Katona et al. (561) and Neuron. D–F modified with permission from Tricoire et al. (1137) and Journal of Neuroscience.]

## FIGURE 4.

**A**




**B**

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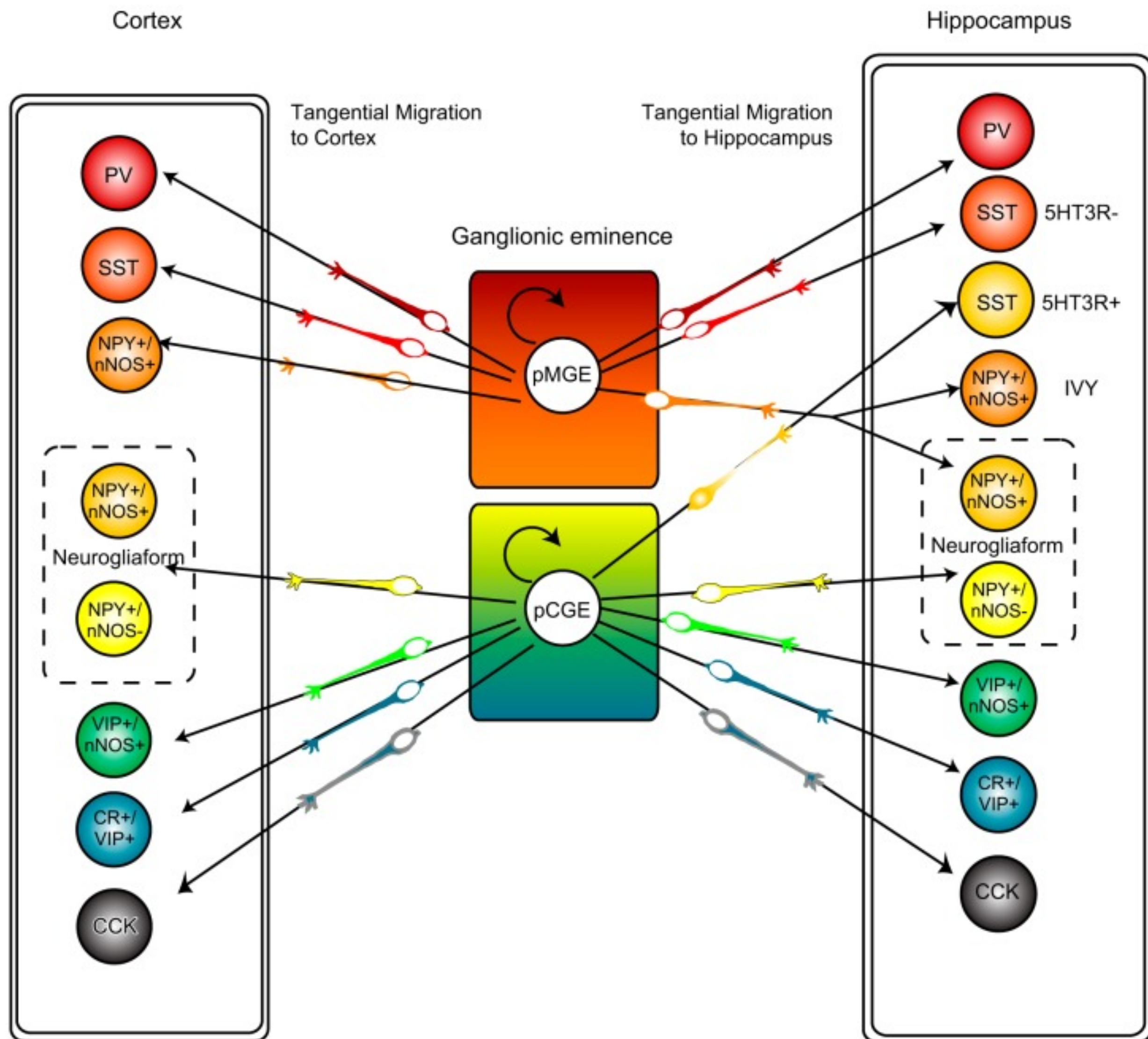
Subpallial embryonic origins, and genetic programs directing genesis/migration/circuit integration of cortical interneurons. A, left panel: schematic illustrating pathways of migration for cortical and striatal interneurons from the GEs. Right panel: diagram of embryonic brain with the subdivisions of the ventral telencephalon in the coronal plane. The three regions where striatal, neocortical, and hippocampal interneurons originate are the medial ganglionic eminence (MGE) (including the dorsal MGE-dMGE), the caudal ganglionic eminence (CGE), and the preoptic area (POA). The lateral ganglionic eminence (LGE) largely gives rise to basal forebrain neurons and striatal medium spiny neurons. Note that the vast majority of cortical interneurons are derived from MGE and CGE. B: genetic programs controlling neurogenesis, cell commitment, tangential, and radial migration as well as maturation of cortical interneurons. The subdivision of the neuroepithelium can be identified by combinatorial expression patterns of transcription factors involved at different stages of cortical interneuron development. Some of these factors participate broadly in interneuron development such as Dlx and CoupTF gene families. Some transcription factors are unique to specific domains and/or stages of differentiation. Nkx2.1 defines the MGE and activates a cascade of genes including Lhx6, Sox6, and Satb1. Nkx6.2 and Gli1 are enriched in the dMGE. Prox1 and Sp8 are expressed in CGE-derived cortical interneurons at all stages of their development. Note that it is unclear whether Sox6 and SatB1 are necessary for the development of nNOS expressing Ivy cells. [Adapted with permission from Kessaris et al. (577) with permission from Current Opinions in Neurobiology and from Wonders and Anderson (1213) with permission from Nature Reviews Neuroscience.]

**FIGURE 5.**

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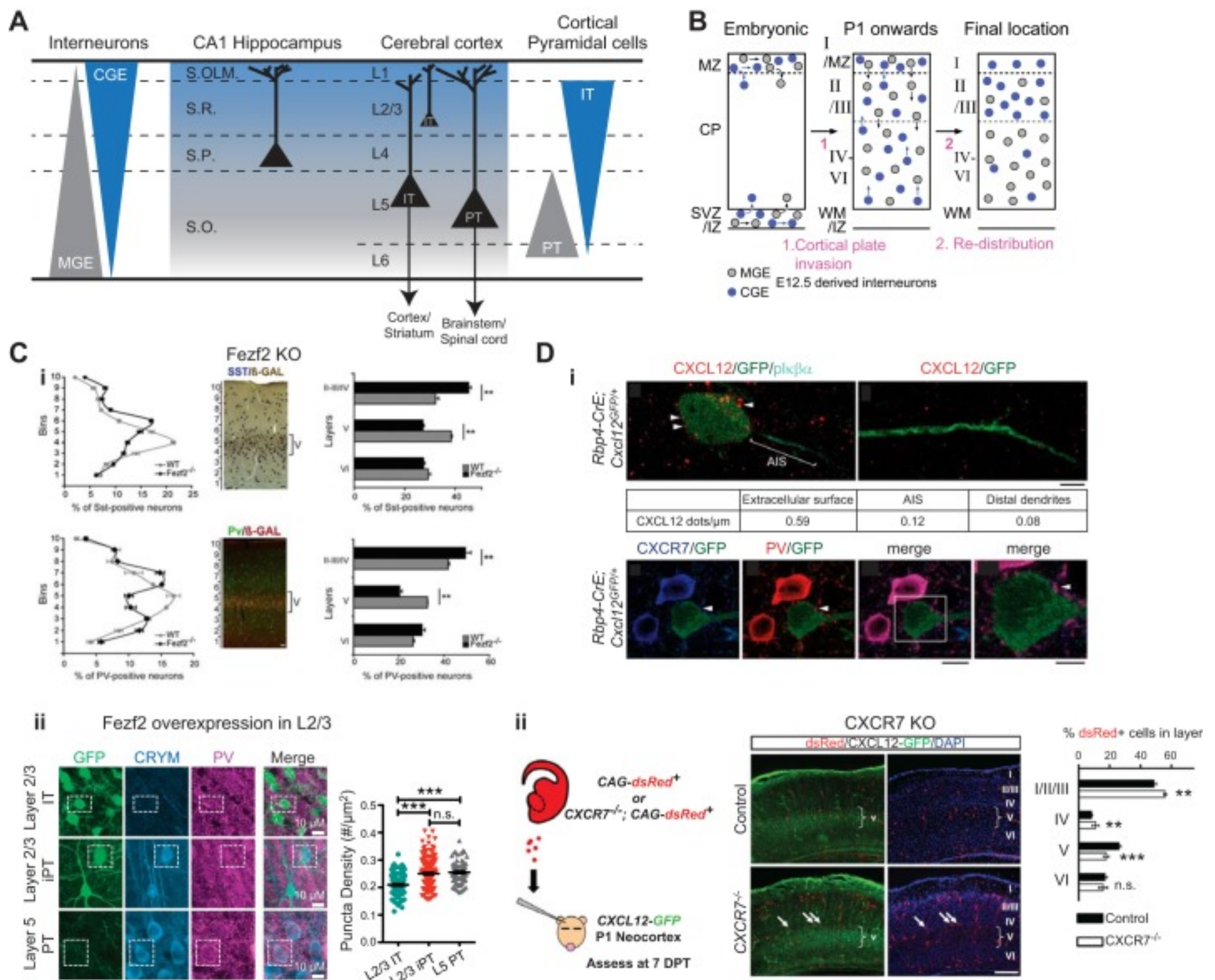
The ganglionic eminence origins for hippocampal interneurons often deviate from the rules underlying neocortical interneuron embryogenesis. In cortex, all PV- and SST-containing (as well as a minor population of NPY-positive/nNOS-positive) interneurons are derived from the MGE, while the remaining populations (including VIP, CCK, and NPY-containing interneurons) are derived from the CGE. While these rules are true for many hippocampal interneuron subpopulations, 5HTR3AR-positive SST-containing interneurons are derived from the CGE. Furthermore, all NGFCs destined to reside in cortex have their origins in the CGE, whereas in hippocampus NPY-positive/nNOS-containing NGFC have their origins in the MGE and NPY-positive, nNOS-negative NGFC arise from CGE origins.

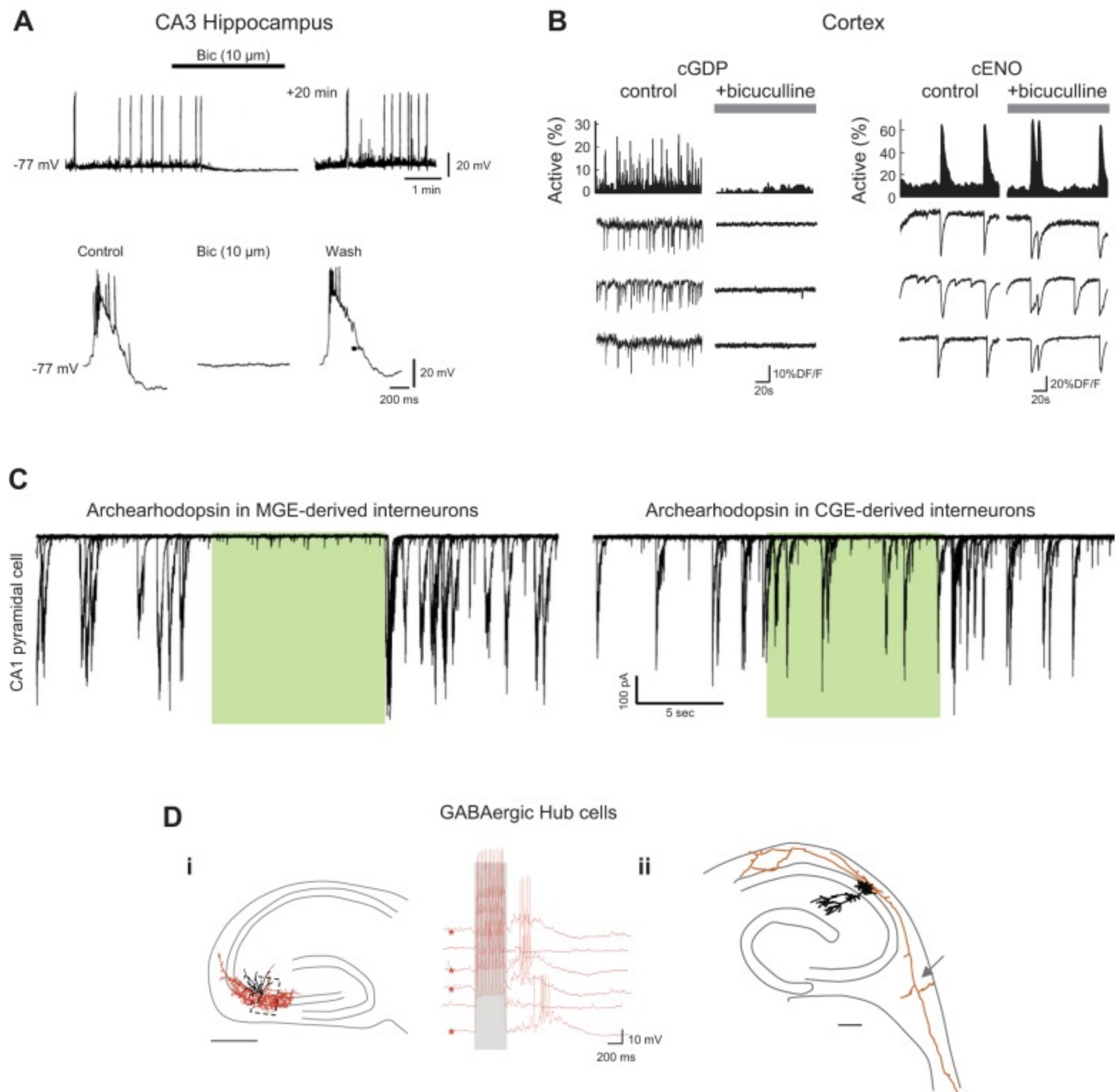
## FIGURE 6.




