Differential distribution and function of GABABRs in somato-dendritic and axonal compartments of principal cells and interneurons in cortical circuits

Differential distribution and function of $GABA_BRs$ in somato-dendritic and axonal compartments of principal cells and interneurons in cortical circuits

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Abstract

$GABA_BRs$ are highly expressed in cortical circuits, controlling neuronal excitability and synaptic transmission in both principal cells and inhibitory interneurons. Light and electron microscopic studies confirmed the wide distribution of receptors and revealed cell type-specific quantitative differences in their cellular and subcellular distributions. At the subcellular level, $GABA_BRs$ are abundant at the peri- and extrasynaptic membrane of somato-dendritic compartments and to lower levels in the axon terminals of both cortical excitatory principal cells and inhibitory interneurons. Differences in the surface densities are particularly prominent between neurochemically-defined interneuron types. Whole-cell recordings further demonstrated that $GABA_BRs$ differentially mediate post- and presynaptic inhibition in principal cells and various GABAergic interneurons by preferentially modulating postsynaptic G-protein-coupled inwardly rectifying K^+ (Kir3) channels and presynaptic high voltage-activated Ca^{2+} (Ca_V) channels. These data convergently indicate that $GABA_BRs$ not only control the overall level of neuronal excitability and activity, but can also fine tune the activation and interactions of excitatory and inhibitory neurons in cortical circuits.

Keywords

dendritic inhibition, presynaptic inhibition, network activity, electron microscopy, synaptic plasticity, ion channels

Abbreviations

BC, basket cell; CA, cornu ammonis; CaMKII, Ca^{2+}/calmodulin-dependent protein kinase II; cAMP, cyclic adenosine monophosphate; Ca_V channel, high voltage-activated Ca^{2+} channel; CCK, cholecystokinin; CNS, central nervous system; DG, dentate gyrus; DG-GC, dentate gyrus granule cell; ER, endoplasmic reticulum; GABA, γ-aminobutyric acid; $GABA_AR$, γ-aminobutyric acid type A receptor; $GABA_BR$, γ-aminobutyric acid type B receptor; $GABA_CR$, γ-aminobutyric acid type C receptor; IN, interneuron; GAD65/67, glutamic acid decarboxylase65/67; GAT1, GABA transporter 1; GAT3, GABA transporter 3; GPCR, G protein coupled receptor; IPSC, inhibitory postsynaptic current; IPSP, inhibitory postsynaptic potential; KCTD, K^+ channel tetramerization domain-containing; Kir2, inward-rectifier potassium channel; Kir3 channel, G-protein-coupled inwardly rectifying potassium channel; LTP, long-term potentiation; MF, mossy fiber; mGluR1α, metabotropic glutamate receptor type 1α; mRNA, messenger ribonucleic acid; NGFC, neurogliaform cell; NMDAR, N-methyl-D-aspartate receptor; PC, principal cell; PKA, protein kinase A; PKC, protein kinase C; PV, parvalbumin; SDS-FRL, sodium dodecyl sulfate-digested freeze-fracture replica labeling; SNAP-25, synaptosomal-associated protein-25; SNARE, soluble N-ethylmaleimide-sensitive factor attachement protein receptor; SL, stratum lucidum; SL-M, stratum lacunosum-moleculare; SOM, somatostatin; SR, stratum radiatum; WT, wild-type.

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1. Introduction

Neuronal circuits of the central nervous system (CNS) require a precise balance of excitation and inhibition to maintain correct network co-ordination and thus function. The inhibitory neurotransmitter γ-aminobutyric acid (GABA), released by many types of cortical GABAergic interneuron (IN), exerts inhibition through ionotropic receptors ($GABA_AR$, $GABA_CR$) and G-protein-coupled metabotropic $GABA_B$ receptors ($GABA_BRs$) (Macdonald and Olsen, 1994; Mody et al., 1994; Misgeld et al., 1995; Kaupmann et al., 1997; Bowery et al., 2002). $GABA_BR$ responses have been observed in all cortical areas in both excitatory principal cells (PCs) and inhibitory INs alike (Newberry and Nicoll, 1984, 1985; Dutar and Nicoll, 1988b). A component of elicited inhibitory postsynaptic potentials (IPSPs) in various neuron types has been shown to be resistant to the $GABA_A$ receptor antagonist bicuculline, but efficiently blocked by the $GABA_BR$ antagonist CGP35348 (Solis and Nicoll, 1992). Furthermore, synaptic transmission at a variety of synapses, both excitatory and inhibitory, has been shown to be powerfully controlled by the activation of presynaptic $GABA_BRs$ (Wu and Saggau, 1995; Doze et a., 1995; Laviv et al., 2011).

Physiological responses of $GABA_BRs$ require the coassembly of one of the isoforms of the $GABA_{B1}$ subunits, preferentially $GABA_{B1a}$ or $GABA_{B1b}$, and $GABA_{B2}$ (Kaupmann et al., 1998a; Marshall et al., 1999; Couve et al., 2000; Calver et al., 2002; Bettler et al., 2004). Association of the these isoforms results in formation of pharmacologically divergent $GABA_{B(1a;2)}$ and $GABA_{B(1b;2)}$ receptors, which target axons and dendrites, respectively. In the heteromeric receptor, $GABA_{B1}$ contains the ligand binding domain, while effector coupling is mediated through $GABA_{B2}$ (Kaupmann et al., 1998a). The functional importance of this heterodimerization is that complexed receptors exhibit a significant increase in ligand binding affinity as compared with individual receptors, and as such, likely represent the predominant native $GABA_BRs$ in the CNS (Gassmann and Bettler, 2012).

