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Review

Amygdala Inhibitory Circuits and the Control of Fear Memory

Ingrid Ehrlich,[1,4] Yann Humeau,[2] François Grenier,[1] Stephane Ciocchi,[1] Cyril Herry,[1,3] and Andreas Lüthi[1,*]
[1]Friedrich Miescher Institute for Biomedical Research, 4058 Basel, Switzerland
[2]Institut des Neurosciences Cellulaires et Intégratives, Université Louis Pasteur and CNRS, UMR7168, F-67084 Strasbourg, France
[3]Present address: INSERM U862, Neurocentre Magendie, 146 Rue Léo-Saignat, 33077 Bordeaux, France
[4]Present address: Hertie Institute for Clinical Brain Research, 72076 Tübingen, Germany
*Correspondence: andreas.luthi@fmi.ch
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Classical fear conditioning is a powerful behavioral paradigm that is widely used to study the neuronal substrates of learning and memory. Previous studies have clearly identified the amygdala as a key brain structure for acquisition and storage of fear memory traces. Whereas the majority of this work has focused on principal cells and glutamatergic transmission and its plasticity, recent studies have started to shed light on the intricate roles of local inhibitory circuits. Here, we review current understanding and emerging concepts of how local inhibitory circuits in the amygdala control the acquisition, expression, and extinction of conditioned fear at different levels.

Introduction

Classical fear conditioning is one of the most powerful models for studying the neuronal substrates of associative learning and the mechanisms of memory formation in the mammalian brain (Davis, 2000; Fanselow and Poulos, 2005; LeDoux, 2000). In unraveling the substrates of memory storage in fear conditioning and other learning paradigms, the major focus has been the study of excitatory elements of the brain. However, interneurons are critical components of neuronal networks, and inhibition plays an important role in shaping network activity, so it is surprising that little is known about the involvement and modification of inhibitory circuits in learning and memory. This situation is starting to change as recent studies point to key roles of inhibitory mechanisms within the amygdala during fear and extinction memory acquisition and expression. Here, we review some of these results and point out how inhibitory circuits contribute to both acquisition and expression of memory traces by multiple mechanisms and at multiple levels in the amygdala.

In classical fear conditioning, the subject is exposed to a noxious unconditioned stimulus (US), such as a foot-shock, in conjunction with a neutral conditioned stimulus (CS), such as a tone or a light. As a result of the training, the tone acquires aversive properties, and, when subsequently presented alone, will elicit a fear response. In rodents, such responses include freezing behavior, alterations in autonomic nervous system activity, release of stress hormones, analgesia, and facilitation of reflexes. Subsequently, conditioned fear can be suppressed when the conditioned stimulus is repeatedly presented alone, a phenomenon called fear extinction. Behavioral studies in animals demonstrate that fear extinction is not simply the forgetting of previously learned fear but rather a new, active learning process (Bouton et al., 2006; Myers and Davis, 2007; Rescorla, 2001). Fear extinction is context dependent; that is, fear responses can still be expressed if the CS is presented in a different context than the one in which extinction was acquired. Moreover, fear extinction is generally not permanent, as the original CS-evoked fear behavior can spontaneously recover over time or can be reinstated by exposing animals to US presentations alone (Myers and Davis, 2007). Thus, fear and extinction memory traces coexist and can be retrieved depending on the behavioral state of the animal.

The amygdala is one of the key brain structures for fear memory acquisition and storage, a notion consistently supported by a large number of studies using different experimental paradigms and measures of conditioned fear responses (Davis, 2000; Fanselow and Poulos, 2005; LeDoux, 2000; Maren, 2001). In addition, the amygdala also modulates fear-related learning in other brain structures, such as the cortex and the hippocampus (McGaugh, 2004). The amygdala consists of several anatomically and functionally distinct nuclei, including the lateral (LA) and basal (BA) nuclei (together referred to as the basolateral amygdala—BLA) and the central nucleus (CEA) (Krettek and Price, 1978b) (Figure 1A). The CEA can be further divided into a lateral (CEl) and a medial (CEm) part (McDonald, 1982). While the CEl has been subdivided on anatomical and immunohistochemical grounds into a lateral-capsular division (CElc), an intermediate division (CEi), and a lateral division proper (CEl) (Cassell et al., 1986; Jolkkonen and Pitkänen, 1998; McDonald, 1982), from a functional perspective it is often considered as a whole (e.g., Samson et al., 2005). The cytoarchitecture and organization of amygdala nuclei are similar to that of other parts of the telencephalon. The lateral structures (BLA) are cortex-like, consisting of a majority of glutamatergic projection neurons and a minority of local GABAergic interneurons (McDonald, 1982) (Figure 1B). The medial structures (CEA) are striatum-like, with the vast majority of neurons being GABAergic (Figure 1B) and exhibiting medium spiny-type morphology (Cassell et al., 1986; McDonald, 1982; Swanson and Petrovich, 1998). The internuclear projections generally follow a dorso-ventral and latero-medial direction (Krettek and Price, 1978b) (e.g., from LA to BA and from BLA to CEA and, within CEA, from the CEl to the CEm) (Figures 1A and 1C). An interesting addition to the cortex- and striatum-like

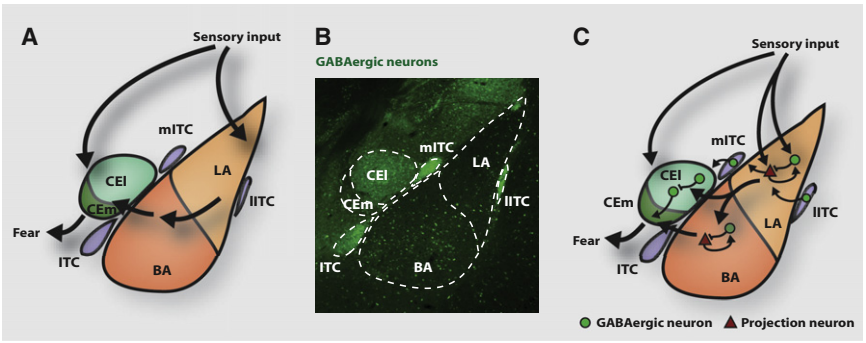

Figure 1. General Organization of Amygdala Circuitry

(A) Scheme of the basic organization and overall flow of information within the amygdaloid complex. LA, lateral amygdala; BA, basal amygdala; CEl, latero-capsular subdivision of the central amygdala; CEm, medial subdivision of the central amygdala; mITC, medial intercalated cell cluster; lITC, lateral intercalated cell cluster.

(B) Coronal brain slice stained for the 67 kD isoform of the GABA synthesizing enzyme glutamic acid decarboxylase (GAD67) illustrating the distribution of GABAergic neurons across the amygdaloid complex. (Image courtesy of Marita Meins.)

(C) Simplified scheme of the organization and function of inhibitory interneurons in amygdaloid nuclei. In the LA and BA, local interneurons are part of feedforward and feedback circuits and control projection neuron output. lITCs and mITCs relay feedforward inhibition to the BLA and CEA, respectively. CEm output neurons are under inhibitory control originating in CEl. Intrinsic CEl inhibition may also participate in controlling CEl output.

nuclear organization is the presence of intercalated cell masses (ITCs) in the amygdala. These specialized clusters of GABAergic interneurons surround the BLA (Millhouse, 1986). Their intra- and internuclear projections generally run in the latero-medial and dorso-ventral direction (Figure 1C). The medial ITC cluster is thought to gate interactions between the BLA and CEA.