| | Extracellular surface | AIS | Distal dendrites |
|---|---|---|---|
| CXCL12 dots/μm | 0.59 | 0.12 | 0.08 |

PCs influence the radial migration of interneurons in the cortex. A: MGE- and CGE-derived interneurons are biased in their distributions between deep and superficial lamina, respectively. In the hippocampus, lamination depth is relative to the direction of the apical dendrite (i.e., s.o. is deep and s.l.m. is superficial). In the cortex, the distribution of interneurons correlates with that of pyramidal cell subtypes: intratelencephalic (IT) type are found primarily in superficial layers while pyramidal tract (PT) type are found only in deep layers. B: MGE- and CGE-derived interneurons born on the same day are initially unsorted among the cortical layers and only achieve their stereotyped laminar distributions over the course of the first postnatal week. C, i: knockout of the transcription factor Fezf2 results in the loss of PT-type projection neurons in deep cortical layers, which are replaced by IT type. In these mice, SST+ and PV+ interneurons accumulate to a greater degree in superficial than deep layers. ii: Layer 5 PT-type projection neurons receive greater PVBC inhibition than layer 2/3 IT type. Overexpression of Fezf2 in layer 2/3 results in the conversion of IT type cells to PT type with concomitant increase in PVBC inhibition. PV puncta density was compared between layer 2/3 IT, layer 2/3-induced PT (iPT), and layer 5 PT-type projection neurons. CRYM is a marker for PT type cells. D, i, top: in layer 5 pyramidal cells CXCL12 is localized to the cell bodies but not AIS or dendrites. Bottom: CXCR7, the receptor for CXCL12, is localized to the soma and axon terminals of PVBCs, which target layer 5 pyramidal cells. Pyramidal cells are labeled with GFP. plkBa is a marker for the AIS. ii: Interneurons expressing dsRed were transplanted from the MGE of control or CXCR7 knockout mice at embryonic day 13.5 (E13.5) into the cortex of CXCL12-GFP mice at postnatal day 1 (P1). Interneurons lacking CXCR7 accumulated in the superficial layers, rather than being attracted to CXCL12 in the deep layers. Bracket indicates the location of layer 5 cell bodies expressing GFP from the CXCL12 gene locus. [B from Miyoshi and Fishell (795) with permission from Cerebral Cortex. Ci from Lodato et al. (687) and Cii from Ye et al. (1249) modified with permission from Neuron. Di from Wu et al. (1221) modified with permission from Cerebral Cortex. Dii from Vogt et al. (1176) with permission from Neuron.]

## FIGURE 7.

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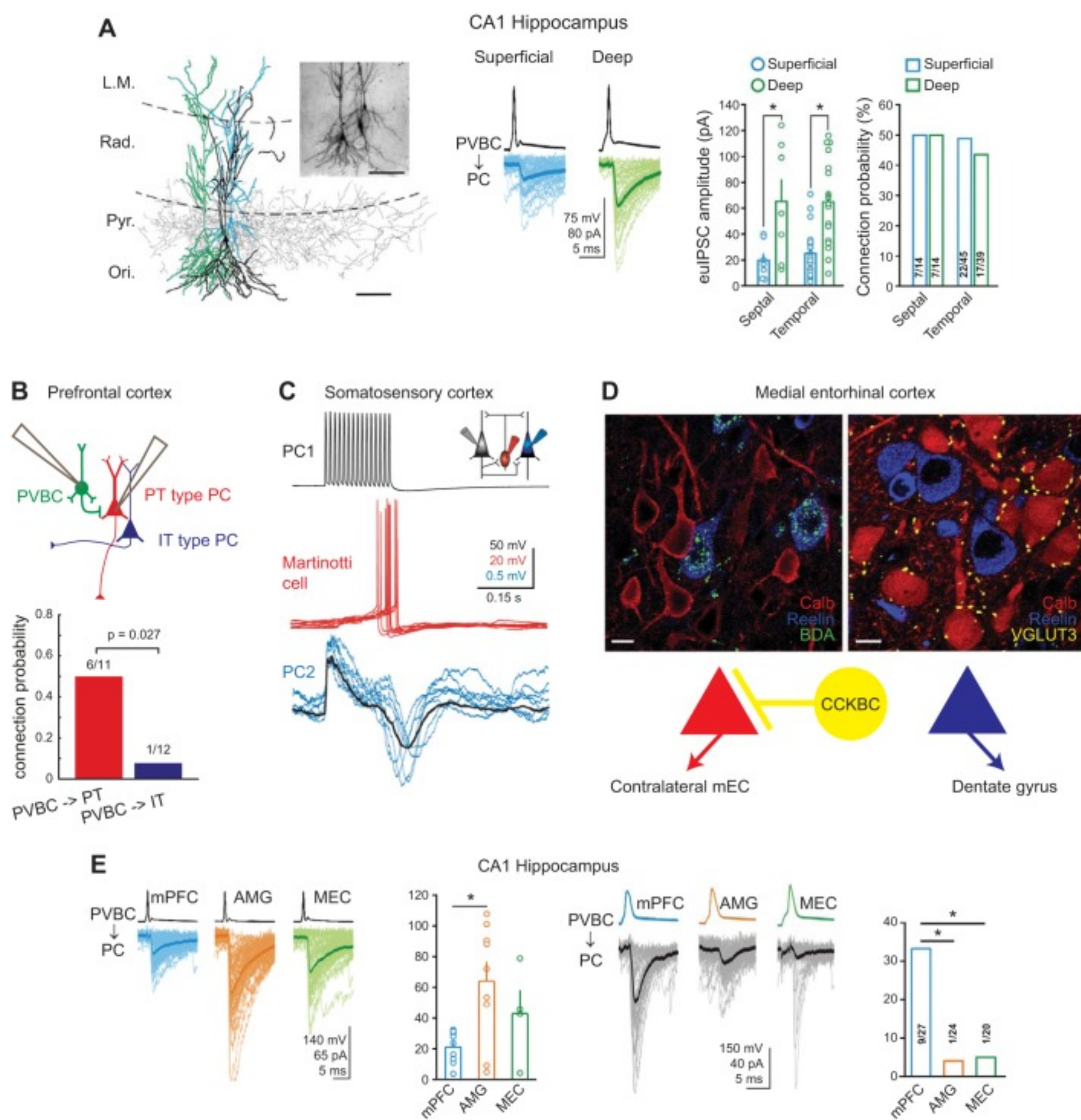
Interneurons contribute to the generation of early network activity in the hippocampus and cortex. A, top: spontaneous GDPs recorded intracellularly in hippocampal CA3 pyramidal cells occur rhythmically and are sensitive to the $GABA_A$ antagonist bicuculline (Bic). Bottom: expansion of individual GDP examples. B: early network activity in the cortex recorded with calcium imaging of a large population of cells. Left: cortical GDPs (cGDPs) occur rhythmically, engage ~30% of imaged cells, and are sensitive to bicuculline. Calcium signals from three representative cells are shown below the population histograms. Right: early cortical network oscillations (eCNOs) are also observed but are not sensitive to bicuculline. C: optogenetic inhibition of MGE- or CGE-derived interneurons with archearhodopsin (green box) in hippocampal CA1 at postnatal day 5. Inhibiting MGE- but not CGE-derived interneurons greatly reduces the frequency of spontaneous GDPs recorded in pyramidal cells. Traces from multiple overlaid trials are shown. D, i: example of a hub cell in hippocampal CA3 that is highly interconnected with neighboring cells and is capable of triggering a GDP when stimulated to fire action potentials. Axon depicted in red. ii: A subset of hub cells generated early during embryonic development project a long-range axon out of the fimbria (indicated by arrow), and thus may coordinate early network activity across different brain regions. In mature animals these interneurons target the septum. [A from Ben-Ari et al. (91) with permission from Journal of Physiology. B from Allene et al. (25) modified with permission from Journal of Neuroscience. C from Wester and McBain (1198) modified with permission from Journal of Neuroscience. D from Bonifazi et al. (114) modified with permission from Science.]

## FIGURE 8.

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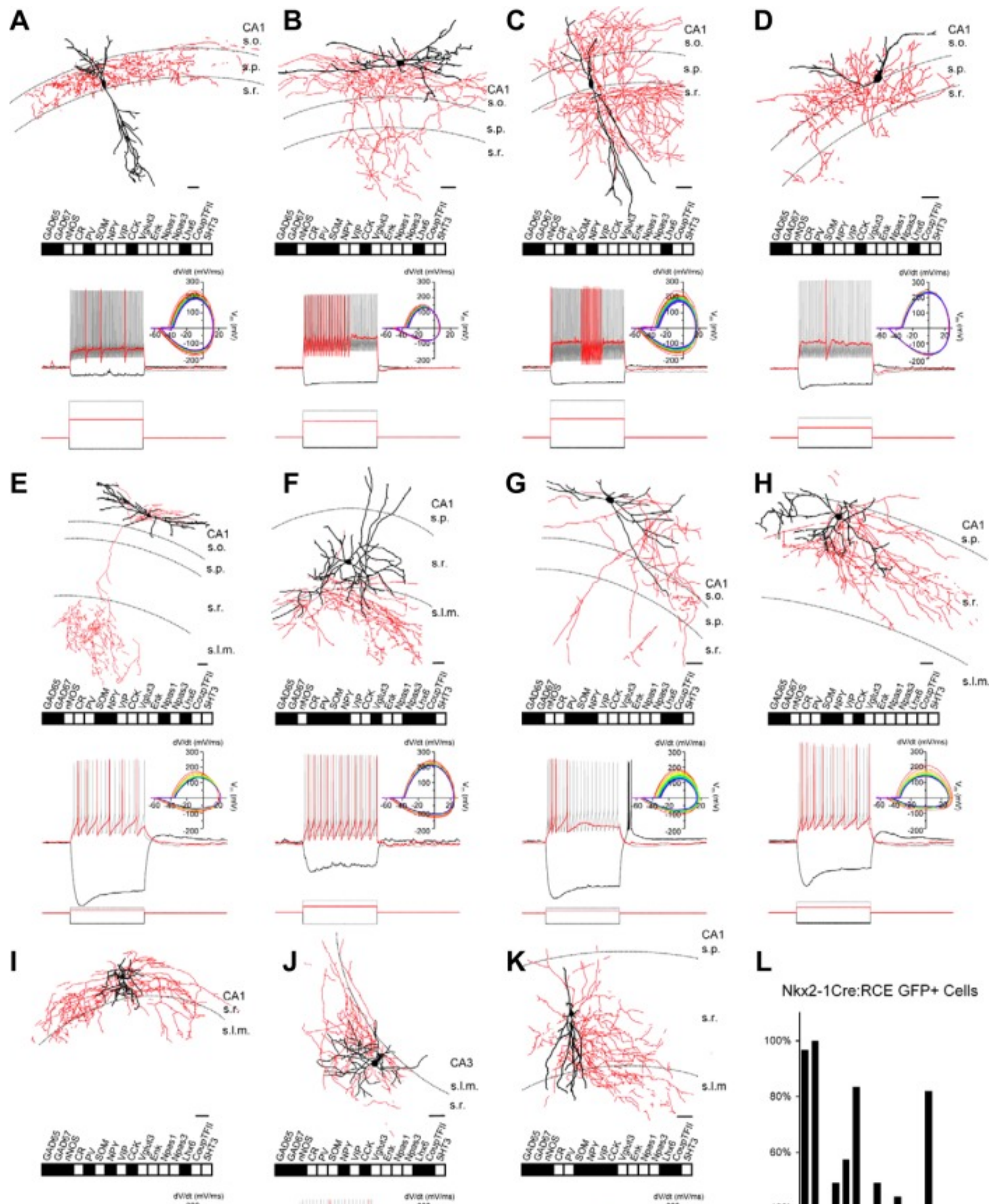
PCs and interneurons form subtype specific microcircuits in both the hippocampus and cortex. A: paired whole cell recordings in hippocampal CA1 between a PVBC (black) and a neighboring deep PC (green) and superficial PC (blue). The probability of observing a connection from a PVBC to either a deep or superficial PC is the same; however, deep PCs demonstrate larger amplitude inhibitory currents. This finding is consistent along the entire axis of the hippocampus (septal to temporal poles). B: in prefrontal cortex, PVBCs connect to PT-type pyramidal cells with greater probability than neighboring IT type. C: in somatosensory cortex, SST+ Martinotti cells mediate disynaptic inhibition between neighboring recurrently connected PT type PCs. D: in medial entorhinal cortex, CCKBCs selectively target PCs that project to the contralateral entorhinal cortex but not neighboring PCs that project to the dentate gyrus of the hippocampus. E, left: in CA1 hippocampus, PVBCs evoke larger amplitude inhibitory currents in PCs that project to the amygdala (AMG) vs. the media prefrontal cortex (mPFC). Right: PCs projecting to the mPFC are more likely to provide synaptic input to neighboring PVBCs than PCs projecting to the AMG or medial entorhinal cortex (MEC). [A and E from Lee et al. (656) modified with permission from Neuron. B from Lee et al. (650) modified with permission from Neuron. C from Silberberg and Markram (1015) modified with permission from Neuron. D from Varga et al. (1162) modified with permission from Nature Neuroscience.]