There is increasing evidence, however, that further functional diversity of the native $GABA_BRs$ results from the co-assembly of the principal subunits, $GABA_{B1}$ and $GABA_{B2}$, with different auxiliary proteins (Schwenk et al., 2016; Bettler and Fakler, 2017). One of the most important constituents of the $GABA_BR$ macromolecular complex is the K^+ channel tetramerization domain-containing (KCTD) family of proteins (Schwenk et al., 2010; Metz et al., 2011). The auxiliary KCTD8, KCTD12, KCTD12b and KCTD16

subunits associate with the $GABA_{B2}$ protein (Schwenk et al., 2010) and shape the efficacy and kinetics of $GABA_BR$ mechanisms in both post- and presynaptic compartments of neurons (Schwenk et al., 2010; Turecek et al., 2014; Booker et al., 2017b; Fritzius et al., 2017).

Our understanding of the cellular and subcellular distribution of $GABA_BRs$, as well as their function in cortical cells has significantly expanded since the receptor subunits were cloned and characterized by the Bettler group (Kaupmann et al., 1997, 1998a). The many immunocytochemical, biochemical, electrophysiological and pharmacological studies convergently demonstrate that functionally distinct $GABA_BRs$ are abundant on somato-dendritic and axonal compartments of neurons, giving rise to cell-type specific post- and presynaptic effects. In this review, we summarize current information on the somato-dendritic and axonal distribution of functional $GABA_BRs$, leading to greater understanding of their role in shaping the activity of excitatory PCs and inhibitory INs in cortical networks, with a focus on the hippocampus.

2. $GABA_BR$ subunits show a wide regional and cellular expression in the brain

Early studies utilizing *in situ* hybridization and autoradiography provided the first description of $GABA_BR$ localization to neuronal populations of various brain regions in the CNS. Mapping mRNA distribution of $GABA_{B1}$ (Fig. 1A) and $GABA_{B2}$ receptor subunits revealed their abundant and concomitant expression in virtually all brain areas. The highest levels of expression of mRNA were found in the cerebellum, hippocampus, neocortex and thalamus (Bischoff et al., 1999; Billinton et al., 1999; Ng et al., 1999; Liang et al., 2000). These findings were in line with data obtained from quantitative receptor autoradiographic studies using [H^3]-GABA under selective conditions (Bowery et al., 1987; Chu et al., 1990; Turgeon and Albin, 1993).

Subsequent light microscopic immunocytochemical studies further revealed a ubiquitous cellular and subcellular distribution of the $GABA_BR$ subunits, strongly suggesting that the proteins are localized both postsynaptically to somato-dendritic processes and presynaptically to axons in PCs and GABAergic INs in cortical areas, including hippocampus, somatosensory, prefrontal and parahippocampal cortices, as well as in other brain regions (Fritschy et al., 1999; Sloviter et al., 1999; Margeta-Mitrovic et al., 1999; Li et al., 2001; Kulik et al., 2002; 2003; Lujan et al., 2004; Bartos et al., 2009; Starostik et al., 2010). In the hippocampus, the pattern of labeling for $GABA_{B1}$ (Fig. 1B)

and $GABA_{B2}$ (Fig. 1C) subunits strongly overlaps in both the CA areas and the dentate gyrus (DG). Immunostaining for both subunits was generally weak to moderate in the CA1 area, with the *stratum radiatum* (SR) showing the weakest and the *stratum lacunosum-moleculare* (SL-M) the highest intensity. The CA3 region exhibited higher immunoreactivity for both proteins than the CA1 region (Fritschy et al., 1999: Margeta-Mitrovic et al., 1999; Kulik et al., 2003). Finally, in the DG, the immunolabeling was weak within the hilus and increased gradually to the outer molecular layer (Fig. 1B and C, Table 1) (Kulik et al., 2003; Degro et al., 2015). In the neocortex, a similar pattern of expression was observed, where distal dendritic/infragranular layers (layers 1-3) showed the strong labeling intensities, while deeper/subgranular layers showed weaker immunostaining (Fritschy et al., 1999).

In addition to the diffuse neuropil labeling, somata of hippocampal PCs and a subset of GAD65/67-positive GABAergic INs, scattered throughout the hippocampus, appeared moderately or intensely immunoreactive for $GABA_{B1}$ (Fig. 1B, Table 1) but not for $GABA_{B2}$ (Sloviter et al., 1999; Fritschy et al., 1999; Margeta-Mitrovic et al., 1999; Kulik et al., 2003). Qualitative electron microscopic investigation further demonstrated that somatic immunogold labeling for the $GABA_{B1}$ subunit was abundant over the surface of the endoplasmic reticulum (ER) (Kulik et al., 2003). The absence of $GABA_{B2}$, which is essential for the translocation of $GABA_{B1}$ to the plasma membrane and for the formation of functional heteromeric receptors (Marshall et al., 1999; Pagano et al., 2001; Billinton et al., 2001), suggests that the ER-bound $GABA_{B1}$ likely represent a reserve pool of this receptor subunit.