One of the main flows of information within the amygdala follows a serial path in the direction of the main internuclear projections, while other parallel inputs and outputs exist (Pitkänen et al., 1997; Sah et al., 2003). In this review, we will mainly focus on this simplified serial model, where the LA serves as the major sensory interface, as it receives multimodal, early sensory information from the thalamus and cortex (McDonald, 1998; Turner and Herkenham, 1991). The CEm serves as the principal output station, as its projection neurons contact different structures in the brainstem and in the hypothalamus to orchestrate conditioned autonomic and motor responses (Krettek and Price, 1978a; LeDoux et al., 1988; Petrovich and Swanson, 1997; Veening et al., 1984). In addition, amygdala nuclei are unidirectionally or reciprocally connected to many cortical and subcortical brain structures, which participate in generating behaviorally relevant outputs (McDonald, 1991, 1998; McDonald et al., 1996; Pitkänen, 2000; Pitkänen et al., 2000). Together with the multitude of inter- and intranuclear projections, this suggests that information can be processed both by mechanisms intrinsic to amygdala networks as well as modified by interactions with other brain structures to integrate sensory inputs, generate fear response outputs, and modulate fear responses according to circumstances, such as in fear extinction (Pitkänen et al., 1997; Sah et al., 2003).

Although previous research has mostly focused on the role of glutamatergic transmission and plasticity, there is accumulating evidence indicating that local inhibitory circuits in the amygdala contribute to, or even mediate, important aspects of fear conditioning and extinction. First, systemic or local treatments that increase GABAergic transmission produce anxiolytic effects (Harris and Westbrook, 1995; Nagy et al., 1979; Pesold and Treit, 1995) and can interfere with the acquisition or expression of conditioned fear responses (Davis, 1979; Harris and Westbrook, 1995, 1999, 2001; Sanger and Joly, 1985). In contrast, pharmacological manipulations that decrease GABAergic transmission induce anxiogenic-like effects (Cole et al., 1995; Sanders and Shekhar, 1995) and can improve learning or retrieval of conditioned fear memories (Guarraci et al., 1999; Tang et al., 2007). Second, fear extinction may involve activation and/or plasticity of inhibitory circuits. For example, decreasing the efficacy of endogenous GABAergic transmission impairs extinction memory retrieval in a context-specific manner (Harris and Westbrook, 1998), while enhancing GABAergic transmission interferes with the acquisition of extinction (Hart et al., 2009). Third, fear behavior and acquired fear responses are subject to modification by neuromodulators and neuropeptides. It is intriguing that, at multiple levels in the amygdala, inhibitory neurons are major targets of neuromodulatory systems (Asan, 1998; Cassell et al., 1999; Fuxe et al., 2003; Muller et al., 2007b; Pinard et al., 2008). This may allow inhibition-dependent functions of amygdala networks to be adjusted according to the environmental conditions and the behavioral state of the animal.

The amygdala microcircuitry has not been studied as extensively as that of other cortical and basal ganglia structures. For example, in cortex and hippocampus, inhibitory interneurons form precise connections within local cortical microcircuits and impinge on distinct subcellular domains of principal cells and, by virtue of these properties, orchestrate many aspects of circuit activity and plasticity (Markram et al., 2004; Somogyi and Klausberger, 2005). In the striatum, a network of GABAergic projection neurons with local axon collaterals, in concert with distinct subgroups of local, inhibitory interneurons generates activity patterns that shape basal ganglia output and motor control (Kreitzer and Malenka, 2008; Tepper and Bolam, 2004). An intriguing aspect of amygdala circuit organization is that it combines cortex-like and striatum-like structures. A key question is how the tasks of memory acquisition and the storage of multiple memory traces are distributed and implemented among these fundamentally different networks in the amygdala. Indeed, work on appetitive conditioning has revealed that the contribution of the BLA and CEA to different aspects of learning and memory can be, at least in part, functionally dissociated, suggesting that BLA and CEA can process information both in series and in parallel (Balleine and Killcross, 2006; Cardinal et al., 2002). Another question is what roles inhibition has at distinct anatomical levels and distinct stages of memory acquisition, expression, and consolidation. Here, we review evidence that inhibitory circuits in cortex- and striatum-like amygdala

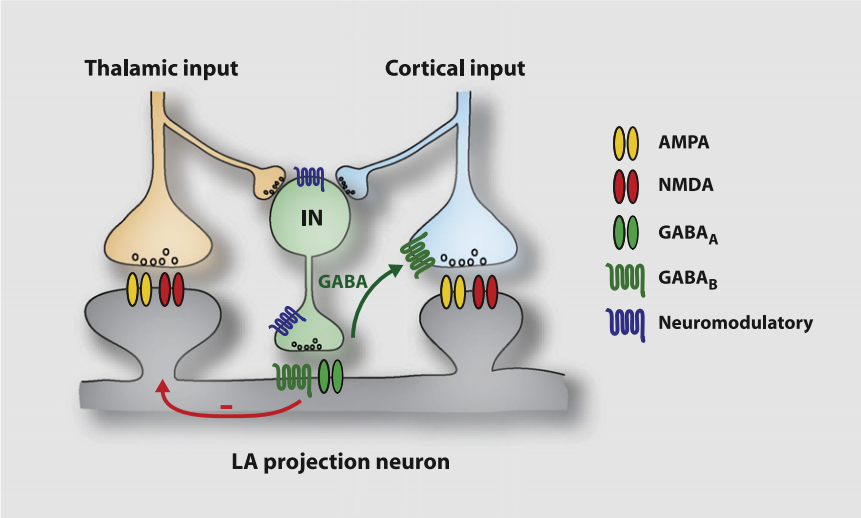

Figure 2. Inhibitory Gating of LTP in the LA
Projection neurons in the LA (gray) receive converging thalamic and cortical sensory afferents. LTP at thalamic and cortical afferents is tightly controlled by GABA released from feedforward interneurons (green). At thalamic afferents, this control is predominantly postsynaptic via $GABA_A$ receptors. At cortical afferents, this control is presynaptic via $GABA_B$ receptors. Interneurons are targets of neuromodulators that modify their output activity. This process gates the induction of glutamatergic LTP by transiently altering the level of pre- and postsynaptic inhibitory drive.

networks participate in distinct aspects of fear expression and memory. Understanding theses processes within the framework of the unique organization of the amygdala and the powerful paradigm of fear conditioning could help shed light on general principles of memory acquisition and storage in cortico-striatal circuits in general.

Acquisition and Expression of Conditioned Fear Responses

Synaptic Plasticity in the Lateral Amygdala

Plasticity at sensory inputs from thalamus and cortex to the BLA, and particularly the LA, has been a major focus of work on the neural mechanisms of acquisition and expression of conditioned fear. Many studies support the notion that the LA is an essential site where early, NMDA receptor-dependent changes in neuronal activity are required for the acquisition of conditioned fear (Gewirtz and Davis, 1997; Goosens and Maren, 2004; Miserendino et al., 1990; Paré and Collins, 2000; Quirk et al., 1995, 1997; Rodrigues et al., 2001). This has led to the idea that NMDA receptor-dependent long-term potentiation (LTP) at sensory afferents to the LA projection neurons underlies this process (LeDoux, 2000; Maren and Quirk, 2004). In line with this concept, blocking and occlusion experiments have consistently supported the notion that LTP, potentiation of sensory evoked activity, and acquisition of conditioned fear share the same mechanisms in the LA (McKernan and Shinnick-Gallagher, 1997; Rogan and LeDoux, 1995; Rogan et al., 1997; Rumpel et al., 2005; Tsvetkov et al., 2002). While substantial evidence supports the notion that thalamo-LA synapses change rapidly during fear acquisition (Quirk et al., 1997), this is less well understood in the cortico-LA pathway. Still, this represents one of the strongest established links between synaptic plasticity (i.e., LTP) and learning behavior.