**FIGURE 9.**

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Multiparametric analysis of MGE-derived hippocampal interneurons. A–K: neurolucida reconstructions of GFP-containing interneurons recorded in slices from P15–P30 Nkx2–1Cre:RCE pups (dendrites and soma in black; axon in red). Scale bar: 100 μm. The dashed lines indicate the approximate boundaries of s.o., s.p., s.r., and s.l.m. Under each camera lucida drawing is the molecular profile obtained from single-cell PCR analysis for the recorded cell with filled boxes indicating transcripts detected. Also shown are the electrophysiological responses of the cells to the indicated square wave current pulses (bottom) from a resting potential near −60 mV. Depolarizing current pulses and corresponding responses are for near-threshold and 2x-threshold stimulation (scale bars shown in K are for all traces). Phase plots of the APs arising from 2x-threshold stimulation are shown at right, with the first AP phase plot colored red and subsequent APs progressing from warm to cool colors ending in violet. L: histogram summarizing the frequency of occurrence for 16 transcripts probed by scPCR among the MGE cohort of recorded cells. GAD65, GAD67 glutamic acid dehydrogenase; nNOS, neuronal nitric oxide synthase; CR, calretinin; PV, parvalbumin; SOM, somatostatin; NPY, neuropeptide Y; VIP, vasoactive intestinal peptide; CCK, cholecystokinin; VGlut3, vesicular glutamate transporter type 3; enk,

preproencephalin; Lhx6, LIM/homeoboxprotein 6; Npas1, Npas3 neuronal PAS domain 1 and 3; COUPTFII, chicken ovalbumin upstream promoter transcription factor II. [From Tricoire et al. (1138) with permission from Society for Neuroscience.]

### Table 1.

Electrophysiological properties of the identified interneuron clusters

| | Cluster 1 (n = 15) | Cluster 2 (n = 23) | Cluster 3 (n = 34) | Cluster 4 (n = 33) | Cluster 5 (n = 19) | Cluster 6 (n = 18) | Comparison |
|---|---|---|---|---|---|---|---|
| Resting potential, mV | −57 ± 5 | −64 ± 7 | −70 ± 10 | −57 ± 10 | −59 ± 10 | −54 ± 6 | 3<<1,2,4,5,6 |
| Input resistance, MΩ | 116 ± 63 | 216 ± 124 | 302 ± 139 | 431 ± 193 | 401 ± 212 | 219 ± 98 | 1<<2,3,4,5,6, |
| Time constant, ms | 13 ± 8 | 46 ± 18 | 25 ± 8 | 44 ± 15 | 38 ± 13 | 22 ± 9 | 1<<3,6<<<2,4,5 |
| Sag index | 0.84 ± 0.06 | 0.79 ± 0.09 | 0.88 ± 0.06 | 0.80 ± 0.10 | 0.80 ± 0.07 | 0.71 ± 0.15 | 1,2,4,5,6 < 3 |
| Frequency at 2X threshold, Hz | 70 ± 26 | 19 ± 9 | 27 ± 10 | 17 ± 7 | 18 ± 6 | 27 ± 13 | 2,4,5<<3,6<<<1 |
| Adaption ratio at 2X threshold | 0.88 ± 0.13 | 0.64 ± 0.22 | 0.80 ± 0.12 | 0.56 ± 0.17 | 0.44 ± 0.17 | 0.46 ± 0.17 | 4,5,6 < 2<<<3 < 1 |
| 1st Spike threshold, mV | −32 ± 4 | −38 ± 3 | −34 ± 4 | −35 ± 3 | −36 ± 3 | −38 ± 4 | 2,4,5,6 < 3,1 |
| 2nd Spike threshold, mV | −32 ± 4 | −37 ± 3 | −34 ± 4 | −35 ± 3 | −35 ± 4 | −37 ± 4 | 1,2,3,4,5,6 |
| 1st Spike amplitude, mV | 47 ± 7 | 62 ± 8 | 52 ± 9 | 62 ± 6 | 48 ± 10 | 59 ± 8 | 1,3,5 < 2,4,6 |
| 2nd Spike amplitude, mV | 48 ± 8 | 61 ± 7 | 52 ± 9 | 61 ± 6 | 48 ± 10 | 60 ± 7 | 1,5 < 3<<2,4,6 |
| 1st Spike half-width, ms | 0.54 ± 0.11 | 0.74 ± 0.11 | 1.06 ± 0.20 | 0.81 ± 0.09 | 1.04 ± 0.15 | 0.72 ± 0.10 | 1<<<2,6<<4<<<3,5 |
| 2nd Spike half-width, ms | 0.54 ± 0.11 | 0.77 ± 0.12 | 1.08 ± 0.21 | 0.86 ± 0.10 | 1.12 ± 0.14 | 0.77 ± 0.10 | 1<<<2,6<<4<<<3,5 |
| 1st Time to repolarize, ms | 3.1 ± 1.2 | 4.3 ± 1.6 | 9.6 ± 4.1 | 10.8 ± 7.8 | 20.4 ± 12.7 | 11.5 ± 6.8 | 1 < 2<<<3,4,6 < 5 |
| 2nd Time to repolarize, ms | 3.1 ± 1.1 | 4.7 ± 1.5 | 9.9 ± 3.7 | 13.1 ± 7.7 | 23.2 ± 10.1 | 16.3 ± 10.0 | 1<<2<<<3,4,6<<5 |
| 1st Maximal decay slope, mV/ms | −112 ± 24 | −96 ± 17 | −55 ± 13 | −79 ± 16 | −50 ± 12 | −83 ± 14 | 1 < 2 <4,6<<<3,5 |
| 2nd Maximal decay slope, | −113 ± 26 | −91 ± 18 | −55 ± 13 | −74 ± 15 | −46 ± 10 | −78 ± 14 | 1<<2<<4,6<<<3<<5 |

n, Number of cells; < indicates significantly smaller with P ≤ 0.05; << indicates significantly smaller with P ≤ 0.01; <<< indicates significantly smaller with P ≤ 0.001. [From Tricoire et al. (1138) with permission from Society for Neuroscience.]

**Table 2.**

Functional properties of major $K^+$ current components in O-LM and PVBCs

| O-LM Interneurons | PVBC |
| --- | --- |
| Fast delayed rectifier | |
| 57 ± 5% | 58 ± 6% |
| Activation curve | Activation curve |
| Midpoint V: −8.0 ± 2.1 mV | Midpoint V: −7.1 ± 0.9 mV |
| k: 16.1 ± 0.7 mV | k: 11.5 ± 0.8 mV |
| Inactivation curve | |
| Midpoint V: −40.6 ± 2.4 mV | |
| k: 7.8 ± 0.8 mV | |
| Noninact. comp.: 8 ± 4% | |
| Deactiv. time constant (−40 mV): 11.1 ± 0.9 ms | |
| Slow delayed rectifier | |
| 25 ± 6% | 26 ± 5% |
| Activation curve | Activation curve |
| Midpoint V: −3.6 ± 4.2 mV | Midpoint V: −3.3 ± 4.9 mV |
| k: 23.1 ± 1.0 mV | k: 17.3 ± 1.5 mV |
| Inactivation curve | Inactivation curve |
| Midpoint V: −52.2 ± 7.7 mV | Midpoint V: −63.8 ± 6.2 mV |
| k: 15.2 ± 1.7 mV | k: 11.1 ± 2.0 mV |
| Noninact. comp.: 7 ± 2% | Noninact. comp.: 37 ± 5% |
| Deactiv. time constant (−40 mV): 21.0 ± 1.7 ms | |
| A-type | |
| 19 ± 2% | 17 ± 4% |
| Activation curve | Activation curve |
| Midpoint V: −0.2 ± 3.0 mV | Midpoint V: −6.2 ± 3.3 mV |
| k: 26.8 ± 0.8 mV | k: 23.0 ± 0.7 mV |
| Inactivation curve | Inactivation curve |
| Midpoint V: −78.5 ± 2.4 mV | Midpoint V: −75.5 ± 2.5 mV |
| k: 6.0 ± 1.2 mV (7) | k: 8.5 ± 0.8 mV (7) |
| Recovery from inactivation time constant: 39.3 ± 18.5 ms | Recovery from inactivation time constant: 30.1 ± 6.4 ms |
| Amplitude: 42 ± 13% | Amplitude: 22 ± 4% |

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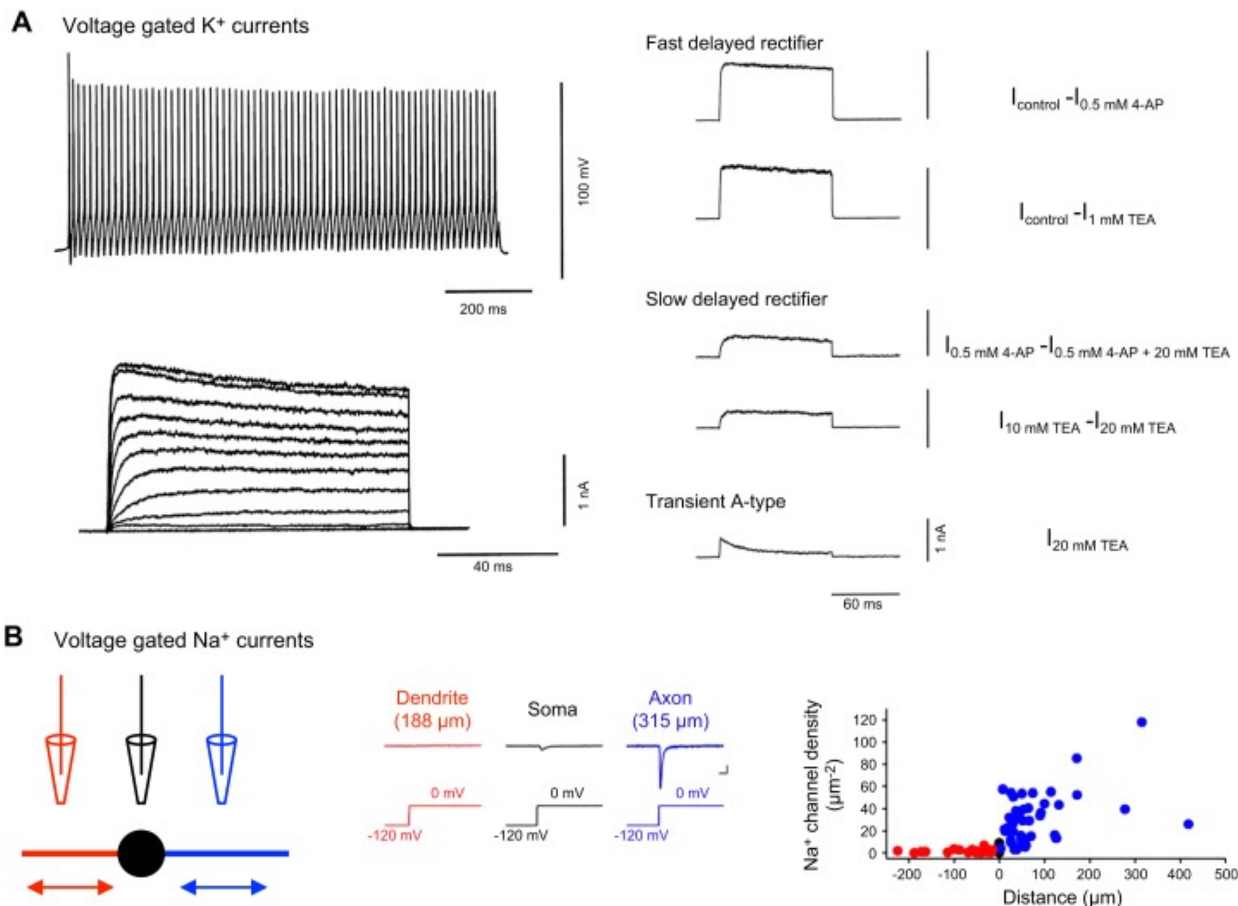
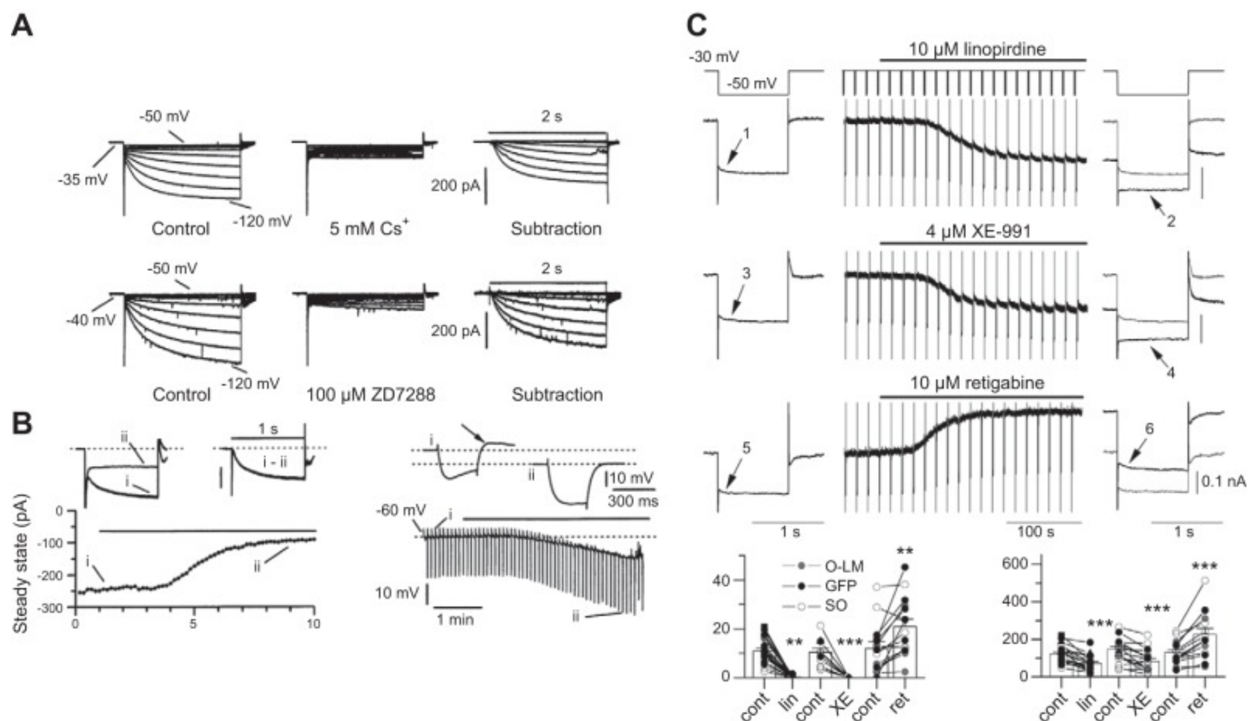
Values are means ± SE. Noninact., noninactivating; deactiv., deactivation. Data were extracted from References 678 and 756.