These data, thus, converged with previous electrophysiological and pharmacological studies, suggesting a wide but finely tuned regional and cellular expression of $GABA_B$Rs throughout the CNS (Dutar and Nicoll, 1988a; Mody et al., 1994; Bowery et al., 2002).

3. Extrasynaptic $GABA_B$Rs require spillover of GABA for their activation

At the subcellular level, the immunolabeling for both $GABA_{B1}$ and $GABA_{B2}$ was detected in postsynaptic and, to a lesser extent, presynaptic microcompartments of hippocampal PCs (Fig. 1D, Table 1) (Kulik et al., 2003, 2006; Guetg et al., 2009; Degro et al., 2015) and INs (Booker et al., 2013, 2017a, 2017b). In postsynaptic compartments, $GABA_B$Rs were most abundant at the perisynaptic location (i.e. in a membrane segment within 60 nm from the edge of synapses) and extrasynaptic plasma membrane of dendritic shafts

and spines of CA PCs and DG granule cells (DG-GCs) (Kulik et al., 2003, 2006; Degro et al., 2015) as revealed by pre-embedding and SDS-digested freeze-fracture replica (SDS-FRL) immunoelectron microscopy (Fig. 1D and H). In addition, immunoparticles were occasionally seen over the main body of the postsynaptic specialization at both glutamatergic and GABAergic synapses (Kulik et al., 2003). Measurements of distances of immunoparticles labeling the receptor subunit from the closest edge of synapses revealed that on dendritic spines, a high density of gold particles was observed between 60 nm and 240 nm away from the synapse, whereas on dendritic shafts a more homogeneous distribution of $GABA_BRs$ was found (Fig. 1E). These results indicate that in hippocampal PCs, postsynaptic $GABA_BRs$ are enriched around glutamatergic but not around GABAergic synapses (Kulik et al., 2003), the source of their endogeneous ligand. A similar subcellular distribution of $GABA_{B1}$ and $GABA_{B2}$ was observed in dendrites of PCs in other brain regions, such as dorsal cochlear nucleus (Lujan et al., 2004), ventrobasal thalamus (Kulik et al., 2002), visual cortex (Gonchar et al., 2001) and cerebellum (Ige et al., 2000; Billinton et al., 2001; Kulik et al., 2002).

The fact that the majority of $GABA_BRs$ were localized to extrasynaptic membrane of dendritic compartments with no apparant association to inhibitory synapses (Ige et al., 2000; Kulik et al., 2002, 2003; Lujan et al., 2004; Kulik et al., 2006) indicates that the activation of $GABA_BRs$ depends on spillover of GABA from IN synapses. Activation of receptors remotely located from synaptic sites results in a slow conductance, which is not precisely time-locked to single presynaptic action potentials rather reflecting the overall activity of the whole network on a slower time scale (Farrant and Nusser, 2005). Consistent with this concept, a $GABA_BR$-mediated conductance was activated by extracellular stimulation of large sets of GABAergic neurons and axons (Newberry and Nicoll, 1985; Dutar and Nicoll, 1988a; Otis et al., 1993) or during synchronous oscillatory activity of large neuronal populations (Isaacson et al., 1993; Scanziani, 2000; Brown et al., 2007), but was essentially absent between synaptically coupled IN-PC pairs (Miles, 1990; Buhl et al., 1994; Vida et al., 1998; Bartos et al., 2001). Recent studies have, however, provided evidence that single neurogliaform cell (NGFC) and somatostatin (SOM)-expressing INs can indeed produce activation of $GABA_BRs$, post- as well as presynaptic ones, on neocortical and hippocampal PCs (Tamas et al., 2003; Price et al., 2005, 2008; Oláh et a., 2009; Urban-Ciecko et al., 2015). Furthermore, in the presence of GABA uptake blockers other IN types can elicit $GABA_BR$-mediated currents in PCs and other INs (Scanziani, 2000; Booker et al., 2013), indicating that under physiological

conditions efficient uptake mechanisms control activation of $GABA_BRs$ in cortical networks. This requires high expression level and appropriate subcellular distribution of GABA transporters relative to synapses and $GABA_BRs$ in cortical neurons. Indeed, *in situ* hybridization, as well as light and electron microscopic immunocytochemical studies provided compelling evidence that the high-affinity plasma membrane GABA transporters 1 (GAT1) and 3 (GAT3) are robustly expressed in pre- and postsynaptic compartments of cortical GABAergic INs, but to a lesser extent in PCs and astrocytes (Minelli et al., 1995; Conti et al., 2004; Melone et al., 2015). Furthermore, they were shown to be highly colocalized with $GABA_BRs$ in neurons in cortical and subcortical brain regions (Gonzalez-Burgos, 2010). At the ultrastructural level, immunoreactivity for GAT1 was mainly observed at perisynaptic and extrasynaptic segments of plasma membrane of axon terminals of GABAergic cells (Gonzalez-Burgos, 2010; Melone et al., 2015). The transporters are, thus, perfectly located to efficiently control GABA levels at the synaptic cleft, as well as the spillover of the transmitter and thereby regulate the phasic and tonic GABA responses mediated by synaptic and extrasynaptic $GABA_BRs$: the strength and duration of $GABA_BR$-mediated effects can be potentiated or weakened depending on the up- or down-regulation of GAT1/3-mediated uptake (Gonzalez-Burgos, 2010).