Inhibitory Gating of Plasticity in the Lateral Amygdala

Glutamatergic synapses made by cortical afferents contact spines in close proximity to those contacted by thalamic afferents, yet are morphologically and functionally different (Humeau et al., 2005). Although the mechanisms underlying LTP induction and expression in thalamic and cortical sensory inputs are distinct, a common feature is that LTP is gated by the activity of local inhibitory circuits (Figure 2). In addition, neuromodulators that are released in the amygdala upon stress can gate induction of plasticity by transiently suppressing pre- or postsynaptic inhibition.

At thalamo-LA synapses, LTP is predominantly induced and expressed postsynaptically. Induction requires postsynaptic depolarization to allow for activation of NMDA receptors, R-type- and L-type voltage-dependent Ca^{2+} channels (Bauer et al., 2002; Humeau et al., 2005; Humeau and Lüthi, 2007; Rumpel et al., 2005; Weisskopf et al., 1999), and this makes thalamo-LA LTP particularly sensitive to the level and temporal properties of postsynaptic $GABA_A$ and $GABA_B$ receptor-mediated inhibition. Indeed, like in other cortical structures, in vitro LTP induction at thalamo-LA synapses is facilitated by the addition of $GABA_A$ and $GABA_B$ receptor blockers (Bissière et al., 2003; Shaban et al., 2006; Shin et al., 2006; Tully et al., 2007). LA projection neurons receive substantial GABAergic feedforward inhibition (Figure 1C), which tightly controls their activity (Lang and Paré, 1997; Li et al., 1996; Szinyei et al., 2000). This inhibitory constraint can be overcome or enhanced by neuromodulators. While dopamine, noradrenaline, or opioids suppress feedforward inhibition, and thereby gate LTP induction postsynaptically (Bissière et al., 2003; Shaban et al., 2006; Tully et al., 2007), other modulators, including gastrin-related peptide and serotonin, enhance inhibition, thereby possibly constraining LTP induction (Shumyatsky et al., 2002; Stutzmann and LeDoux, 1999). The cellular mechanisms of this control are diverse and, in the case of dopaminergic input, include modulation of inhibitory synapses onto projection neurons and local interneurons as well as direct control of interneuron excitability leading to increased spontaneous inhibitory network activity but decreased stimulus-evoked inhibition (Bissière et al., 2003; Kröner et al., 2005; Lorétan et al., 2004) (Figure 2). Neuromodulation of inhibitory activity and gating of LTP in this pathway are attractive candidate mechanisms in line with the requirement for neuromodulatory input for fear conditioning in vivo at the physiological and behavioral level (Rosenkranz and Grace, 2002b).

In contrast, at cortico-LA synapses, LTP is mediated by different mechanisms. Induction requires coincident pre- and postsynaptic activity or concomitant activation of thalamo- and

cortico-LA afferents (Huang and Kandel, 1998; Humeau et al., 2003, 2005). Induction converges on a presynaptic expression mechanism that requires cAMP/PKA signaling (Fourcaudot et al., 2008; Huang and Kandel, 1998; Tsvetkov et al., 2002) and the presynaptic active zone protein RIM1α (Fourcaudot et al., 2008; Huang and Kandel, 1998; Tsvetkov et al., 2002). Although presynaptic LTP is insensitive to postsynaptic inhibition, it remains under the control of feedforward inhibitory pathways (Figure 2). GABA released from local feedforward interneurons activates presynaptic $GABA_B$ receptors, which negatively control glutamate release from sensory afferents (Szinyei et al., 2000). Abolishing $GABA_B$ receptor-mediated presynaptic inhibition at cortico-LA synapses unmasks a nonassociative, NMDA receptor-independent form of presynaptic LTP (Shaban et al., 2006). As presynaptic $GABA_B$ receptors on glutamatergic inputs onto projection neurons, but not onto local interneurons (Shaban et al., 2006; Pan et al., 2009), are activated by volume transmission, excitation/inhibition balance and induction of NMDA receptor-independent presynaptic LTP may be controlled by changes in inhibitory transmission associated with distinct patterns of neuromodulation and network activity (Paré and Collins, 2000; Pelletier and Paré, 2004). In addition, changes in inhibition associated with altered GABA release (Bauer and LeDoux, 2004; Mahanty and Sah, 1998; Szinyei et al., 2007) may result in a shift of the induction-threshold for associative LTP at cortico-LA synapses. At the behavioral level, genetic loss of presynaptic $GABA_B$ heteroreceptors leads to generalized fear responses (Shaban et al., 2006). Consistent with this, a similar generalization phenotype is observed when the activity-dependent GABA-synthesizing enzyme GAD65 is knocked out (Bergado-Acosta et al., 2008). Together, this suggests that GABAergic control of presynaptic LTP and GABA release at cortico-LA synapses likely determine stimulus specificity and generalization of fear responses.

Diversity of Local Interneurons

Inhibition plays a central role in gating pre- and postsynaptic plasticity in the LA, suggesting that local interneurons participate in this process. Interneurons in the BLA comprise several major subtypes when differentiated by expression of the molecular markers parvalbumin (PV), somatostatin (SOM), cholecystokinin (CCK), calbindin, calretinin, and vasoactive intestinal peptide (Kemppainen and Pitkänen, 2000; Mascagni and McDonald, 2003; McDonald and Mascagni, 2001, 2002). Likely, more subtypes exist with distinct functional and morphological properties. For example, characterization of PV-positive and CCK-positive neurons in the BLA yielded heterogeneous electrophysiological and anatomical properties within each population (Jasnow et al., 2009; Katona et al., 2001; Woodruff and Sah, 2007b). Overall, PV-positive neurons make up the largest subgroup of interneurons (about 50%), and a substantial portion are fast-spiking cells that target projection neuron somata and proximal dendrites and possibly the axon initial segment (Muller et al., 2006; Rainnie et al., 2006; Woodruff et al., 2006; Woodruff and Sah, 2007a). In contrast, SOM-positive interneurons contact mostly distal dendrites and spines of BA projection neurons (Muller et al., 2007a), suggesting that they may interact with and affect plasticity at distal inputs. At the circuit level, feedforward and feedback inhibition is observed in the BLA (Samson and Paré, 2006) (Figure 1C). It is unclear if and which specific interneuron subtypes can be assigned to these tasks, particularly in the LA (Sosulina et al., 2006). In the BA, PV-positive interneurons are probably part of both feedback (Smith et al., 2000) and feedforward inhibitory circuits (Woodruff and Sah, 2007b). In the LA, fast-spiking interneurons were identified that receive converging thalamic and cortical sensory input and mediate feedforward inhibition to projection neurons (Bauer and LeDoux, 2004; Mahanty and Sah, 1998; Shin et al., 2006; Szinyei et al., 2000). Thus, they are good candidates for participating in gating of sensory afferent LTP. Overall, distinct types of BLA interneurons exists that perhaps control separate cellular functions of projection neurons, such as synaptic/dendritic integration, somatic integration/axonal output, and synaptic plasticity both locally and globally.

