Biological Psychiatry

Review

Amygdala Inhibitory Circuits Regulate Associative Fear Conditioning

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ABSTRACT

Associative memory formation is essential for an animal's survival by ensuring adaptive behavioral responses in an ever-changing environment. This is particularly important under conditions of immediate threats such as in fear learning. One of the key brain regions involved in associative fear learning is the amygdala. The basolateral amygdala is the main entry site for sensory information to the amygdala complex, and local plasticity in excitatory basolateral amygdala principal neurons is considered to be crucial for learning of conditioned fear responses. However, activity and plasticity of excitatory circuits are tightly controlled by local inhibitory interneurons in a spatially and temporally defined manner. In this review, we provide an updated view on how distinct interneuron subtypes in the basolateral amygdala contribute to the acquisition and extinction of conditioned fear memories.

Keywords: Amygdala, Extinction, Fear learning, Interneuron, Neuronal circuits, Plasticity

https://doi.org/10.1016/j.biopsych.2017.10.006

The ability to associate environmental stimuli with an appetitive or aversive outcome is crucial for an animal's survival through adaptive behavior. Conversely, there is accumulating evidence suggesting that different forms of psychiatric conditions, including different forms of anxiety disorders, addiction, and possibly other mental diseases, are based, at least in part, on maladaptive learning (1). Learning is mediated by activity-dependent functional and structural changes in neuronal circuits. For a long time, studies on the neurobiological basis of learning and memory have focused on the synaptic and cellular mechanisms of plasticity at excitatory glutamatergic synapses. However, by dynamically regulating neuronal excitation in a cell type– and even subcellular compartment–specific manner, gamma-aminobutyric acidergic (GABAergic) inhibition exerts temporally precise control over the activity in neuronal circuits. A large body of work provided insight into how inhibition dynamically controls and orchestrates neuronal circuit activity in easily accessible parts of the brain, like the cortex. With the help of novel tools, we can now study inhibition in deeper brain areas that are intimately involved in simple, experimentally tractable forms of learning, such as classical fear conditioning. In this review, we discuss recent progress in our understanding of how specific subtypes of amygdala interneurons dynamically regulate the function and plasticity of local amygdala circuits and their long-range projections during the acquisition, retrieval, and extinction of conditioned fear memories.

Pavlovian fear conditioning is a widely used model to study the neuronal correlates and mechanisms of associative learning in the brain (2–4). During auditory fear conditioning, an initially neutral tone (conditioned stimulus [CS]) is paired with an aversive unconditioned stimulus (US), typically a mild foot shock, such that after pairing, the CS presentation alone elicits a conditioned fear response, which consists of motor (e.g., freezing or flight), neuroendocrine, autonomic, and other components (2–4). Subsequent repeated nonreinforced CS presentations result in a gradually decreased conditioned response, a phenomenon called fear extinction, which is not the erasure of the initial fear memory, but by itself a new learning process (5–7). Dysregulated fear learning and particularly impaired extinction of fear have been implicated in the development and persistence of human anxiety disorders, including posttraumatic stress disorder (1,8,9).

One of the key brain regions for the acquisition, expression, and extinction of conditioned fear behavior is the amygdala, a highly conserved temporal lobe nucleus (2). The amygdala consists of several interconnected subnuclei with distinct anatomical and physiological features. The basolateral amygdala (BLA) is a cortex-like structure composed of 80% glutamatergic principal neurons and 20% GABAergic interneurons (10,11) (Figure 1A). The dorsal part of the BLA, the lateral amygdala (LA), is the main input site for sensory information to the amygdala complex, and receives strong inputs from sensory cortex and thalamus (12,13). The basal amygdala (BA) receives less direct sensory information, but is rather reciprocally connected with other brain regions, such as the prefrontal cortex or ventral hippocampus (12,14–17). Furthermore, the BLA also sends projections to the central nucleus of the amygdala (CEA), a striatum-like major output region of the amygdala, which contains GABAergic medium spiny neurons (18). The CEA mediates motor and autonomic responses to fear and stress by targeting nuclei in the midbrain and in the hypothalamus [(19), for a review, see Tovote *et al.* (3)]. In addition, surrounding the BLA, there are several small clusters of GABAergic neurons, the so-called intercalated cell masses