4. Postsynaptic $GABA_BRs$ and their effectors in cortical principal cells

Combined morphological, pharmacological, physiological and behavioral analysis of $GABA_{B1a}$ knock-out ($1a^{-/-}$) and $GABA_{B1b}$ knock-out ($1b^{-/-}$) mice clearly established that the two most abundant proteins of $GABA_{B1}$, $GABA_{B1a}$ and $GABA_{B1b}$ (Kaupmann et al., 1997), can combine with the $GABA_{B2}$ subunit to constitute two independently regulated $GABA_{B(1a;2)}$ and $GABA_{B(1b;2)}$ receptor subtypes, which differentially compartmentalized and fulfill distinct functions in cortical neurons (Pérez-Garci et al., 2006; Vigot et al., 2006; Guetg et al., 2009). Pre-embedding immunoelectron microscopy revealed that the $GABA_{B1b}$ protein mainly localized to dendritic spines and shafts of CA1 and CA3 PCs, whereas immunoparticles for the $GABA_{B1a}$ transcript were observed on both postsynaptic and presynaptic compartments of the cells (Vigot et al., 2006; Guetg et al., 2009). In good agreement with this finding, in CA1 PCs of $1b^{-/-}$ mice, the receptor agonist baclofen-induced outward current was reduced by approximately 60% compared to wild-type (WT) or $1a^{-/-}$ mice (Vigot et al., 2006), indicating that predominantly $GABA_{B(1b;2)}$ receptors mediate postsynaptic inhibition. A similar spatial segregation of $GABA_{B1}$ isoforms was

observed in the cortex: in layer 5 PCs of the somatosensory cortex the postsynaptic inhibition of Ca^{2+} spikes was mediated by the $GABA_{B(1b;2)}$ receptors, but not the $GABA_{B(1a;2)}$ receptors, which rather mediate presynaptic inhibition of GABA release (Pérez-Garci et al., 2006). Interestingly, however, somatic whole-cell patch-clamp recordings from CA3 PCs demonstrated that application of high concentration of baclofen (100μM) elicited smaller outward K^+ currents in both $1a^{-/-}$ and $1b^{-/-}$ mice in comparision to WT animals. The maximal K^+ currents, however, were similar in both genotypes indicating that $GABA_{B(1a;2)}$ and $GABA_{B(1b;2)}$ receptors activate Kir3 channels to a similar extent (Guetg et al., 2009) in these neurons.

Postsynaptic $GABA_B$Rs activity is primarily mediated by G-protein-coupled inwardly rectifying K^+ (Kir3) channels (Gähwiler and Brown, 1985; Andrade et al., 1986; Thompson and Gähwiler, 1992; Sodickson and Bean, 1996; Lüscher et al., 1997; Kaupmann et al., 1998b), which control neuronal excitability by producing slow inhibitory synaptic responses and contributing to the resting membrane potential (Chen and Johnston, 2005). Functional Kir3 channels exist as homotetrameric or heterotetrameric complexes formed upon co-assembly of the Kir3.1-3.4 subunits (Inanobe et al., 1995; Slesinger et al., 1996; Liao et al., 1996; Dascal 1997). In the cortex, Kir3 channels are known to be mainly composed of the Kir3.1 and Kir3.2 subunits (Fig. 1F) (Lesage et al., 1995; Leaney, 2003) and the latter protein is responsible primarily for the assembly and surface localization of functional channels (Inanobe et al., 1999; Ma et al., 2002). It was also shown that the lack of Kir3.2 results in loss of slow inhibitory postsynaptic responses in hippocampal PCs (Lüscher et al., 1997). At the electron microscopic level, immunoreactivity for Kir3.2 was predominantly found in postsynaptic elements (Fig. 1G and H, Table 1), dendritic shafts and spines, of PCs and INs (Koyrakh et a., 2005; Kulik et al., 2006; Booker et al., 2013; Degro et al., 2015; Booker et al., 2017b).

The pattern of subcellular distribution of Kir3.2 was very similar to that of $GABA_B$Rs: on dendritic shafts of PCs and INs the channel subunit was distributed over the extrasynaptic membrane, but showed no association with inhibitory synapses (Kulik et al., 2006; Booker et al., 2013; Degro et al., 2015; Booker et al., 2017b), whereas on dendritic spines Kir3.2 was found to be preferentially localized and co-clustered with $GABA_{B1}$ near asymmetrical excitatory synapses (Fig. 1G and H) (Koyrakh et al., 2005; Kulik et al., 2006). The spatial relationship of the channel and receptor subunits was also quantified by measuring the distances between clusters of Kir3.2 and the closest clusters of $GABA_{B1}$ over the surface of postsynaptic compartments of PCs. This analysis revealed

that, on dendritic shafts, 28% of clusters of the channel and receptor were within 100 nm, while on dendritic spines 96% of the clusters were located within this distance (Kulik et al., 2006), indicating the functional association of $GABA_BRs$ and Kir3 channels on dendritic shafts and, to a much larger extent, on dendritic spines of PCs.