## FIGURE 10.



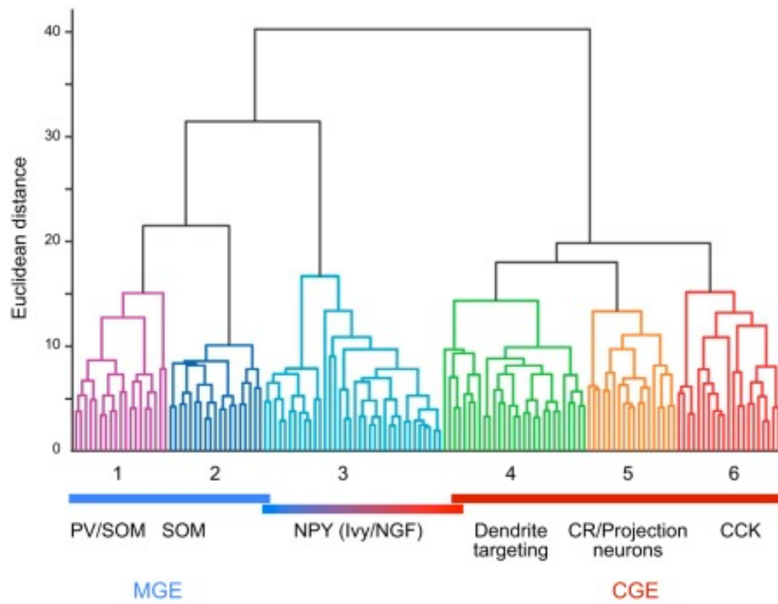

Voltage-gated potassium and sodium currents in PVBCS. A, top left: a train of action potentials evoked by a 1-s depolarizing current pulse in a fast spiking basket cell in current-clamp configuration. Bottom left: voltage-gated $K^+$ currents evoked in a nucleated patch isolated from a FSBC (holding potential −90 mV and test potentials delivered between −80 and 70 mV in 10-mV increments). Right: current subtraction analysis reveals three kinetically and pharmacologically distinct $K^+$ current components in nucleated patches from FSBC. Top: a fast delayed rectifier $K^+$ current component, [isolated by $I_{control} - I_{0.5\ mM\ 4\text{-}AP}$ (top trace) or $I_{control} - I_{1mM\ TEA}$ (bottom trace)]. Middle: a slow delayed rectifier $K^+$ current component (isolated by $I_{0.5mM\ 4\text{-}AP} - I_{0.5mM\ 4\text{-}AP + 20mM\ TEA}$ or $I_{1mM\ TEA} - I_{20mM\ TEA}$). Bottom: an A-type $K^+$ current component (isolated in the presence of $I_{20\ mM\ TEA}$). Currents were evoked by test pulses to 70 mV (from a holding potential of −90 mV). B: voltage-gated $Na^+$ channel spatial distribution profiling in FSBCs. Channel density measured in the outside-out patch configuration is plotted against distance, with negative values indicating dendritic location (red) and positive values indicating axonal location (blue). Note the absence of an appreciable $Na^+$ conductance in the dendrites and a stepwise increase of $Na^+$ channel density from the soma to the proximal axon, followed by a gradual increase to the distal axon. [A from Martina et al. (756) with permission from Society for Neuroscience. B from Hu et al. (502) with permission from Science.]

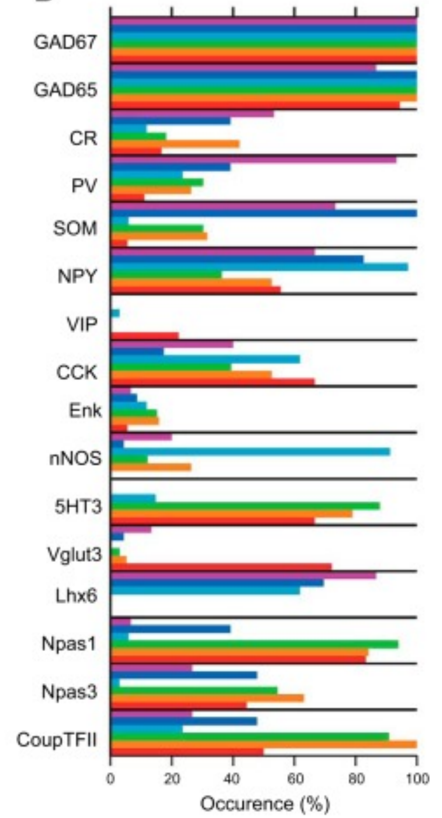
**FIGURE 11.**




$I_h$ and $I_M$ in O-LM interneurons. A: whole cell voltage-clamp recordings from CA1 O-LM interneurons showing a family of $I_h$ traces elicited by hyperpolarizing test pulses ($V_h$ = −35 mV) in the range −50 to −120 mV in control (left panel) and after addition of extracellular $Cs^+$ (5 mM, middle panel). The $Cs^+$-sensitive current was obtained by digital subtraction (right panel). Bottom traces: similar results were obtained using the $I_h$ antagonist ZD7288 (100 µM). B: time course of ZD7288 block: $I_h$ was activated with repetitive steps to −120 mV ($V_h$ = −40 mV). ZD7288 blocks the time-dependent inward current leaving only the leak and capacitive artifact (inset: i, control; ii, ZD7288; and i-ii, subtracted). Bottom right: under current-clamp recording conditions, ZD7288 induces a hyperpolarization of the cell, concomitant with a block of the sag and the rebound depolarization (arrow) elicited by hyperpolarizing current steps (insets: i, control; and ii, in the presence of ZD7288) ($V_h$ = −60 mV). C: $I_M$ in SO interneurons can be identified using the antagonists, linopirdine, XE-991, and retigabine. Under whole cell voltage-clamp conditions, steps from −30 to −50 mV at 15-s intervals activate the time-dependent current $I_M$ (traces 1, 3, and 5). Addition of linopirdine, XE-991, and retigabine removes the time-dependent component. Traces enumerated in each condition are the average of three traces. Control traces (gray) are overlaid for comparison with drug conditions (black). Bottom panels: isolated $I_M$ amplitudes and changes in holding current ($I_{hold}$) in the presence of linopirdine, XE-991, and retigabine conditions. GFP-positive s.o. interneurons, anatomically identified O-LM cells, and unidentified s.o. interneurons are indicated by black symbols, gray symbols, and open symbols, respectively. [A and B from Maccaferri and McBain (718) with permission from Journal of Physiology. C from Lawrence et al. (645) with permission from the Society for Neuroscience.]

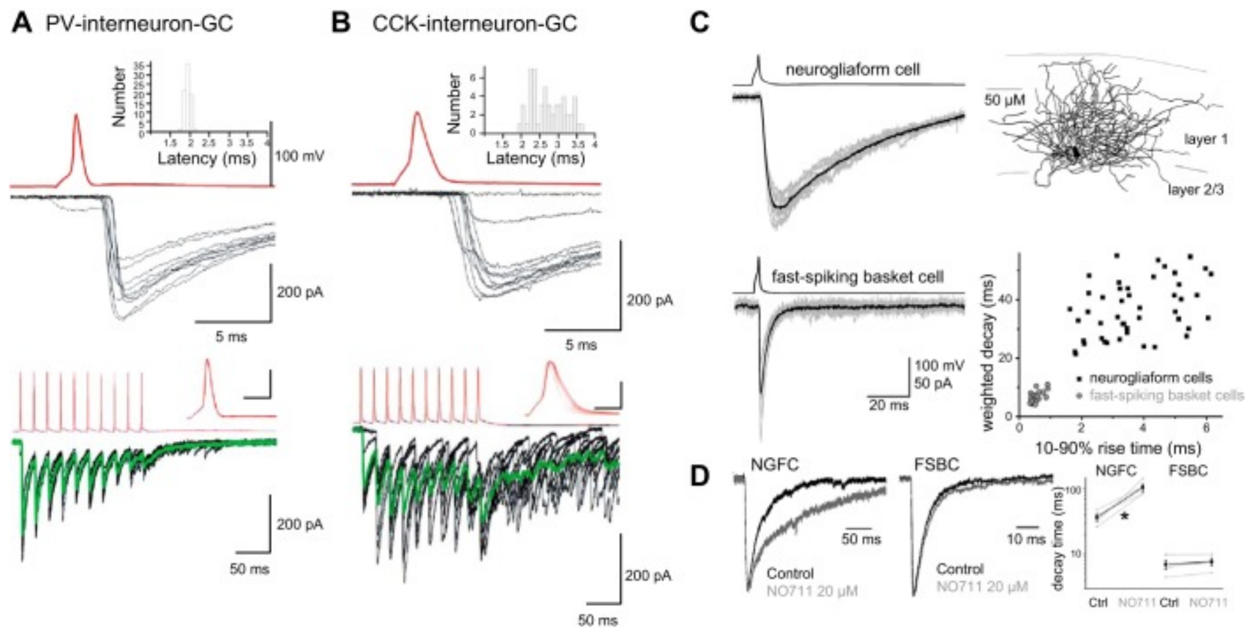
**FIGURE 12.**



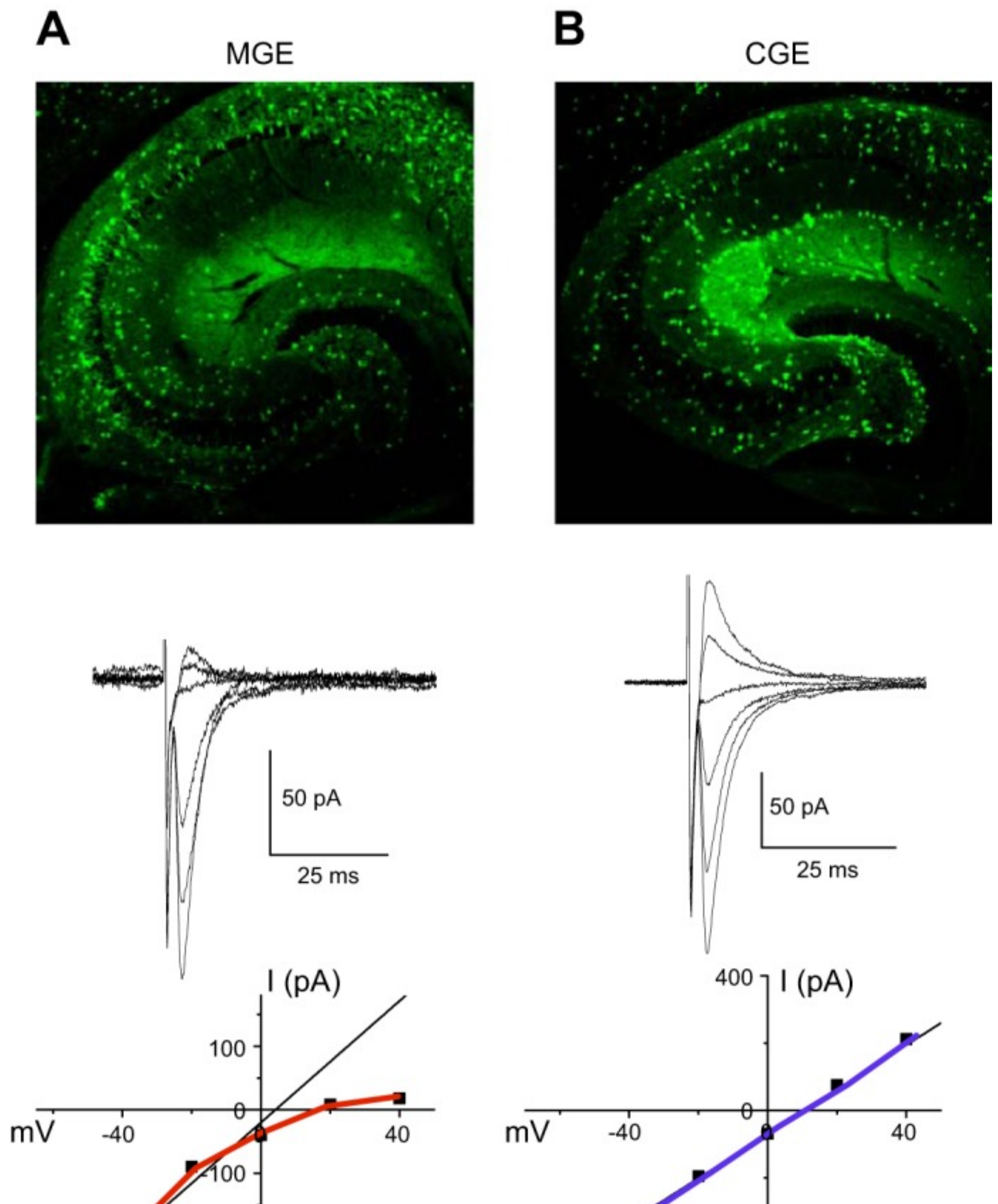

Unsupervised cluster analyses of hippocampal GABAergic interneurons based on developmental, electrophysiological, and molecular properties. A: Ward's clustering applied to a sample of 142 recorded MGE- and CGE-derived interneurons. In this dendrogram, the x-axis represents individual cells, and the y-axis represents the average Euclidean within-cluster linkage distance. B: histogram summarizing the frequency of occurrence of each of the 16 transcripts probed by single cell PCR within each cluster obtained with the K-means clustering (K 6). See A for cluster color code. [Data from Tricoire et al. (1138) with permission the Society for Neuroscience.]