Other Functions of Local Inhibition during Fear Acquisition and Expression

In analogy to other brain areas where interneurons orchestrate many aspects of circuit activity, BLA interneurons may have additional functions during acquisition and expression of conditioned fear. For example, cortical and hippocampal feedforward inhibition sets integration time windows during which glutamatergic inputs are able to generate action potentials in principal neurons (Gabernet et al., 2005; Pouille and Scanziani, 2001), whereas feedback circuits are proposed to determine the spatio-temporal spread of incoming sensory stimulation, thereby regulating the dynamic range of the cortical network (Fellous and Sejnowski, 2003; Kapfer et al., 2007). Furthermore, interneurons are instrumental in setting up synchronous and oscillatory activity, particularly, the generation of theta- and gamma-band oscillations (Bartos et al., 2007; Buzsaki, 2002). The amygdala exhibits theta activity that phase-locks with hippocampal theta during retrieval of aversive memories (Paré et al., 2002; Seidenbecher et al., 2003). A recent study indicated that activity of a subset of PV-positive interneurons could entrain rhythms by setting firing probability and synchronizing principal cell activity in the BA (Woodruff and Sah, 2007a), suggesting that these interneurons could participate in rhythmic activity and facilitate interactions of the BA with other brain structures during the retrieval of fear memory.

In many ways, the LA resembles sensory cortex in that it receives direct input from sensory thalamus, and a substantial fraction of principal neurons are tuned to stimulus features such as the frequency of auditory stimuli (Bordi and LeDoux, 1992; Bordi et al., 1993). In primary sensory cortex, local feedforward and feedback inhibition sharpens sensory tuning and receptive field properties of pyramidal neurons (Miller et al., 2001; Priebe and Ferster, 2005; Wehr and Zador, 2003; Wilent and Contreras, 2005). Plasticity of inhibition contributes to cortical receptive field plasticity during development or after experimental manipulations (Foeller et al., 2005; Zheng and Knudsen, 1999). We speculate that, in analogy, receptive field plasticity may be one mechanism by which BLA projection cells could become responsive to conditioned stimuli or discriminate between or generalize across stimuli. Changes in local GABAergic control could contribute to shaping principal cell activity during perception of emotionally salient stimuli during fear memory expression or retrieval (Figure 3A). In the BLA, one could envision at least two

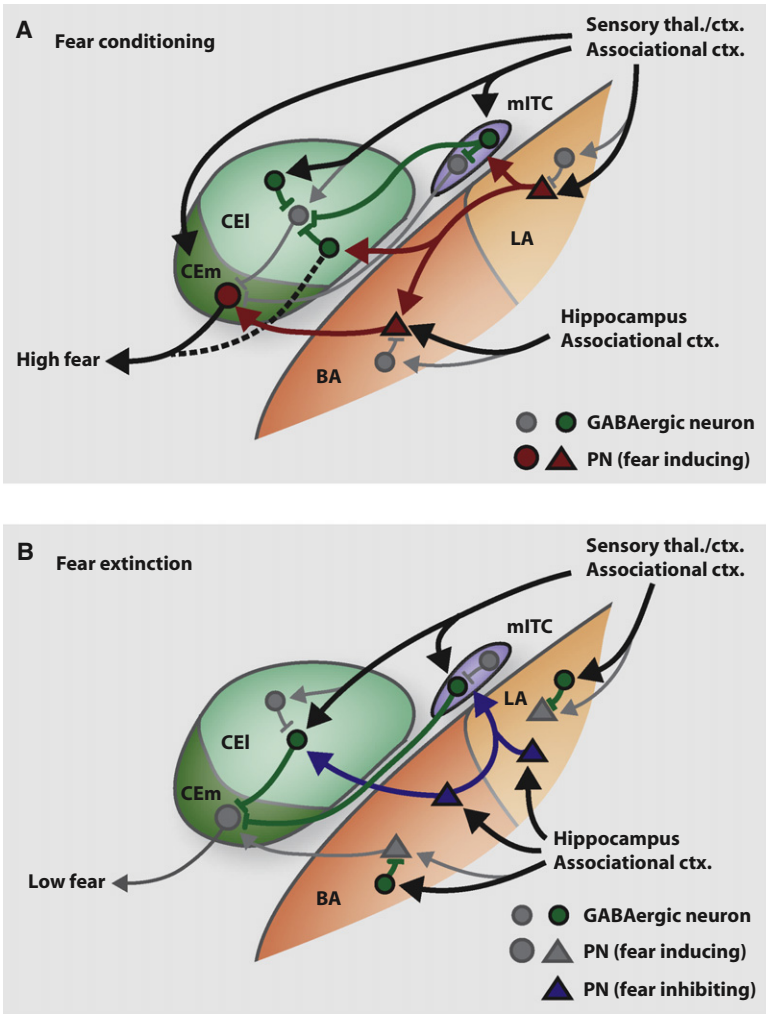

Figure 3. Key Processes of Fear Conditioning and Extinction Regulated by Local Inhibition

(A) During fear acquisition, suppression of feedforward inhibition in the LA enables glutamatergic LTP at sensory cortical and thalamic afferents to projection neurons. Fear consolidation and expression may involve a long-term decrease in local GABAergic drive in feedforward and feedback circuits within the BLA, thereby increasing output activity of fear-inducing projection neurons. In parallel processes, fear acquisition and expression can be coded in the CEA. This could occur in multiple ways: either by increasing sensory drive to CEm output neurons directly or, second, by increasing excitatory drive to subpopulations of CEl neurons locally inhibiting CEm projecting neurons or increasing mITCs activity, both of which would lead to disinhibition of CEm output.

(B) During acquisition of extinction, plasticity of contextual inputs could lead to increased activity of fear-inhibiting projection neurons in the BLA. During consolidation, long-term enhancement of local GABAergic drive within the BLA occurs, which could serve to suppress activity of fear-inducing projection neurons. Neuropeptide-mediated increases in BLA to mITC transmission result in inhibition of CEA output during extinction learning. During retrieval of extinction memory, mITC inhibitory activity, controlled by several inputs, including those from medial prefrontal cortex, reduces CEm output to suppress fear responses.