The preferential dendritic localization, the heterogeneous distribution of $GABA_BRs$ and Kir3 channels along the somatodendritic axis of the hippocampus (Degro et al., 2015) and enrichment of the $GABA_BR$-Kir3 channel complexes around glutamatergic synapses on dendritic spines of PCs together indicate that this signaling cascade may control excitability of neurons in a layer-specific manner (Larkum, 2013; Degro et al., 2015) offering an optimal position for the control of resting membrane potential, synaptic integration and plasticity (Takigawa and Alzheimer, 2002; Chen and Johnston, 2005). Indeed, $GABA_BR$-Kir3 complexes can efficiently counteract excitatory postsynaptic responses by hyperpolarizing and shunting excitatory synaptic currents (Takigawa and Alzheimer, 2003). Furthermore, $GABA_BRs$ can suppress NMDA receptor (NMDAR) Ca^{2+} signals, which depends on G protein signaling and involves the protein kinase A (PKA) pathway (Chalifoux and Carter, 2010, 2011a) or attenuate NMDAR responses by opening K^+ channels (Deng et al., 2009). The resulting hyperpolarization enhances Mg^{2+} blockade of NMDRs leading to a reduced synaptic plasticity (Otmakhova and Lisman, 2004; Malenka and Bear, 2004). Conversely, activation of NMDARs and Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII), as well as rise in postsynaptic Ca^{2+} results in the potentiation of the $GABA_BR$-Kir3-mediated slow inhibitory response (Huang et al., 2005) paralleling long-term potentiation (LTP) of excitatory transmission. The functional significance of this inhibitory postsynaptic current (IPSC) potentiation is to sharpen the coincidence detection of synchronous excitatory inputs (Huang et al., 2005), a hallmark for learning and memory. Furthermore, activation of NMDARs along with CaMKII can regulate the function and surface availability of $GABA_BRs$: prolonged activation of glutamate receptors leads to endocytosis and subsequent lysosomal degradation of $GABA_BRs$ (Terunuma et al., 2010; Guetg et al., 2010).

Postsynaptic $GABA_BRs$ have further been shown to inhibit constitutively active Kir2 channels (Rossi et al., 2006) and modulate Ca_v channels in central neurons (Mintz and Bean, 1993; Pfrieger et al., 1994; Breton and Stuart, 2012). Recent electrophysiological studies provided evidence that $GABA_BRs$ can inhibit L- ($Ca_v1.2$), P/Q- ($Ca_v2.1$), N- ($Ca_v2.2$) and R- ($Ca_v2.3$) type channel-mediated dendritic spikes throughout the dendritic arbor of prefrontal cortical neurons (Chalifoux and Carter, 2011b), the apical tufts of

layers 2/3 and 5 pyramidal cells (Pérez-Garci et al., 2006; Larkum et al., 2007). Given the importance of Ca^{2+} influx via Ca_V channels and its role in various intracellular processes and synaptic plasticity (Holthoff et al., 2006; Clapham, 2007) these observations indicate that postsynaptic $GABA_BRs$ have important long-term cellular functions beyond controlling the excitability of dendritic membranes.

5. Postsynaptic $GABA_BRs$ and their effectors in cortical interneurons

The presence of functional $GABA_BR$-mediated IPSCs/IPSPs in specific IN subtypes has remained far more contentious given their high anatomical, physiological and neurochemical heterogeneity in comparision to PCs (Freund and Buzsáki, 1996; Klausberger and Somogyi, 2008; Kubota, 2014). Indeed, a differential expression of $GABA_BR$ subunits was observed in various neurochemical IN types (Table 1) in earlier light (Sloviter et al., 1999) and more recent electron microscopic studies (Booker et al., 2013, 2017b). Immunogold particles for $GABA_{B1}$ were found to localize to the perisynaptic and extrasynaptic plasma membrane of dendritic shafts of NGFCs (Price et al., 2005), cholecystokinin (CCK)- (Fig. 2A, Booker et al., 2017b) and parvalbumin (PV)-expressing cells (Fig. 2B, Booker et al., 2013) (Table 1), as well as mGluR1α-positive putative SOM-positive dendrites (Booker et al., unpublished observations). Quantitative analysis of intensity of immunogold labeling revealed that the surface density of particles for $GABA_{B1}$ on PV (13.0 ± 1.7 particles/μm^2 - obtained from pre-embedding material) was comparable to that of PC dendritic shafts (12.1 ± 2.1 particles/μm^2 - pre-embedding; Booker et al., 2013), whereas on CCK dendrites (32.8 ± 3.5 particles/μm^2 - pre-embedding) the density of the $GABA_{B1}$ subunit was approximately twofold higher than on PCs (15.4 ± 2.1 particles/μm^2 - pre-embedding; Booker et al., 2017b).