## FIGURE 13.




The three modes of GABA release from PV-containing, CCK-containing and NGFC interneurons. A and B: superimposed IPSCs (black) evoked by single presynaptic action potentials (red) in a PV-containing interneuron-granule cell (GC) pair (A) and a CCK interneuron-granule cell pair (B). Insets: histograms of IPSC latency. A and B, bottom panels: superimposed IPSCs (black) evoked by trains of 10 action potentials (red) in a PV interneuron-granule cell pair (left) show a predominant synchronous mode of inhibitory output. In contrast, repetitive transmission in a CCK interneuron-granule cell pair (right) shows a large asynchronous component of transmission as the train proceeds. Green: average IPSCs. Insets: presynaptic action potentials aligned to the stimulus onset at expanded time scale (scale bars: 2 ms, 50 mV). C: $GABA_A$ IPSCs evoked by NGFCs (top right panel) are comparatively slower than those observed at FSBC synapses. Top: 10 consecutive IPSCs (gray) and their average (black) in a layer 2/3 PC after single action potentials in a layer 1 NGFC (top). Middle traces show equivalent IPSCs evoked by a layer 2 FSBC for comparison. Bottom right panel: comparison of the kinetics of postsynaptic responses evoked by NGFCs (black squares) and FSBCs (gray circles). Each point represents an individual connection. D: modulation of GABA responses evoked by NGFCs by GABA uptake. Fast IPSCs evoked from FSBC are not sensitive to the GABA uptake inhibitor NO711. In contrast, $GABA_A$,slow IPSCs arising from NGFCs are markedly prolonged in the presence of NO711, demonstrating a differential sensitivity of the two modes of transmission to inhibition of GABA uptake. [A and B from Hefft and Jonas (477) with permission from Nature Neuroscience. C and D from Szabadics et al. (1074).]

**FIGURE 14.**

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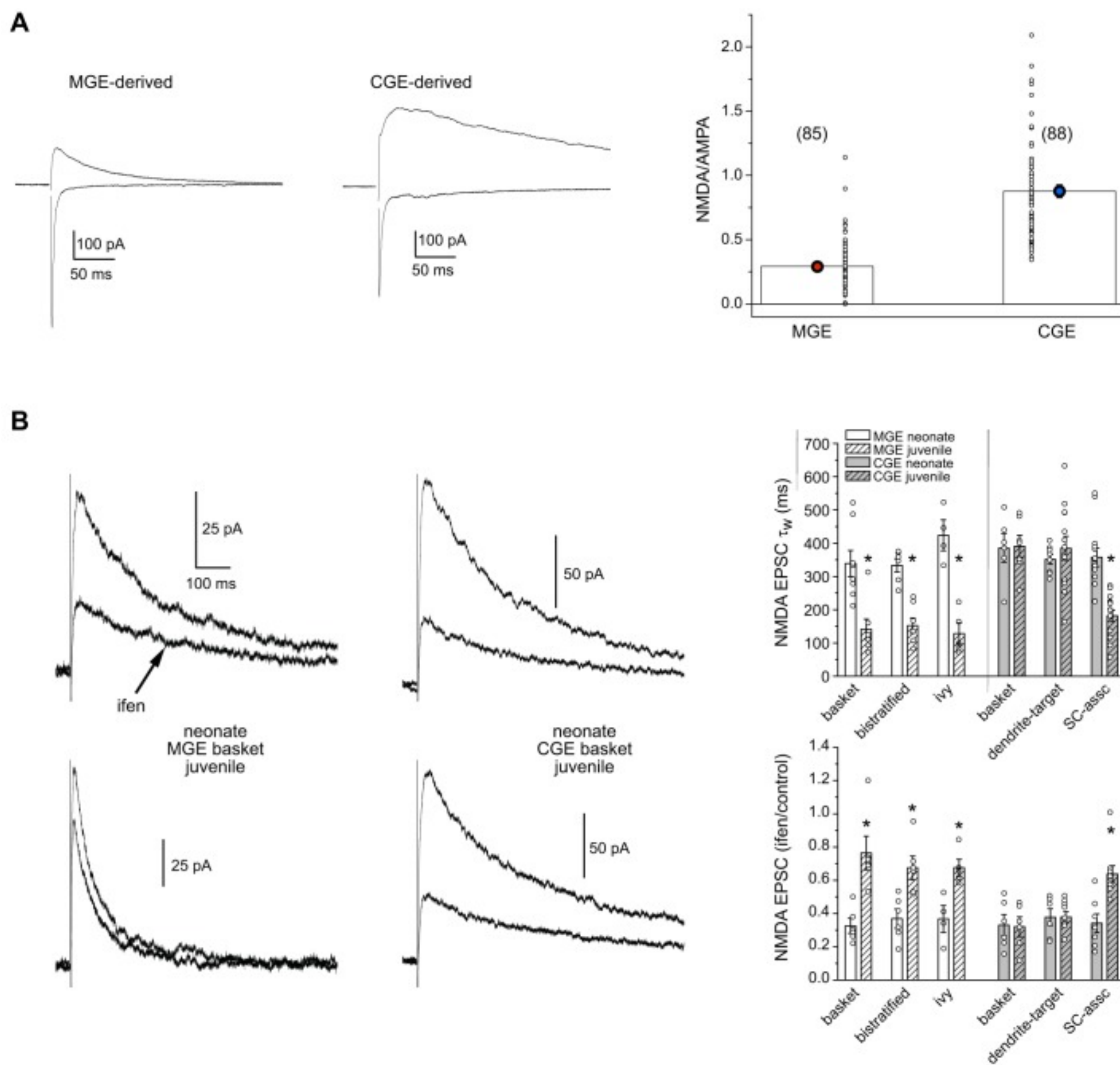
MGE and CGE-dependent expression of synaptic AMPAR-preferring glutamate receptors. A and B, top panels: interneurons that were targeted for recording using hippocampal slices derived from Nkx2–1-cre:RCE GFP and Htr3a-GFP reporter mouse lines, respectively (Scale bars, 100 μm). Middle panels: representative current-voltage relationships of Schaffer collateral-evoked AMPAR-mediated EPSCs in MGE- vs. CGE-derived CA1 interneurons. MGE-derived interneurons typically possess GluA2-lacking CP-AMPARs that possess strong inward rectification (left bottom panels). CGE-derived interneurons typically expressed GluA2-containing CI-AMPARs which possess near linear rectification properties. Individual dots in bottom panels represent data from a single recording; numbers in parentheses represent the number of cells recorded. [Data from Matta et al. (763).]

## FIGURE 15.

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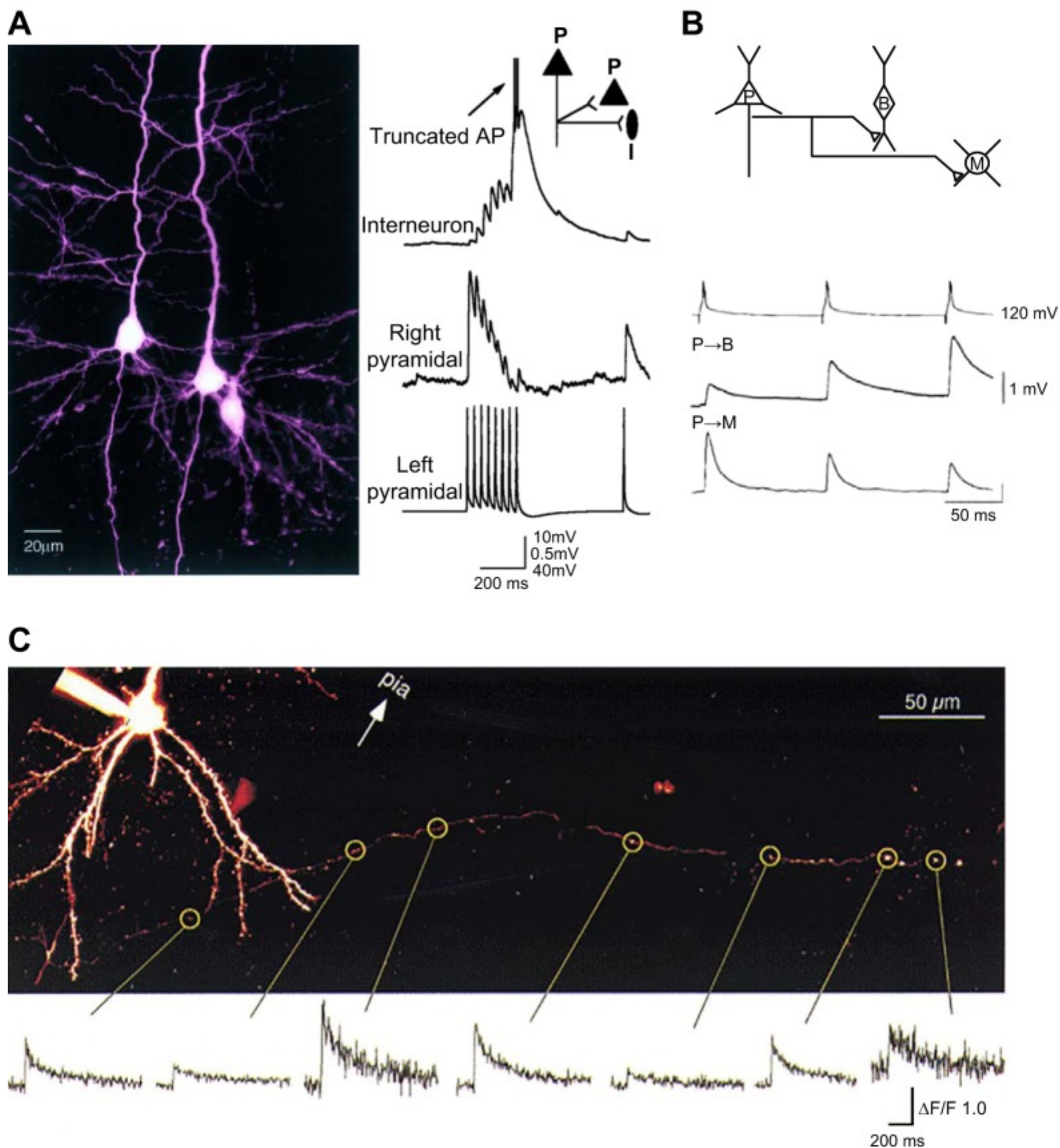
MGE and CGE-dependent expression of synaptic NMDAR-preferring glutamate receptors and the cell type developmental expression of synaptic GluN2 receptors. A, left: MGE-derived interneurons typically possess small NMDAR-mediated EPSCs that have rapid kinetics. Schaffer collateral evoked synaptic traces show AMPAR-mediated inward currents and NMDAR-mediated outward currents ($V_h$ = −70 and +40 mV, respectively). A, middle: in contrast, CGE-derived interneurons typically possess large and kinetically slow evoked NMDAR-mediated currents. Right panel: AMPA/NMDAR amplitude ratios to be ~0.25 for MGE-derived interneurons and close to unity for CGE-derived interneurons. B: synaptic NMDARs at Schaffer collateral synapses onto CA1 MGE-derived interneurons undergo a developmental switch in NMDAR subunit expression. Left column: MGE-derived interneurons transition from GluN2B containing NMDARs to GluN2A-containing in juvenile receptors as evidenced by a loss of ifenprodil sensitivity and decrease in the time constant of decay. Middle panels: in contrast, CGE-derived interneurons possess GluN2B-containing receptors that persist through both neonate and juvenile states. Right panels, top: summary plot for the NMDAR EPSC decay kinetic weighted time constant (τw) for both neonate and juvenile MGE- and CGE-derived identified interneurons. Bottom panels: summary graph of the developmental regulation of ifenprodil sensitivity expressed as the ratio of the NMDAR EPSC peak amplitude measured in the presence of ifenprodil divided by the control NMDA EPSC peak amplitude. [Data taken from Matta et al. (763).]