sets of modifications: First, altered inhibitory drive to projection neurons and, second, altered input to inhibitory neurons themselves. Consistent with a reduction in overall postsynaptic GABAergic drive in the BLA following fear memory acquisition, ex vivo studies show a reduction in benzodiazepine binding, as well as a reduction in the mRNA and protein levels of distinct $GABA_A$ receptor subunits and the $GABA_A$-R associated protein gephyrin within hours (Chhatwal et al., 2005; Heldt and Ressler, 2007). However, functional and mechanistic evidence supporting these findings is lacking, and the contribution to acquisition versus expression of memory is unclear. Consistent with alterations in GABA release or availability during acquisition and consolidation of fear memory, fear conditioning acutely decreases extracellular GABA levels in the BLA (Stork et al., 2002). Furthermore, ex vivo studies show reduced mRNA levels for the GABA-synthesizing enzymes GAD67 and GAD65 within hours and days, respectively (Heldt and Ressler, 2007; Pape and Stork, 2003). A candidate mechanism for the acute changes could be a form of inhibitory long-term depression (LTDi) observed in BLA slices, which is CB1 receptor-dependent and mediated by a decrease in presynaptic GABA release (Azad et al., 2004; Marsicano et al., 2002). The issue whether fear conditioning can change glutamatergic drive onto BLA interneurons that could alter their output is not resolved. In slice preparations, various forms of LTP of glutamatergic, sensory inputs onto fast-spiking LA interneurons have been described. For example, stimulation that also evokes excitatory LTP in principal cells induces a heterosynaptic, NMDA receptor-dependent form of LTP in interneurons that coincides with presynaptic potentiation of feedforward inhibition onto principal cells (Bauer and LeDoux, 2004). Other studies show input-specific NMDA receptor-independent LTP that depends on the activation of Ca^{2+}-permeable AMPA receptors (Mahanty and Sah, 1998; Szinyei et al., 2007). Interestingly, this LTP also caused an increase in disynaptic feedforward inhibition mediated by interneurons (Mahanty and Sah, 1998; Szinyei et al., 2007), and potentiation of this disynaptic inhibition was reduced following fear conditioning (Szinyei et al., 2007). Currently, no clear concept or conclusions emerge from these cellular studies. Overall, it appears that GABAergic inhibition in the BLA can be altered by experimental and behavioral manipulations, with most evidence indicating a decrease in GABAergic drive following fear conditioning. More functional work is required to address which forms of plasticity accompany and perhaps are necessary for different phases of fear memory and which inhibitory networks are involved. Still, the best established function of local inhibition in the BLA is the neuromodulation-dependent gating of sensory afferent plasticity onto LA principal cells, a process that underlies fear memory acquisition.

The Central Amygdala: A Plastic (Dis-) Inhibitory Network

Accumulating evidence suggests that the CEA is not only a passive relay station of basolateral activity to fear effector structures (Samson et al., 2005; Wilensky et al., 2006). First, processing

of information by inhibitory circuits intrinsic to CEA allows for CEA-intrinsic modulation of behavioral output. Second, plasticity within CEA and of afferents to CEA may also contribute to fear memory acquisition and formation of CS-US associations.

The CEA is, besides the bed nucleus of the stria terminalis (BNST), the principal output structure of the amygdaloid complex. Output neurons projecting to the hypothalamus and various brainstem nuclei that mediate the endocrine, autonomic, and motor-related aspects of fear responses are predominantly located in the medial part of CEA, the CEm (Cassell et al., 1986; Hopkins and Holstege, 1978; Veening et al., 1984), although a subpopulation of CEl neurons also projects to brain stem targets important for fear conditioning (Veening et al., 1984; Cassell et al., 1986). Converging anatomical and physiological evidence indicates that CEm output neurons are under inhibitory control originating in CEl (Cassell et al., 1999; Huber et al., 2005; Petrovich and Swanson, 1997; Sun et al., 1994; Veinante and Freund-Mercier, 1997, 2003). This is consistent with the vast majority of CEl neurons being GABAergic and exhibiting medium spiny neuron-type morphology (Cassell et al., 1986; McDonald, 1982). Based on its cytoarchitecture and ontogenetic origin, the CEA has been proposed to function as a striatum-like structure (Cassell et al., 1999; McDonald, 1982; Swanson and Petrovich, 1998). One subpopulation of CEl neurons sends confined inhibitory projections to CEm and other targets within the so-called central extended amygdala, such as the BNST, whereas another subpopulation also projects to targets outside of the central extended amygdala, including the lateral hypothalamus and the parabrachial nucleus (PB), while both subpopulations have local collaterals also (Veinante and Freund-Mercier, 1998, 2003). Notably, some CEl neurons project directly to brainstem effector structures, in a pathway that could bypass CEm for mediating fear responses (Gray and Magnuson, 1987, 1992; Koob, 2008). The CEl receives BLA inputs and substantial inputs from areas outside the amygdala, including sensory and higher-order cortical areas, and from subcortical structures such as the PB (McDonald, 1998; Savander et al., 1995; Sun et al., 1994; Yasui et al., 1991). Overall, this has led to the hypothesis that the CEl may function as an inhibitory interface, gating CEm output by integrating sensory cortical and subcortical inputs (Figure 1C).

Dynamic Control of Fear Behavior by Inhibition of Central Amygdala Output

The first direct evidence for this idea came from studies of cellular neuropeptide effects in the CEA. Both CEl and CEm exhibit some of the highest expression levels for a number of neuropeptides and their receptors in the brain (Asan, 1998; Cassell et al., 1999; Roberts et al., 1982). Thus, anxiety- and stress-related behavioral effects of neuropeptides may be mediated through their actions on distinct subpopulations of neurons in CEA with distinct outputs and/or by modulating CEl-CEm inhibitory interactions (Koob, 2008). In line with the latter hypothesis, Huber and colleagues (Huber et al., 2005) demonstrated that oxytocin, a neuropeptide with strong anxiolytic effects, excites a subpopulation of GABAergic, CEm-projecting neurons in CEl. These neurons, when activated by oxytocin, exert tonic inhibition onto postsynaptic CEm neurons. Importantly, this tonic inhibition reduced the excitability of CEm neurons, so that they were less likely to fire action potentials when glutamatergic inputs from the BA and basomedial amygdala were activated (Huber et al., 2005). Similarly, ethanol is thought to exert its anxiolytic effects, at least in part, by increasing GABAergic synaptic transmission in the CEA (Roberto et al., 2003). Interestingly, this effect appears to be mediated via presynaptic corticotrophin releasing factor (CRF) type 1 receptors, suggesting that GABAergic circuits within the CEA may be a point of convergence for central stress promoting and anxiolytic/stress coping systems. Together, these findings support that CEm output is tightly controlled by local inhibition from CEl.

Currently, evidence from a multitude of studies using pharmacological manipulations, electrical stimulation, or lesions suggests that diminishing the activity of CEm attenuates fear and anxiety responses, while increasing CEm output leads to stronger fear responses (Davis, 2000). In contrast, the only electrophysiological study directly examining fear conditioning-induced changes in the activity of brainstem-projecting CEA neurons (identified by antidromic invasion) revealed that they display low spontaneous firing rates and reduced CS-evoked activity after fear conditioning (Pascoe and Kapp, 1985). Clearly, further characterization of the activity of CEA neurons in relation to fear behavior are needed to definitely settle this question and reconcile these results.

Moreover, since fear conditioning leads to increased activity of LA cells (Quirk et al., 1995, 1997), which can project to CEl (Krettek and Price, 1978b; Pitkänen et al., 1995; Smith and Paré, 1994), this could lead to increased activity of CEl neurons, and in turn a decreased output of CEm cells, rather than disinhibition. However, there are other possibilities, given the known amygdala circuitry. First, LA input could activate a population of CEl neurons that directly facilitates fear responses or influences fear memory, such as the CRF-containing neurons projecting to the locus coeruleus (Van Bockstaele et al., 1998) (Figure 3A). Second, LA cells also project to ITCs (Royer et al., 1999; Jüngling et al., 2008). Third, the similarity between CEA and striatal circuitry (GABAergic projection cells with local axon collaterals, local inhibitory interneurons) suggests that similar computational principles may apply in both structures. It has been proposed that the striatal circuitry leads to winners-take-all situations between neurons in the same layer of the circuit, with a group of cells having increased activity in response to a specific input, while others actually get inhibited (Wickens et al., 2007). In the latter scenario, internal processing in the CEl could lead to disinhibition of CEm neurons (Figure 3A).