Consistent with these anatomical findings, earlier electrophysiological studies revealed $GABA_BR$-Kir3 currents in unidentified INs of the DG (Mott et al., 1999) and CA regions (Buhl et al., 1995; Khazipov et al., 1995). Further analysis of these currents in identified IN subtypes has shown that there is a high degree of diversity. Perisomatic inhibitory basket cells (BCs), of both CCK (Fig. 2A) and PV (Fig. 2B) subtypes, showed comparable large amplitude $GABA_BR$-Kir3 currents (Table 1). This result was, however, at odds with the markedly higher $GABA_BR$ expression in CCK IN dendrites (see above) when compared to those of PV and PCs, suggesting a differential functional coupling of receptors and effectors in distinct neuron types (Booker et al., 2013, 2017b). Indeed, a

lower expression of Kir3 channels and a selective high expression of KCTD12 observed in CCK INs (Booker et al., 2017b) may explain this difference. In contrast to BCs, dendritic inhibitory neurons with the same neurochemical markers, PV and CCK (Fig. 2C), displayed very small functional Kir3 channel-mediated currents (Booker et al., 2013, 2017b). Moreover, our recent data further showed that in the archetypal dendritic inhibitory SOM IN, activation of $GABA_BRs$ produces minimal Kir3 channel-mediated postsynaptic current, rather $GABA_BRs$ coupled to and inhibit high voltage-activated $Ca_V1.2$ channels and thereby can control the induction of LTP in these INs (Booker et al., unpublished observations).

6. Presynaptic $GABA_BRs$ in cortical principal cells and interneurons

In general, presynaptic receptors are commonly divided into autoreceptors and heteroreceptors depending on whether they control the release of the cell's own transmitter or act at axon terminals of other cells, respectively. Pre-embedding and SDS-FRL immunoelectron microscopic studies showed consistent labeling for the $GABA_BR$ subunits in presynaptic compartments of cortical glutamatergic PCs and GABAergic INs (Kulik et al., 2003, 2006; Vigot et al., 2006; Shaban et al., 2006; Booker et al., 2017a), in boutons of the excitatory granule cells in the dorsal cochlear nucleus (Lujan et al., 2004), as well as in axon terminals of glutamatergic and GABAergic neurons in the visual cortex (Gonchar et al., 2001) and cerebellum (Ige et al., 2000; Kulik et al., 2002). However, the immunoreactivity for the proteins was substantially weaker in axonal than in dendritic compartments. Nevertheless, similar to postsynaptic receptors, presynaptic receptors were preferentially observed on the extrasynaptic plasma membrane and less often over the presynaptic membrane specialization of axon terminals of CA PCs (Fig. 1D) and DG-GCs making asymmetrical excitatory synapses with dendritic spines in the hippocampus (Kulik et al., 2003; Vigot et al., 2006; Guetg et al., 2009), at glutamatergic afferents to amygdala (Shaban et al., 2006), as well as boutons of hippocampal INs targeting the perisomatic domain of neurons in the CA1 area (Table 1, Booker et al., 2013, 2017a). In the hippocampus, quantification of immunoreactivity of $GABA_BRs$ revealed that in axon terminals of perisomatic-targeting INs showed varied strength of labeling: while CCK boutons had consistently high density, comparable to that of glutamatergic synapses, PV terminals showed a dichotomy with approximately 50% of them containing significantly lower density and the others being negative for $GABA_BRs$ (Booker et al., 2017a). In line

with these immunocytochemical findings, electrophysiological experiments demonstrated that $GABA_BR$ activation markedly reduced transmission at CCK BC output synapses, but had an approximately twofold weaker effect at PV BC synapses (Fig. 3A, Booker et al., 2017a). At the output synapse of dendritic-inhibitory CCK and PV IN types, the effect of $GABA_BR$ activation was more pronounced than at those of BCs with Schaffer collateral associated CCK INs showing the strongest presynaptic inhibitory effect (Fig. 3B, Table 1, Booker et al., 2013, 2017a).

Taking advantage of the availability of genetically modified mice that selectively express either $GABA_{B1a}$ or $GABA_{B1b}$ protein (Vigot et al., 2006), morphological and electrophysiological studies provided compelling evidence that hippocampal and a subset of neocortical glutamatergic terminals predominantly express the $GABA_{B(1a;2)}$ receptor (Vigot et al., 2006; Shaban et al., 2006; Guetg et al., 2009). Quantitative pre-embedding immunoelectron microscopy in the hippocampal CA1 SR and CA3 *stratum lucidum* (SL) demonstrated that approximately 20% of all counted immunogold particles were localized at synaptic and extrasynaptic sites of small Schaffer collateral terminals and mossy fiber (MF) boutons targeting dendritic spines of CA1 and CA3 PCs, respectively (Vigot et al., 2006; Guetg et al., 2009), while the remaining 80% were associated with postsynaptic structures of PCs. In mice lacking the $GABA_{B1a}$ protein, more than 90% of the particles were observed on spines and dendritic shafts of PCs, indicating that the $GABA_{B1b}$ and $GABA_{B1a}$ proteins differentially localize to postsynaptic and presynaptic elements, respectively (Vigot et al., 2006; Guetg et al., 2009). Accordingly, it was found that predominantly the $GABA_{B(1a;2)}$ receptors inhibit glutamate release in response to synaptically released GABA at hippocampal CA3-CA1 and MF-CA3 PC synapses and thus they play role in the generation of LTP on Schaffer collateral synapses (Vigot et al., 2006) and mediate heterosynaptic depression of MF transmission (Guetg et al., 2009). Similarly, the $GABA_{B(1a;2)}$ receptor-mediated inhibition sets the balance between associative, NMDAR-dependent LTP and nonassociative, NMDAR-independent LTP at cortical afferents to lateral amygdala (Shaban et al., 2006). In contrast, both $GABA_{B(1a;2)}$ and $GABA_{B(1b;2)}$ receptor types are present at GABAergic terminals impinging onto CA1 PCs (Vigot et al., 2006), however GABA release in layer 1 of the somatosensory cortex is exclusively controlled by the $GABA_{B(1a;2)}$ receptors but not $GABA_{B(1b;2)}$ receptors (Pérez-Garci et al., 2006), indicating that the extent of axonal segregation of the two receptor types can vary according to brain region and cell type.