## FIGURE 16.

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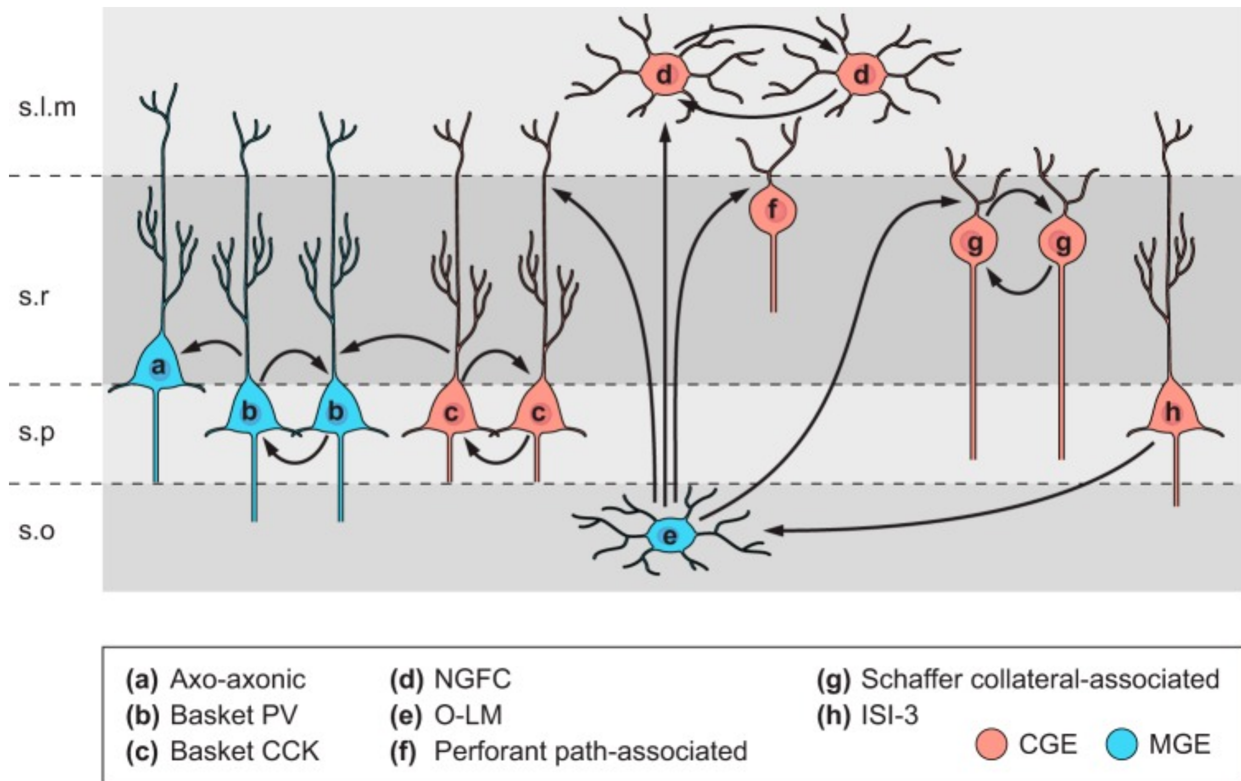
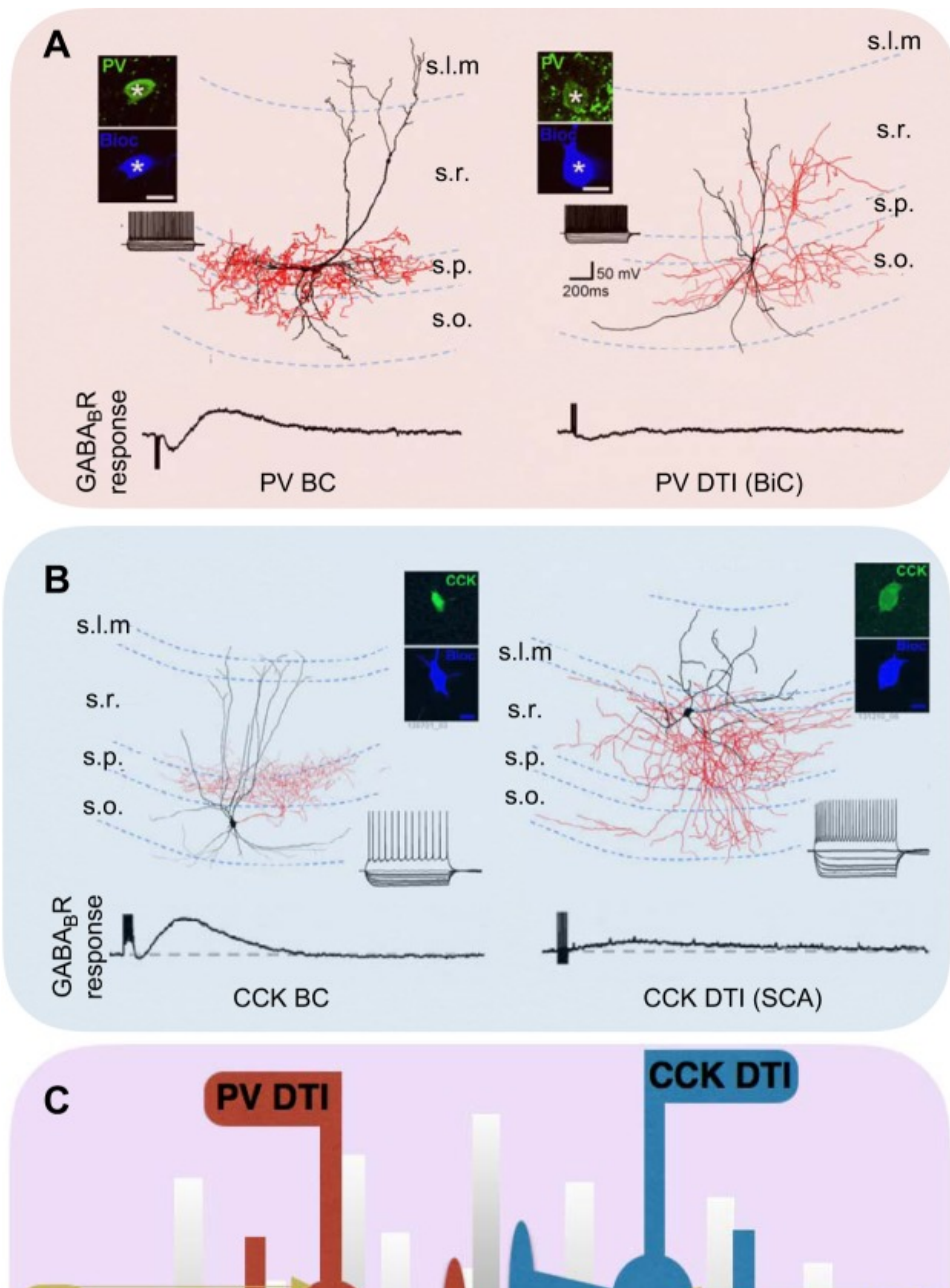
Target-cell-dependent inhibitory transmission. A, left: image of three biocytin-filled neurons in layer 5 somatosensory cortex. The pyramidal neuron on the left innervated another pyramidal neuron and a bipolar interneuron, both on the right. A, right: single-trial responses (30 Hz) to the same action potential train (evoked in the presynaptic left pyramidal cell) for the simultaneously recorded postsynaptic interneuron and pyramidal cell targets. Note the strong frequency facilitation and depression of synaptic events in the interneuron and pyramidal postsynaptic targets, respectively. B: data from a triple-patch recording in layer2/3 somatosensory cortex, revealing differential short-term plasticity in two classes of interneurons innervated by a single pyramidal neuron. Three action potentials evoked at 10 Hz in the presynaptic pyramidal cell (top trace), evoked short-term facilitation of unitary EPSPs evoked in the bitufted cell (middle trace, P-B connection), whereas the amplitude of EPSPs evoked simultaneously in the multipolar cell decreased (bottom trace, P-M connection). C: presynaptic $Ca^{2+}$ transients at divergent release sites of the same axon exhibit target-cell dependence. A single layer 2/3 pyramidal cell loaded with $Ca^{2+}$ indicator (upper fluorescence image) displays a large degree of heterogeneity in single action potential-evoked $Ca^{2+}$ transients (bottom traces) at various boutons (circles) along a single axon collateral. [A from Markram et al. (749). B from Reyes et al. (940) with permission from Nature Neuroscience. C from Koester and Sakmann (591) with permission from Journal of Physiology.]

## FIGURE 17.




Schematic illustrating the major $GABA_A$R-mediated functional connectivity among hippocampal interneurons. This schematic summarizes the known $GABA_A$R-mediated cross-talk, as assessed by paired electrophysiological recordings in identified CA1/CA3 hippocampal interneuron subtypes. It must be noted that anatomical studies have demonstrated additional putative interactions between interneuron subtypes that have not been included in this summary. s.o., Stratum oriens; s.p., stratum pyramidale; s.r., stratum radiatum; s.l.m., stratum lacunosum moleculare.

## FIGURE 18.

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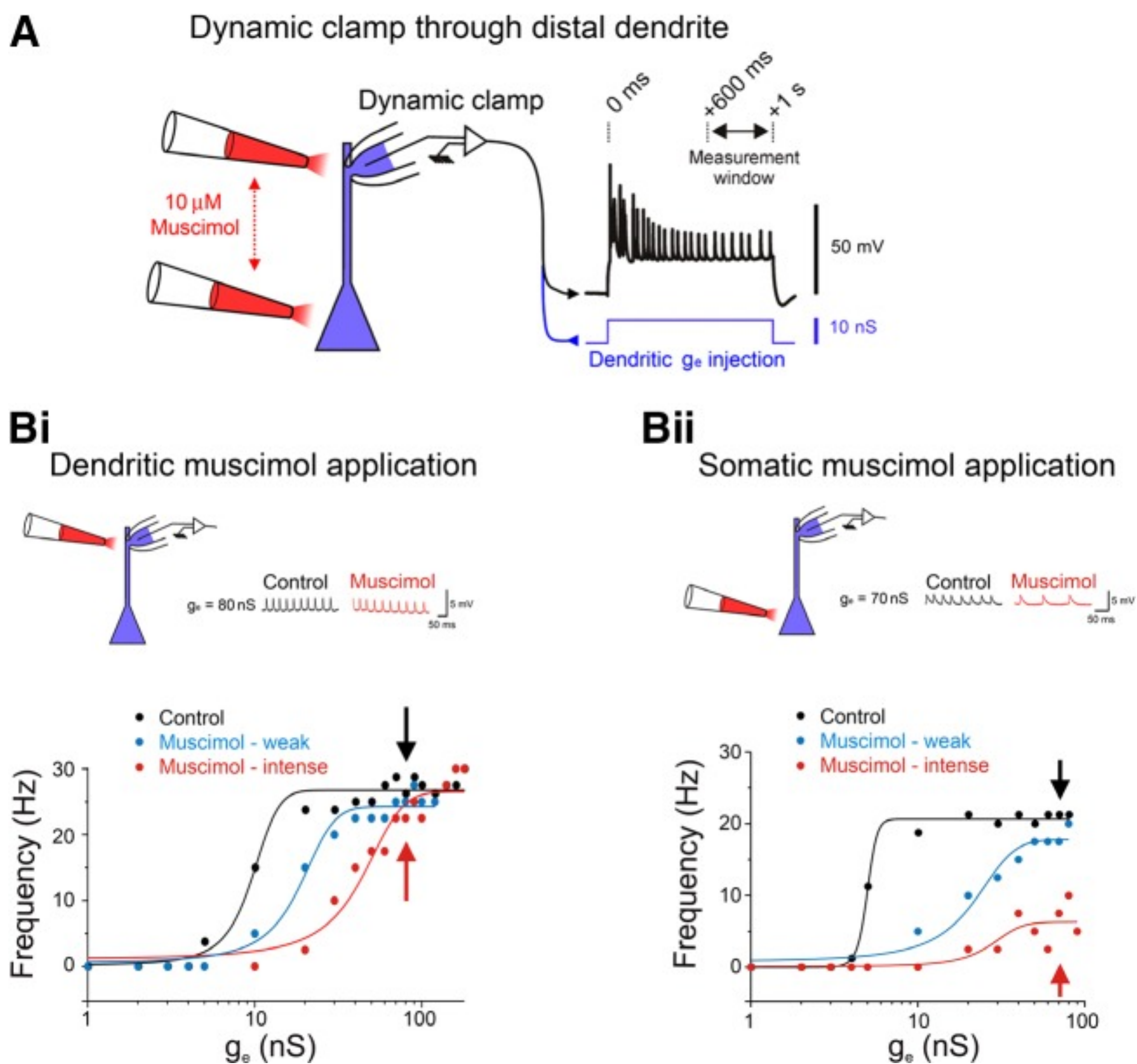
Selectivity of postsynaptic GABA$_B$R-mediated responses at perisomatic vs. dendritic targeting PV- and CCK-containing interneuron subtypes. A and B: trains of stimuli elicit robust GABA$_B$R-mediated postsynaptic IPSCs (traces at bottom of cell reconstructions) in PV- and CCK-BC subtypes (see insets for post hoc immunocytochemistry and membrane voltage responses including action potential firing patterns in response to hyperpolarizing and depolarizing current steps) with minimal or no response at their dendrite targeting (DTI) counterparts. Based on axonal arborization, the PV and CCK DTIs in these examples correspond to bistratified (BiC) and Schaffer-collateral associated cells, respectively (SCA). C: schematic summarizing this selectivity as described in these studies. PC, pyramidal cell. [PV cell reconstructions and traces from Booker et al. (116) with permission from Journal of Neuroscience. CCK cell reconstructions and traces from Booker et al. (115) with permission from Cerebral Cortex.]