Formation of Stimulus Associations in the Central Amygdala

Another appealing hypothesis is that CEl-CEm inhibitory circuits also participate in acquisition or expression of fear memory. While the LA is thought of as the principal site where CS-US associations are formed and stored, recent evidence indicates a role of the CEA in this process. For instance, acute and reversible inactivation of the CEA using the $GABA_A$ receptor agonist muscimol during fear conditioning, or local blockade of NMDA receptors, result in impaired acquisition of conditioned fear responses (Goosens and Maren, 2003; Wilensky et al., 2006). Moreover, in animals with BLA lesions, conditioned fear responses can be acquired by overtraining in an associative and CEA-dependent manner (Rabinak and Maren, 2008; Zimmerman et al., 2007).

Finally, recordings from CEA neurons during fear conditioning have revealed differential changes in CS^+ and CS^--evoked activity in a discriminative fear conditioning paradigm (Pascoe and Kapp, 1985). Taken together, this strongly suggests that the CEA is an additional site that can actively contribute to the formation of CS-US associations.

Based on evidence from cellular studies in slices, different potential mechanisms for the formation of CS-US associations in the CEA emerge. A first possibility that does not require intrinsic CEA inhibitory circuits is that plasticity occurs directly on sensory drive to CEm output neurons, independent of their control by CEl. Indeed, CEm projection neurons receive monosynaptic excitatory inputs from sensory thalamus (LeDoux et al., 1985; Turner and Herkenham, 1991). These afferents exhibit input-specific, NMDA receptor-dependent presynaptic LTP (Samson and Paré, 2005) and thus could lead to increased CEm output. However, the relevance and contribution of this LTP to learning-related behavioral changes remains to be tested. A second possibility is that inputs from different sources impinging onto CEl neurons undergo activity-dependent synaptic plasticity. Altered drive of CEl neurons could set the level of inhibitory control in the CEl-CEm circuit, thereby changing downstream CEm output (Figure 3A). For example, afferents from the PB form strong and reliable synapses onto CEl neurons, which exhibit distinct forms of bidirectional plasticity (Lopez de Armentia and Sah, 2007). PB afferents convey ascending nociceptive information to CEl (Neugebauer et al., 2004), and their modification may be the neural substrate underlying the emotional and behavioral modifications accompanying states of persistent pain (Delaney et al., 2007; Neugebauer et al., 2004). A second set of afferents that show input-specific LTP in vitro are CEl inputs from the basolateral complex (Fu and Shinnick-Gallagher, 2005). However, other important inputs, such as those originating in the insular cortex, have not been examined. Again, central open questions are the role of the different forms of activity-dependent plasticity in behavioral learning and how they affect CEl and, ultimately, CEm output. One interesting property of CEl neurons is that synapses made by their extrinsic inputs express high levels of the NMDA receptor subunit NR2B into adulthood (Lopez de Armentia and Sah, 2003), a feature that discriminates them from BLA neurons and may enable them to express distinct forms of signaling and cellular plasticity. It is intriguing to speculate that the disruption of fear memory acquisition in behavioral pharmacological experiments that interfered with NR2B signaling (Rodrigues et al., 2001) could be, at least partially, mediated by the CEl.

Together, this strongly supports the notion that modification of local, intra-CEA inhibitory gating may be intimately involved in controlling fear and anxiety behavior and fear learning depending on the behavioral state. In analogy to striatal circuits, one could envision a heterogeneous population of local inhibitory neurons within CEl with distinct inputs and outputs and, as a result, distinct roles in shaping output activity (Figure 3A). While we emphasized GABAergic processes, the role of peptidergic neurotransmission in CEA circuits and their effector structures clearly needs to be addressed. Furthermore, it will be important to identify neuronal subpopulations, address plasticity mechanisms at the level of identified subtypes, and determine how local interactions control CEl activity and CEm output.

Intercalated Cells Relay Feedforward Inhibition

The last main players conferring inhibitory control onto multiple targets in the amygdala are the ITCs. These GABAergic neurons surround the BLA and are organized in a baso-medially located main cluster (ITC) and smaller paracapsular clusters (lITC, mITC; Figure 1). Axon collaterals from paracapsular ITCs target principal cells in neighboring nuclei, the BLA and CEA (Geracitano et al., 2007; Millhouse, 1986; Royer et al., 1999). Functional studies demonstrated that lateral paracapsular ITCs (lITCs) convey feedforward inhibition to the BLA, while medial paracapsular ITCs (mITCs) participate in feedforward inhibition from BLA to CEA (Marowsky et al., 2005; Royer et al., 1999). Together, this has led to the concept that ITCs function as an inhibitory gate for input and output stations of the amygdala (Pape, 2005; Paré et al., 2004) and could be a major regulatory site controlling CEA excitability and fear expression (Paré et al., 2003) (Figure 1C). Recent studies provide first evidence that these specialized interneurons can contribute to fear expression and memory.

The paracapsular ITCs are mostly small to medium size spiny interneurons, located in several small clusters within the intermediate and external capsules. Their dendritic trees are largely confined in the capsules and are contacted by cortical afferents in these fiber tracts (Millhouse, 1986). Indeed, capsular stimulation in slices reliably yields monosynaptic, excitatory synaptic responses in mITCs and lITCs (Jüngling et al., 2008; Marowsky et al., 2005). The lITCs can directly inhibit projection neurons in the BLA (Marowsky et al., 2005). The mITCs send projections to and convey feedforward inhibition to CEA, while some have axon collaterals within the intermediate capsule targeting mITCs in the same or adjacent clusters (Geracitano et al., 2007; Jüngling et al., 2008; Paré and Smith, 1993; Royer et al., 1999), suggesting inhibitory interactions among ITCs themselves. In guinea pigs, inhibition between mITCs is thought to be organized in a latero-medial direction (Royer et al., 2000). This, together with a general latero-medial topography of mITC afferents from the LA and BA, and efferents to the CEl and CEm, respectively, has been proposed to shape BLA to CEA information transfer (Royer et al., 1999). Such a topographic organization would allow for different sets of ITCs to shape amygdala output differentially: for example, the most lateral mITCs could inhibit CEl and medial mITCs, resulting in disinhibition of CEm, whereas activation of more medial mITCs by BA inputs could lead to direct inhibition of CEm (Paré et al., 2003) (Figure 3A). The first direct evidence for inhibitory connections between several mITCs in one cluster came from a recent study in mice, but a topographic organization of connectivity either within the cluster or to the CEA was not detected (Geracitano et al., 2007). Inhibitory synaptic transmission between mITCs was facilitating or depressing, and all synapses of a given presynaptic neuron onto multiple postsynaptic partners exhibited the same short-term dynamics, while postsynaptic neurons received inputs with heterogeneous properties (Geracitano et al., 2007). The authors propose that this would support network stability and the high firing rates observed in mITCs in vivo (Collins and Paré, 1999). The prevailing hypotheses are that lITCs gate information relayed from cortical afferents to the main sensory interface (BLA) and that mITCs gate information transfer between the principal input (BLA) and output stations (CEA) of the amygdala. The potential to dynamically

shape incoming and outgoing information of the BLA, and the inhibitory control over CEA output, puts ITCs in a prime spot to control fear expression and extinction.