The dominant $GABA_BR$-mediated presynaptic mechanism of action is the suppression of neurotransmitter release by inhibiting presynaptic Ca_v channels via a direct G protein interaction (Bettler et al., 2004). Recent high-resolution quantitative immunocytochemical studies revealed the expression and nano-architecture of distinct types of Ca_v channels, such as $Ca_v2.1$, $Ca_v2.2$ and $Ca_v2.3$ in extrasynaptic membrane and over the presynaptic membrane specialization of excitatory (Holderith et al., 2012; Parajuli et al., 2012; Althof et al., 2015) and inhibitory (Bucurenciu et al., 2008; Lenkey et al., 2014; Althof et al., 2015) axon terminals of hippocampal neurons. $GABA_BRs$ have been shown to inhibit predominantly the $Ca_v2.1$ and $Ca_v2.2$ channels at hippocampal presynaptic boutons, and control the release of glutamate and GABA (Wu and Saggau, 1995; Doze et al., 1995; Laviv et al., 2011). This inhibition of transmitter release not only reduces presynaptic release probability and thereby the postsynaptic conductances, but may also lead to altered short-term plasticity independent of the change in release probability (Lei and McBain, 2003; Booker et al., 2017a) pointing to more direct interactions with the release machinery.

Indeed, there is evidence that the inhibition of Ca_v channels is not the only mechanism by which GABA can inhibit neurotransmitter release: whole-cell recordings from CA1 PCs of the hippocampus demonstrated that $GABA_BRs$ can inhibit quantal GABA release and this inhibition is reduced by an activator of protein kinase C (PKC) (Jarolimek and Misgeld, 1997). Furthermore, using whole-cell pach-clamp recording at the calyx of Held, $GABA_BRs$ were found to attenuate the recruitment of synaptic vesicles during sustained activity and after short-term depression. This inhibition occurs through a reduction of cyclic AMP (cAMP), which blocks the stimulatory effect of increased Ca^{2+} concentration on vesicle recruitment (Sakaba and Neher, 2003). In addition to the above mentioned mechanisms, $GABA_BRs$ have been shown to be a member of a group of G protein coupled receptors (GPCRs), which exert their influence by decreasing exocytosis of synaptic vesicles. The mechanism by which $GABA_BRs$ act is through direct interaction of the $G\beta\gamma$ subunit with members of the SNARE complex downstream of Ca_v channels, and specifically with synaptosomal-associated protein-25 (SNAP-25) and syntaxin1A (Wells et al., 2012).

As indicated above, $GABA_BRs$ dominantly mediate inhibition pre- and postsynaptically, however, recently two elegant studies demonstrated that presynaptic $GABA_BRs$ can mediate excitation by amplifying Ca^{2+} entry through $Ca_v2.3$ channels into boutons of medial habenula cholinergic neurons and thereby potentiating co-release of glutamate,

acetylcholine and neurokinin-B to excite postsynaptic GABAergic INs in the midbrain interpeduncular nucleus (IPN; Zhang et al., 2016). This activity-dependent synaptic potentiation of habenula-IPN synapses was shown to be dependent on the release of GABA from postsynaptic IPN neurons and the subsequent retrograde activation of axonal $GABA_BRs$ (Koppensteiner et al., 2017) resulting in a reduction of the expression of cued fear memory in behavioral tests.

7. Conclusion and Perspectives

In summary, over the past two decades a large data set has been accumulated regarding the distribution, molecular composition and function of metabotropic $GABA_BRs$ in PCs and various types of INs in different brain regions of the CNS. In this review we brought together this knowledge particularly focusing on the predominant peri- and extracellular location of functional $GABA_BRs$ in post- and presynaptic compartments of cortical neurons (Fig. 4). These results corroborated by complementary pharmacological and electrophysiological data, demonstrate that $GABA_BRs$ can differentially control postsynaptic excitability, as well as the synaptic in- and outputs of excitatory PCs and inhibitory INs in cortical networks.

Functional properties of pre- and postsynaptic $GABA_BRs$, their pharmacology and kinetics of their responses, critically depend on a variety of auxiliary proteins and effector ion channels, together forming a highly complex receptor-associated network. In this respect, further extensive biochemical, immunocytochemical, pharmacological and electrophysiological studies are required to identify and localize additional constituents of the $GABA_BR$ nano-environment. Unravelling the precise molecular composition, dynamics of assembly of native $GABA_BRs$ receptors, as well as their functional interaction with other molecular constituents of this environment and other signal cascades, such as glutamate receptors will help us to better understand the full impact of $GABA_B$ receptor-mediated signalling in dendritic and axonal compartments of neurons in cortical and subcortical regions of the CNS. This information will enable us to develope novel therapeutic approaches for the treatment of the broadening list of $GABA_B$ receptor-related disorders.

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Figure legends

Fig. 1. Cellular and subcellular localization of $GABA_BR$ and Kir3 channel subunits.