**FIGURE 19.**

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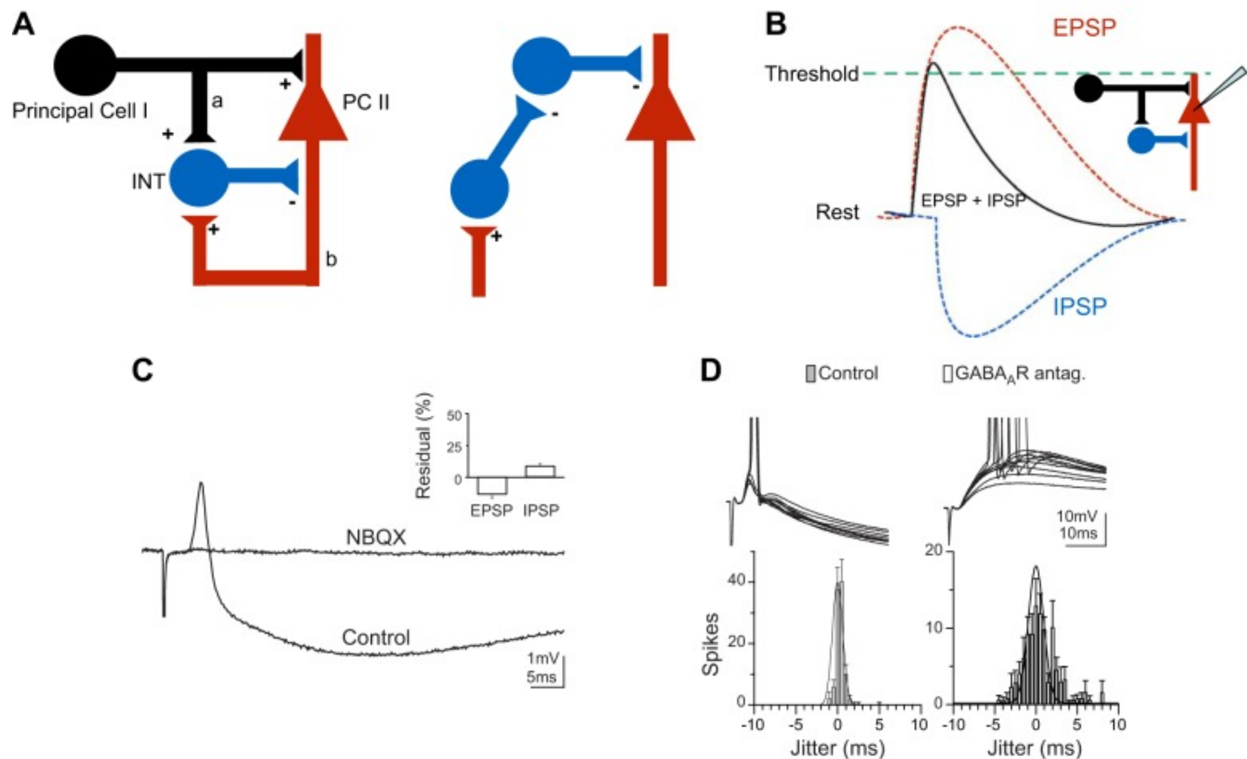
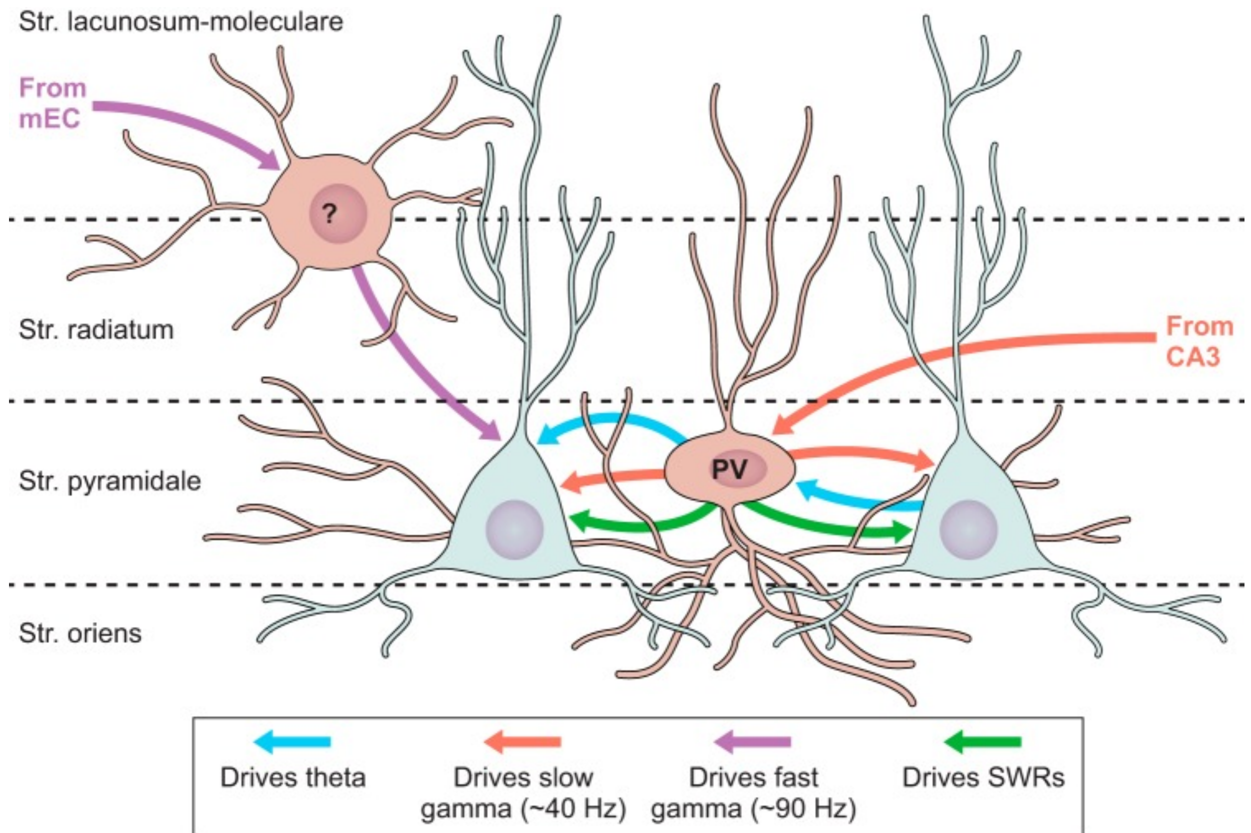
The differential impact of inhibitory inputs arriving at distal vs. proximal dendritic locations. A: schematic showing the two different experimental protocols, with application of the $GABA_A$ agonist muscimol either to the soma and proximal apical dendritic trunk, or to the more distal apical trunk close to the location of a patch pipette. A steady-state excitatory conductance ($E_{rev}$ = 0 mV) is simulated by dynamic clamp over a 1-s period, and the steady-state firing rate is derived from the final 400 ms of this. B: input-output (IO) functions at different levels of ambient muscimol for dendritic (Bi) and somatic (Bii) applications. Muscimol is applied by a continual series of low pressure puffs, and the concentration is varied by changing the frequency of pressure puffs. Note that in the configuration where muscimol is applied to the distal dendritic compartment, the maximal attainable firing frequency is unchanged in contrast to when muscimol is applied to the somatic/proximal dendritic compartment. [Data from Pouille et al. (924) with permission from Physiological Reports.]

**FIGURE 20.**



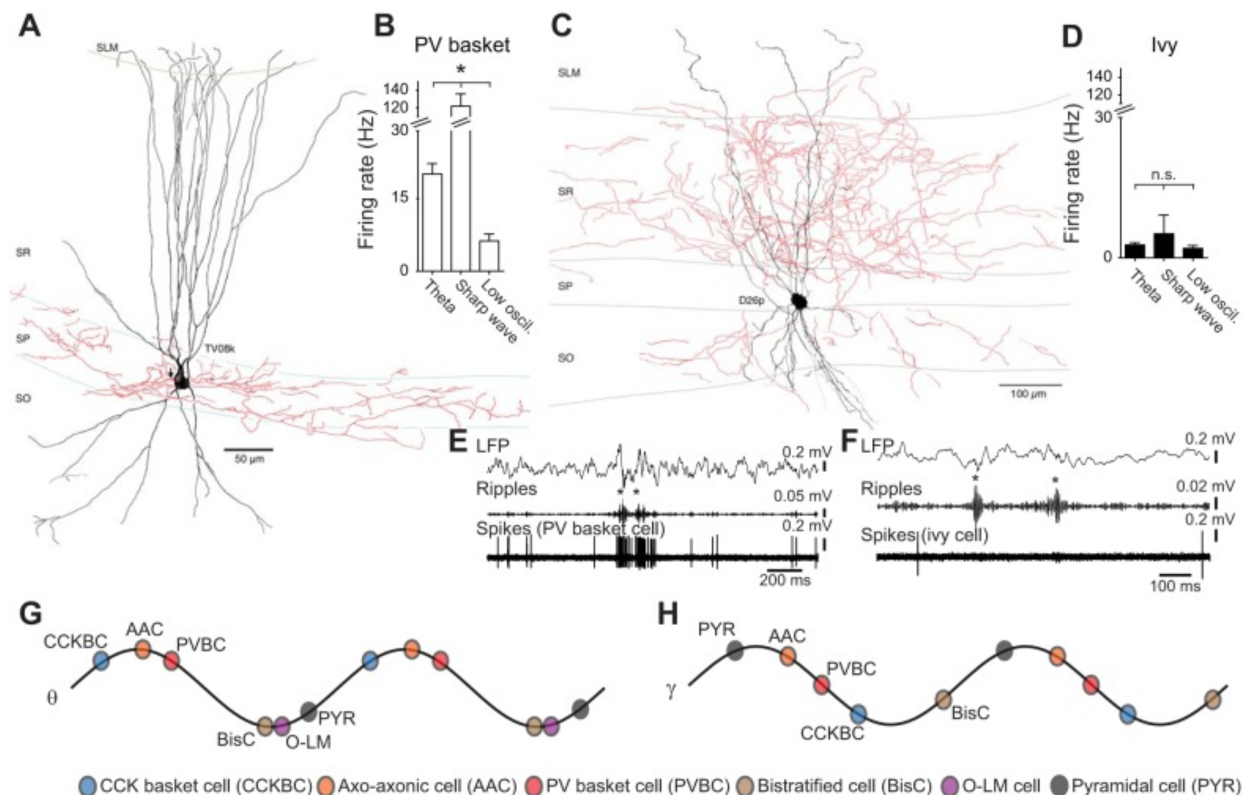

Common motifs of inhibition within cortical and hippocampal circuits. A, left: feedforward (a) and feedback (b) inhibitory control of principal (PC) cell circuits are the most common circuits within hippocampus and cortex. In feedforward inhibitory circuits, a common afferent (PCI) makes monosynaptic connections to both PCII and inhibitory interneurons. The inhibitory interneuron then makes a monosynaptic inhibitory connection onto PCII. Thus the same principal cell (PCI) drives monosynaptic excitation and disynaptic inhibition onto a common PC (B and D). In feedback inhibitory circuits, the output of PCII makes a monosynaptic excitatory input onto interneurons which then return monosynaptic inhibition onto the same cell or population of cells. A, right: some interneuron subpopulations make only inhibitory connections with other interneurons. In this configuration afferent excitatory drive onto these types of interneurons drives disinhibition of principal cells by an inhibition of inhibitory input. B–D: a schematic representation of feedforward inhibitory control of the temporal window for excitation. Inset shows a hypothetical electrophysiological recording from PCII (inset). Monosynaptic excitation of the principal cells (red trace) results in a prolonged excitatory synaptic event that has a long temporal window in which to exceed threshold. The concomitant activation of the disynaptic inhibitory input (IPSP) summates with the EPSP and narrows the temporal window (black trace) for the EPSP to exceed threshold. C: under current-clamp conditions, stimulation of this feedforward inhibitory circuit triggers an early EPSP and a later IPSP, both of which are blocked by the AMPAR antagonist NBQX confirming that the EPSP-IPSP sequence is being driven by glutamatergic afferents. D: voltage traces for current-clamp recordings from CA1 PCs upon stimulation of two Schaffer collateral pathways under control (left) and in the presence of a $GABA_A$ receptor antagonist, illustrating that inhibitory input enforces a narrow temporal window for coincidence detection, which is lost in the absence of inhibitory control. [C and D from Pouille and Scanziani (922) with permission from Science.]