Behavioral-State-Dependent Control of Amygdala Output by Intercalated Cells

Evidence that ITC activity contributes to fear expression and memory is provided by a combination of behavioral and cellular effects of neuromodulators. Dopamine (DA) affects fear-related behavior, with activation enhancing (Borowski and Kokkinidis, 1998; Guarraci et al., 1999) and inhibition depressing fear learning and retrieval (Greba et al., 2001; Greba and Kokkinidis, 2000; Guarraci et al., 2000; Nader and LeDoux, 1999). Behavioral studies further emphasized the importance of D1 receptor subtypes in these processes. At the circuit level, DA appears to disinhibit BLA activity (Rosenkranz and Grace, 2002b), a finding that could initially not be reconciled with cellular actions of DA on BLA principal cells and interneurons (Kröner et al., 2005; Lorétan et al., 2004). However, ITC clusters receive the densest dopaminergic afferents in the amygdala and express high levels of D1 receptors (Fuxe et al., 2003). Subsequently, Marowsky and colleagues (Marowsky et al., 2005) showed that DA, acting through D1 receptors, hyperpolarizes paracapsular ITCs, reduces their output, and thereby also reduces the amount of feedforward inhibition to BLA and CEA principal neurons, leading to a net disinhibition of principal cells in these structures. Thus, DA effects at the circuit and behavioral level are congruent when considering DA modulation of ITCs and suggest a critical role for ITC activity in the generation of fear responses and fear memory expression.

Acquisition and Expression of Fear Extinction

Extinction of conditioned fear is a striking example of how fear expression can be suppressed by new learning in a context-dependent manner. The presence of a fear memory trace without fear expression following extinction training strongly suggests the involvement of inhibitory mechanisms and their plasticity in extinction learning. For example, systemic application of the benzodiazepine receptor inverse agonist FG-7142, which decreases the efficacy of endogenous GABAergic transmission, impaired extinction memory retrieval in a context-specific manner (Harris and Westbrook, 1998). This suggests that enhanced inhibitory activity contributes to signaling the safety of a particular context and the suppression of conditioned fear responses. Such changes in inhibitory drive could occur in several brain structures, since accumulating evidence points to extinction memory being encoded in a distributed network including the amygdala, hippocampus, and prefrontal cortex (Myers and Davis, 2007; Quirk and Mueller, 2008). Here, we focus on the critical role of the amygdala in acquisition and expression of extinction.

Cellular Plasticity in the Basolateral Amygdala during Acquisition of Fear Extinction

Several lines of evidence suggest that cellular plasticity in the BLA underlies the acquisition of fear extinction. Behavioral pharmacological studies indicate that local interference with glutamatergic synaptic plasticity in the BLA, such as infusion of NMDA receptor antagonists or blockers of ERK/MAPK signaling, prevents or attenuates extinction (Falls et al., 1992; Herry et al., 2006; Lin et al., 2003; Lu et al., 2001; Sotres-Bayon et al., 2007). Interestingly, enhancing endogenous GABAergic transmission by local application of a benzodiazepine receptor agonist into the BLA interferes with extinction learning (Hart et al., 2009). At the cellular level, fear extinction decreases CS-evoked unit activity in the LA in a context-specific manner (Hobin et al., 2003; Quirk et al., 1997), while another population of cells appears resistant to extinction training (Repa et al., 2001). In the BA, extinction training is associated with a rapid switch in the balance of CS-evoked activity between two distinct populations of projection neurons (Herry et al., 2008). Although the cellular basis and the mechanisms of these rapid activity changes are not clear, these experiments establish a strong case for cellular plasticity in the BLA during the acquisition phase of extinction. A candidate mechanism for extinction acquisition is NMDA receptor-dependent synaptic plasticity at different circuit elements, including projection neurons and perhaps subsets of interneurons, which express NMDA receptors and can display NMDA receptor-dependent plasticity (Bauer and LeDoux, 2004; Szinyei et al., 2003). Inhibitory transmission could gate extinction learning by enabling cellular plasticity in the BLA, very much like it gates cellular changes associated with fear conditioning in the LA.

Increases in Local Inhibition in Basolateral Amygdala during Expression of Fear Extinction

The expression of extinction memory requires the behavioral-state-dependent suppression of the fear memory trace. Persistent changes in inhibitory drive to projection neurons that would decrease their output or input activity could mediate this function. One possibility is that extinction learning directly enhances inhibitory synaptic transmission by adding or strengthening GABAergic synapses (Figure 3B). Indeed, fear extinction is associated with increased benzodiazepine receptor binding and upregulation of mRNA levels for postsynaptic components such as the $GABA_A$ receptor subunits $\alpha 2$ and $\beta 2$ and gephyrin, a structural protein at GABAergic synapses, within several hours following training (Chhatwal et al., 2005; Heldt and Ressler, 2007). Within the same timeframe, mRNA levels for the GABA-synthesizing enzyme GAD67 increase while levels of the GABA transporter GAT-1 that mediate presynaptic reuptake decrease, indicating enhanced presynaptic function (Heldt and Ressler, 2007). Together, this leads to the notion that, following extinction, GABAergic transmission is enhanced in the BLA by upregulation of pre- and postsynaptic elements, although functional support is still lacking. The apparent general nature of changes in inhibitory markers (i.e., throughout the BLA) is currently difficult to reconcile with the observed CS and context specificity of extinction at the behavioral level (Myers and Davis, 2007). It will be important to use more sophisticated approaches to identify which specific inhibitory circuits are altered and address the underlying mechanisms. Potential mechanisms could include long-term strengthening of subsets of GABAergic synapses triggered by GABAergic LTP-like mechanisms (Nugent and Kauer, 2008) and may affect several types of interneurons that constrain principal cell activation at distinct levels.

Another possibility is an increase in state-dependent recruitment of inhibitory circuits in the BLA during retrieval of extinction memory. Enhanced activation of inhibitory circuits within the

BLA constrains the impact of sensory input at the level of principal neurons (Lang and Paré, 1997; Li et al., 1996; Rosenkranz and Grace, 1999; Rosenkranz et al., 2003). Stimulation of afferents from the mPFC leads to disynaptic inhibition of BLA principal cells, probably via local GABAergic interneurons (Rosenkranz and Grace, 2002a). An appealing hypothesis is that, following extinction, interneurons are more strongly recruited by the mPFC, resulting in decreased sensory-driven activity in BLA principal cells (Figure 3B). This could be achieved by direct strengthening of synaptic inputs from mPFC onto BLA interneurons. Although cortical inputs onto fast-spiking interneurons in the LA can be potentiated in slices (Mahanty and Sah, 1998; Szinyei et al., 2007), it is not known whether similar processes occur during extinction. Alternatively, plasticity within the mPFC that accompanies extinction consolidation could lead to increased mPFC output (Burgos-Robles et al., 2007; Herry and Garcia, 2002; Milad and Quirk, 2002), which would then drive interneurons more strongly. Overall, it emerges that an increase in local inhibition within the BLA plays a critical role in expression of extinction. It will be important in the future to determine which mechanisms are intrinsic to the BLA and involve local microcircuits and which ones emerge through interactions with other brain structures such as the mPFC. However, these mechanisms require a certain degree of specificity, because fear memory can be expressed following extinction learning in a context-dependent manner.