A: Pan-$GABA_BR$ mRNA distribution in major structures of the rat forebrain as detected by *in situ* hybridization. Abbreviations: CA1/CA3 - cornu ammonis of hippocampus, MH - medial habenula, Thal - thalamus, Rt - reticular nucleus, HTM – hypothalamus.

B, C: Light micrographs illustrate the distribution pattern of $GABA_{B1}$ (B) and $GABA_{B2}$ (C) in the rat hippocampus.

D: Electron micrographs showing the perisynaptic (arrowhead), synaptic (double arrowhead) and extrasynaptic (arrows) location of $GABA_{B1}$ postsynaptically in dendritic spines (s) and presynaptically in boutons (b, double arrows) of CA1 principal cells (PCs).

E: Bar chart showing the distribution of immunoparticles for $GABA_{B1}$ on PC spines relative to glutamatergic (asymmetric) synapses (filled columns) and on dendritic shafts of PCs relative to GABAergic (symmetric) synapses (open columns) as assessed by pre-embedding immunogold labeling.

F: Light micrograph of the distribution pattern of Kir3.2 in the rat hippocampus.

G: Electron micrographs show the perisynaptic (arrowhead), synaptic (double arrowhead) and extrasynaptic (arrows) location of Kir3.2 postsynaptically in dendritic shaft (Den) and spine (s), as well as presynaptically in axon terminals (T, double arrows) of CA1 PCs.
H: Colocalization of $GABA_{B1}$ (10 nm particles, arrowheads) and Kir3.2 (5 nm, double arrows) on dendritic shaft (Den) and spine (s) of CA1 PC as assessed by the SDS-FRL technique. Excitatory synapse on the spine head is indicated by immunorectivity for PSD-95 (15 nm, arrow). Scale bars: B, C, F: 200 μm, D, G, H: 0.2 μm. Abbreviations: o, stratum (str.) oriens; p, str. pyramidale; r, str. radiatum; l-m, str. lacunosum-moleculare; m, str. moleculare; g, str. granulosum; h, hilus. Reproduced from: Bischoff et al., 1999 (A); Kulik et al., 2003 (B, C, D, E); Kulik et al., 2006 (F, G).

Fig.2. Functional postsynaptic $GABA_B$Rs in hippocampal interneurons.
A: Presence of functional postsynaptic $GABA_B$Rs in cholecystokinin (CCK)-positive basket cells in CA1 of the hippocampus. Upper, $GABA_{B1}$ subunits (immunogold particles) are present in CCK labeled dendrites (Den, immunoperoxidase) at a high level. Middle, 3-dimensional reconstruction of a CCK basket cell from CA1, showing a vertically oriented somato-dendritic-axis (black) and an axon (red) predominantly ramifying in stratum (str.) pyramidale (Pyr). Lower, $GABA_B$R-Kir3-mediated IPSC recorded in the same CCK basket cell, following stimulation of the str. Radiatum/lacunosum-moleculare border, which is blocked by the selective $GABA_B$R antagonist CGP55845 (CGP).
B: According to the same scheme as (A), $GABA_B$Rs are present on the dendrites of parvalbumin (PV)-expressing basket cells, albeit at a lower level than that of CCK cells. The same synaptic stimulation produces $GABA_B$R-Kir3-mediated IPSCs of comparable amplitude in PV BCs, which are equally sensitive to CGP.
C: Large $GABA_B$R-Kir3-mediated currents are absent from dendritic-inhibitory INs (reconstruction, left), independent of whether they contain PV or CCK. Scale bars: 0.5 μm. Abbreviations: Ori, str. oriens; Rad, str. radiatum; Lac, str. lacunosum; Mol, str. moleculare. Reproduced from: Booker et al., 2017b (A, C); Booker et al., 2013 (B).

Fig. 3. Diversity of presynaptic $GABA_B$R actions at identified INs.
A: Paired recordings between synaptically coupled basket cells (BCs) and CA1 PCs (schematic) where a presynaptic action potential in the IN (top) results in a fast $GABA_A$R-mediated IPSC in the CA1 PC (bottom). These reveal differences in presynaptic

$GABA_BR$-mediated inhibition following agonist application (10 μM baclofen), which are recovered by the antagonist CGP.
B: The same paired recordings performed between dendritic-inhibitory INs reveal stronger inhibition of GABA release in both PV and CCK dendritic-inhibitory cells. Reproduced from: Booker et al., 2013, 2017a.

Fig. 4. Summary of pre- and postsynaptic localization of $GABA_BRs$ and functionally related proteins in hippocampal CA1 area.
Schematic drawing summarizing the pre- and postsynaptic localization of $GABA_BRs$, their effectors and associated proteins at synapses made by Schaffer collateral (SC) and Perforant-path (PP) terminals onto CA1 principal cells (PCs – 1, 2, 3), as well as various types of interneurons, including neurogliaform cell (NGFC - 2), somatostatin-expressing cell (SOM oriens/lacunosum-moleculare INs - 3), dendritic-inhibitory cell (DI - 4), PV and CCK basket cells (BC - 5) and PCs.

Table 1. Summary of celleular and subcellular location of $GABA_B$ receptor subunits and the receptor-mediated post- and presynaptic effects in hippocampal PCs and GABAergic INs.