**FIGURE 21.**



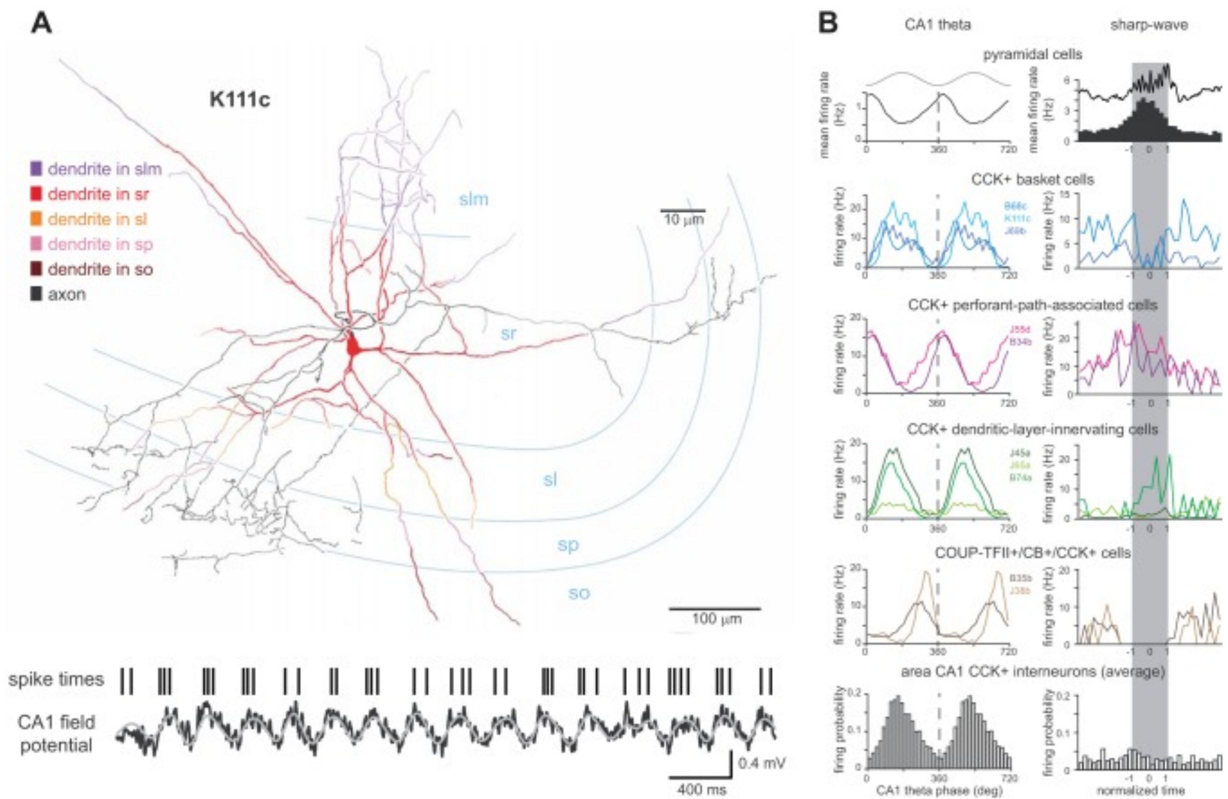

Entrainment of oscillations in CA1. CA1 pyramidal cells are important for generating theta oscillations in CA1, although fast-spiking PV basket cells play an important role in entraining CA1 network oscillations at theta frequencies. Slow gamma oscillations are driven by inputs from CA3 and, as such, show peak amplitude in stratum radiatum. The slow CA3 gamma oscillation recruits CA1 fast-spiking PV basket cells, which in turn drive slow gamma rhythms in CA1 pyramidal cells and other interneurons. Fast gamma oscillations are driven by inputs arriving from the medial entorhinal cortex and appear to drive an as yet unidentified group of interneurons that, in turn, entrain the local network to this faster rhythm. Remarkably, sharp wave-ripples can be driven by a single fast-spiking PV basket cell.

## FIGURE 22.



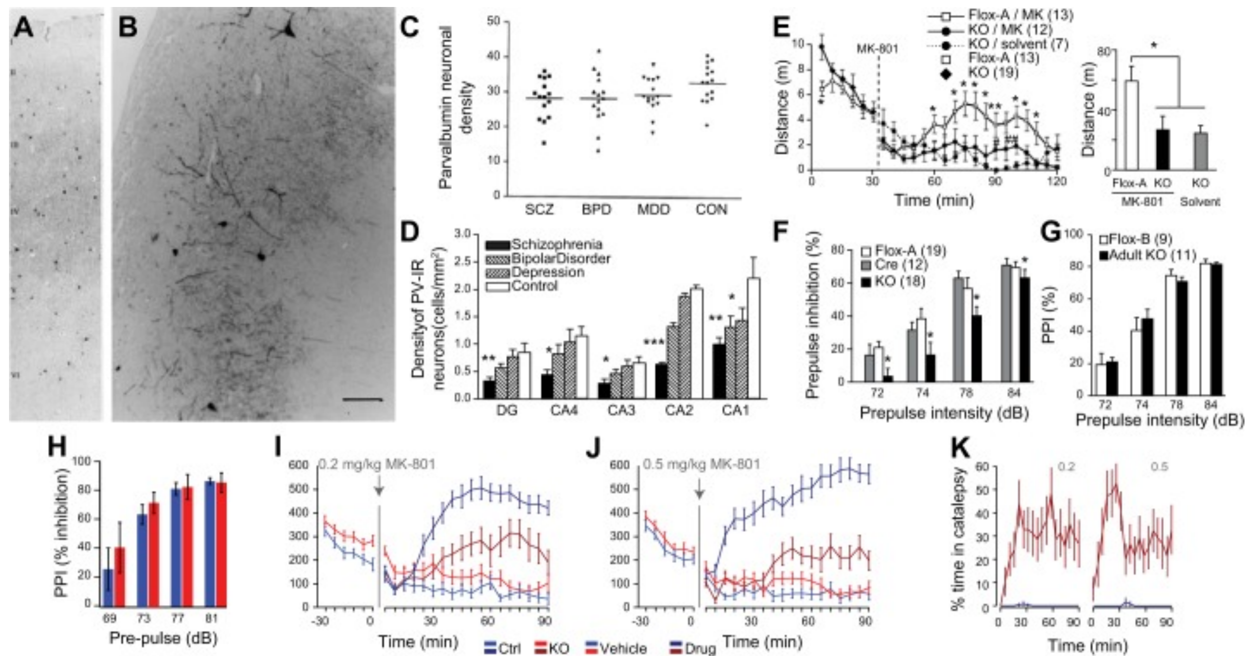

Firing of different interneurons during network oscillations. A: reconstruction of a CA1 PVBC recorded juxtacellularly in vivo from an awake rat. B: firing rate of CA1 PV basket cells during different network oscillations. C: reconstruction of a CA1 ivy cell recorded juxtacellularly in vivo from an awake rat. D: firing rate of CA1 ivy cells during different network oscillations. Example traces showing spiking activity of PV basket cell (E) and ivy cell (F) during sharp wave-ripple oscillations. G: preferred firing phase of CA1 interneurons during the theta cycle. Projecting interneurons are not shown, but most tend to fire around the trough of the theta cycle (537). H: preferred firing phase of CA1 interneurons during the gamma cycle. O-LM cells do not significantly phase-lock to the gamma cycle. Note that while all cell types shown have a phase preference, the depth of gamma modulation varies significantly between cell types, with the firing rate of bistratified cells being most strongly modulated by gamma (1141). [A–F adapted from Lapray et al. (635) with permission from Nature Neuroscience.]

## FIGURE 23.



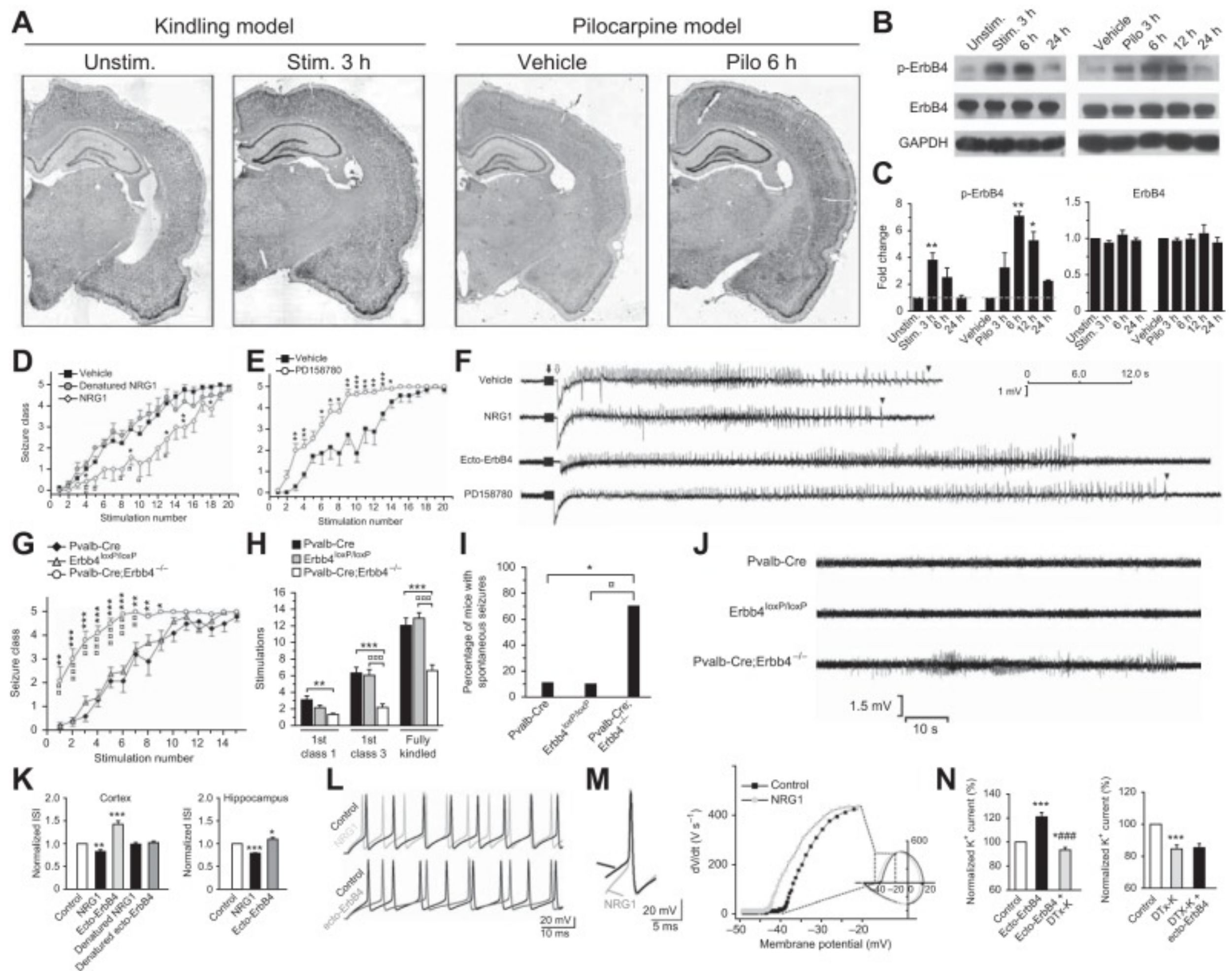

Firing of CA3 CCK-positive interneurons during network oscillations. The advent of optogenetic tools and interneuron-specific Cre driver lines has led to a wealth of data on how different interneuron "subtypes" can influence behavior. However, these data, taken from juxtacellular recordings of CCK-expressing CA3 interneurons, show that cells expressing the same neuropeptides or $Ca^{2+}$-binding proteins can behave very differently during rhythmic activity. A: firing pattern of a CCK-expressing basket cell relative to theta oscillations in CA1. Note that the cell tended to fire at the peak of the theta oscillation. B: juxtacellular recordings from other CCK-expressing interneurons in CA3 show that different cell types display remarkably divergent behaviors during both theta and sharp wave-ripple oscillations. [Adapted from Lasztoczi et al. (638) with permission from the Society for Neuroscience.]

**FIGURE 24.**




Parvalbumin-containing interneurons in schizophrenia. One of the most consistent findings from postmortem studies of patients with psychiatric disease is a reduced density of PV interneurons in cases of schizophrenia and, to lesser extent, bipolar disorder. PV-expressing neurons from human prefrontal cortex (A) and hippocampal region CA1 (controls) (B). PV cell density is significantly reduced in prefrontal cortex (C) and hippocampus in human psychiatric disease (D). Deleting the NMDAR subunit NR1 from GAD67-expressing interneurons (including PV interneurons) early in development causes a resistance to MK801-induced hyperlocomotion (E) and a reduction in prepulse inhibition (PPI) (F), implying that reduced NMDAR function in these cells is a cause of schizophrenia-like behaviors. However, deleting NR1 from the same neurons in adulthood fails to cause the same behavioral phenotypes (G), and PV interneuron-specific deletions of NR1 fail to cause deficits in PPI (blue: controls, red: KOs) (H). Mice with PV interneuron-specific deletions of NR1 show lower levels of hyperlocomotion than controls when dosed with MK801 at both 0.2 mg/kg (I) and 0.5 mg/kg (J), but this appears to be due to these animals displaying a greater sensitivity to MK801 and spending a large amount of time in a cataleptic state. These data suggest that NMDAR hypofunction in PV-containing interneurons is not an underlying factor in schizophrenia-like behavioral deficits, but that loss of functional NMDAR in PV-containing interneurons may actually be a risk factor instead of a cause of schizophrenia, by making neural circuits more susceptible to impaired NMDAR function in other types of neuron. [A and C adapted from Beasley et al. (77), with permission from Biological Psychiatry. B and D adapted from Zhang and Reynolds (1272), with permission from Schizophrenia Research. E– G from Belforte et al. (82), with permission from Nature Neuroscience. H–K from Bygrave et al. (155), with permission from Translational Psychiatry.]

## FIGURE 25.

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PV interneurons become more excitable via neuregulin1/ErbB4 signaling during epileptogenesis. A: in situ hybridization shows increased expression of neuregulin1 (NRG1) in the hours after seizure kindling or exposure to pilocarpine in rats. B and C: increased NRG1 expression is associated with increased activation of its receptor, ErbB4, measured through increased levels of phosphorylated ErbB4 (p-ErbB4). D: intracerebroventricular infusion of NRG1 delayed kindling-induced epileptogenesis. E: inhibiting ErbB4 activity with the tyrosine kinase inhibitor PD158780 exacerbated the effects of kindling. F: representative traces. G and H: deleting ErbB4 from PV interneurons is sufficient to increase susceptibility to kindling. I: the incidence of spontaneous seizures in kindled mice. J: example traces. K: NRG1 increases firing rate of PV interneurons in both cortex and hippocampus, while neutralizing endogenous NRG1 with the Ecto-ErbB4 peptide reduces the firing rate. L: example traces. M: application of NRG1 enhances initiation of action potentials in PV interneurons. N: neutralizing endogenous NRG with Ecto-ErbB4 increases $K^+$ currents in PV interneurons, and this increase is completely blocked by the Kv1.1-specific blocker DTx-K. These data together show that NRG1 increases the excitability of PV interneurons through inhibition of Kv1.1 potassium channels, providing a homeostatic response to increase inhibition in the network during epileptogenesis. [A–J adapted from Tan et al. (1087). K–N adapted from Li et al. (674). Figures used with permission from Nature Neuroscience.]

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