Increased Activation of Intercalated Cells Constrains Central Amygdala Output

Particularly the mITCs have received much attention as an inhibitory gate between the BLA and the CEA (Paré et al., 2004; Paré and Smith, 1993; Royer et al., 1999). One current model is that, following extinction learning, activation of mITCs by amygdala-intrinsic or -extrinsic glutamatergic afferents (e.g., from the mPFC) leads to inhibition of their targets in the CEA, suppressing CEm output and fear responses (Figure 3B). Taking into account inhibitory interactions among mITCs and projection topography (Geracitano et al., 2007; Royer et al., 1999), another scenario is that decreased LA activity decreases synaptic drive to a subset of ITCs, which reduces inhibition of other ITCs and CEl neurons. This would also result in suppression of CEm output. The hypothesis that, through their inhibitory control, ITCs participate in coding of extinction memory has, until recently, rested on indirect evidence. mITCs are targeted by dense axonal projections from the infralimbic region (IL) of the mPFC (McDonald et al., 1996; Vertes, 2004). Activity patterns of IL neurons change following extinction, and these changes appear critical for the expression of extinction (Burgos-Robles et al., 2007; Milad and Quirk, 2002; Sotres-Bayon et al., 2008). Stimulation of the IL in vivo reduces CEA output, and mITCs have been proposed to mediate this inhibition (Quirk et al., 2003; Berretta et al., 2005), thus linking enhanced IL activity to decreased amygdala output and decreased fear responses. Recently, Likhtik and colleagues (Likhtik et al., 2008) aimed at directly testing whether mITCs are required for extinction memory by developing a method to specifically target mITCs using receptor-coupled toxins. Ablation of the largest cluster of mITCs following extinction training compromised extinction retrieval, while within-session extinction was evident and subsequent fear conditioning was unaltered (Likhtik et al., 2008). Although this does not allow strong conclusions about the acquisition mechanisms or the involvement of the IL-ITC pathway in extinction retrieval, it supports a critical role for mITCs in the expression of extinction memory.

The mITCs also receive glutamatergic inputs from the BLA, which could be an additional substrate for plasticity in extinction. Indeed, bidirectional, NMDA-R-dependent synaptic plasticity can be induced at these inputs (Royer and Paré, 2002, 2003), but the link to behavioral changes has not been established. Recently, a novel mechanism pointing to ITCs and the LA-ITC projection as key players in extinction has emerged from a comprehensive study of the neuromodulator neuropeptide S (NPS) (Jüngling et al., 2008). Behaviorally, NPS facilitates extinction training when locally applied in the amygdala, while NPS receptor antagonists attenuate both acquisition and retrieval of extinction memory, suggesting a critical role for endogenous NPS. At the cellular level, NPS specifically enhanced LA to mITC excitatory transmission by a presynaptic mechanism, without affecting other cell types in the BLA or other ITC input pathways. On the network level, NPS enhanced feedforward inhibition from BLA to CEA (Jüngling et al., 2008), which may result in inhibition of amygdala output and reduction of the fear response.

These studies lend considerable support for a critical and specific role of inhibition meditated by mITCs in the acquisition, expression, and retrieval of extinction. Most likely, excitatory activity from BLA and IL inputs is integrated at the level of mITCs and contributes to inhibitory control of CEA activity. It is attractive to speculate that acute and long-term changes of synaptic activity in the LA, BA, and IL to mITC pathways play perhaps distinct roles in the acquisition versus expression of extinction. Many open questions remain, some fueled by two other recent findings: one is the considerable heterogeneity in mITCs properties and projection patterns (Geracitano et al., 2007), and the second is an unexpected correlation between the lack of behavioral extinction and the activation patterns of mITCs by immediate-early gene analysis (Hefner et al., 2008). Together, these findings suggest that different subpopulations of ITCs exist, which effect CEA activity differentially (Figures 3A and 3B). Clearly, we need to better understand how ITCs control CEA output. This could happen either by synaptic and cellular interactions and control within the mITC clusters or by differential control of subtypes of neurons within the CEA inhibitory network. It is possible that mITC activity has a dual function, to either inhibit or disinhibit CEm output, depending on the behavioral state.

Conclusions

Over the past two decades, the main focus of research on the neuronal substrates of associative learning has been on the function of glutamatergic projection neurons in the cortex-like nuclei of the amygdala and in other brain regions, as well as on the mechanisms underlying long-term synaptic plasticity at glutamatergic synapses. Recent work reviewed here indicates, however, that addressing the functions of local inhibitory circuits may be key to achieving a deeper understanding of amygdala circuit function in the context of classical conditioning.

At first sight, inhibitory circuits appear to be involved in a myriad of different processes in distinct parts of the amygdaloid complex. While this is certainly true, a few key concepts start to emerge. First, inhibition in the lateral amygdala gates the induction of synaptic plasticity. Inhibitory gating of LTP induction is not unique to the amygdala and has been described in other brain areas. However, addressing these issues in the amygdala offers the possibility to relate increased or decreased gating efficiency to behavioral consequences, such as specificity or generalization of associative learning. Second, inhibitory circuits control output of projection neurons at all levels within the amygdaloid complex. This output control appears to be involved in modulating fear expression as well as establishing a new, perhaps competing memory trace following inhibitory learning such as extinction. Insight from studies on mostly GABAergic structures such as mITCs and the CEA indicate that output control may not only be achieved by inhibition, but also contribute to the generation of fear responses via disinhibitory processes. Third, inhibitory circuit function, both in terms of gating plasticity during acquisition and with regard to output control, are prime targets of various neuromodulatory and neuropeptidergic systems. It is likely that neuromodulation of select inhibitory circuits might be a fundamental process shaping and adapting neural network function to specific behavioral demands. Finally, emerging evidence supports the notion that local inhibitory neurons are not merely orchestrating the activity of projection neurons but that their inputs and outputs are directly subject to various forms of long-term synaptic plasticity. This suggests that they may be involved in the adaptation of circuit function allowing the animal to adjust its learning mechanisms according to previous experience.

It is clear that we are just starting to understand the role of amygdala inhibitory circuits in fear memory coding and that a number of important questions wait to be addressed. On the one hand, future experiments need to address the specific function of identified subtypes of BLA, CEA, and ITC interneurons within the local microcircuitry. Undoubtedly, tackling this question will be aided by novel experimental tools such as the cell-type-specific expression of fluorescent markers to identify interneuron subtypes or the use of genetic tools to specifically manipulate the activity of select cell populations.

On the other hand, more general questions arise. Why is it, for example that in the amygdala two fundamentally different circuit structures, one cortex-like and the other striatum-like, are combined in order to control fear behavior and to acquire and store fear memories? The parallel and serial circuit arrangement may serve to optimize speed, signal-to-noise ratio, and reliability of signal processing. Engagement of both circuits may enable the integration of excitatory and disinhibitory signals that could act in an instructive and permissive manner to set CEA output. At the same time, a parallel arrangement would allow for maximal control and flexibility: the two circuits could independently generate fear output depending on stimulus, context, and behavioral state of an animal. Elucidating how defined inhibitory circuits contribute to the acquisition and extinction of conditioned fear can inform us about what each specific circuit is optimized for, and what roles similar circuits play in other behavioral tasks and other brain structures.

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