ISSN: 0006-3223

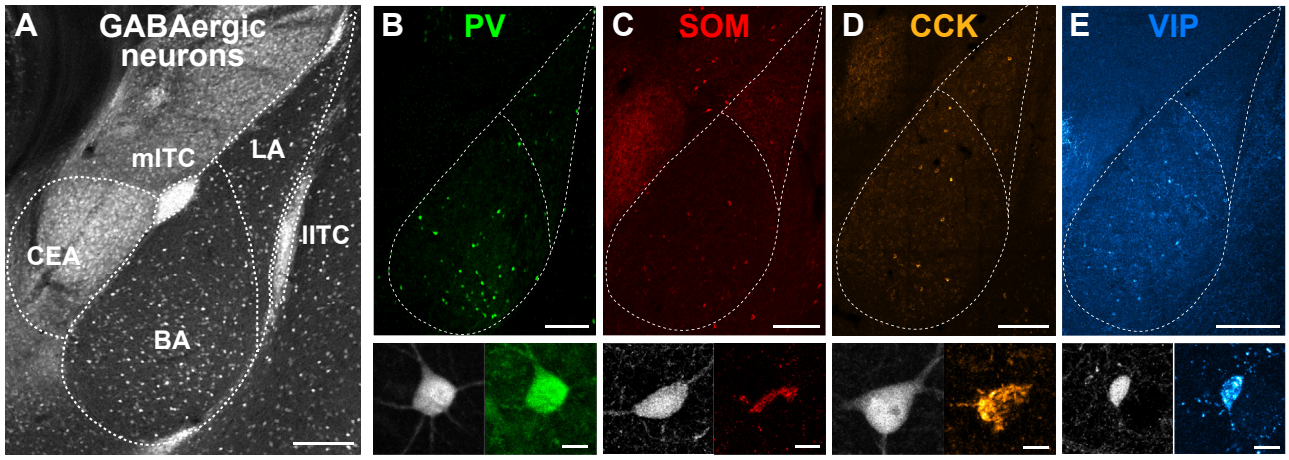

Figure 1. Interneuron classes in the basolateral amygdala. **(A)** Coronal brain section of a mouse expressing enhanced green fluorescent protein (EGFP) in gamma-aminobutyric acidergic (GABAergic) cells (GAD67-EGFP) showing the distribution of inhibitory neurons in different amygdala subnuclei. GABAergic neurons are sparsely distributed in the basolateral division of the amygdala, and densely packed in the central amygdala (CEA) and intercalated cell clusters. Scale bar = 200 μm. **(B–E)** Immunofluorescent stainings of calcium-binding proteins and peptides in GAD67-EGFP–positive cells (gray) of the basolateral amygdala. The major interneuron classes are defined by the expression of molecular markers such as parvalbumin (PV), somatostatin (SOM), cholecystokinin (CCK), and vasoactive intestinal peptide (VIP). Scale bars = 200 μm (top panels), 10 μm (bottom panels). BA, basal amygdala; LA, lateral amygdala; lITC, lateral cluster of intercalated cell masses, mITC, medial cluster of intercalated cell masses.

(ITCs) (20). A lateral cluster of ITCs provides feedforward inhibition to the BLA, while a medial cluster mainly gates interactions at the interface between the BLA and CEA (21–23).

So far, research on the neuronal basis of classical fear conditioning has primarily focused on excitatory, pyramidal-like principal neurons in the BLA, which are considered as main sites of synaptic plasticity during the acquisition and extinction of conditioned fear behavior. Until recently, the role of local interactions between BLA principal neurons and interneurons remained largely elusive. This was due to a lack of appropriate tools, which would allow for spatially and temporally defined recordings and manipulations of distinct neuronal subtypes in freely behaving animals. Over the past few years, converging evidence points to an important role for GABAergic inhibition in gating and regulating neuronal plasticity and learning (24–29). A key step was the development of transgenic mouse lines that express Cre recombinase in specific interneuron subtypes (30). The combination with novel techniques for virally mediated gene transfer, optogenetic identification, and manipulation, as well as calcium imaging, now provides unprecedented access to distinct cell types in deep brain regions such as the amygdala (31–34). Monitoring the activity of individual BLA interneurons in freely behaving rodents over the course of several days is still challenging but will help to understand their role in sensory processing and in neuronal circuit plasticity for learning, retrieval, and extinction of conditioned fear memories.

INTERNEURON SUBTYPES IN THE BLA

Only 20% of BLA neurons are GABAergic interneurons (Figure 1A), yet they tightly control the activity of the remaining large population of principal neurons (10,11,35,36). In contrast to excitatory principal neurons, GABAergic interneurons have thin, aspiny dendrites, and their axonal arbor is usually restricted to the BLA (35,37). Intriguingly, a small subset of GABAergic BLA neurons with yet unknown function have long-range projections to remote regions including the basal forebrain or entorhinal cortex (38–40). Different classes of BLA interneurons are typically defined by their expression pattern of calcium binding proteins or neuropeptides, which correlates with neuronal morphology, postsynaptic targets, and cellular physiology (41). These groups are remarkably similar to interneuron populations observed in other brain areas such as the cortex or hippocampus (42).

Based on earlier immunohistochemical studies, two major, nonoverlapping groups of BLA interneurons can be defined by the expression of the calcium binding proteins calbindin (CB) and calretinin. CB interneurons account for about 60% of BLA interneurons and can be further subdivided into parvalbumin (PV)-, somatostatin (SOM)-, neuropeptide Y-, and cholecystokinin (CCK)-expressing cells (37,43–45) (Figure 1). Substantial overlap of SOM and neuropeptide Y expression has been reported, while the other groups are largely separate (44,46,47). Approximately 20% of BLA interneurons are calretinin positive, many of which coexpress CCK or vasoactive intestinal peptide (VIP), both individually and with some overlap (37,45).

PV Interneurons

BLA PV interneurons mainly target the perisomatic region of principal neurons (37,48–52) and can be further subdivided in basket and axoaxonic cells. In contrast to PV basket cells, axoaxonic cells have been shown to be immunonegative for CB (52). PV basket cells form basket-like synapses around principal cell somata, but also contact the proximal dendrites and the proximal part of the axon initial segment (37,48,50,52) (Figure 2A). On the other hand, axoaxonic cells form specialized synapses onto the axon initial segment, with the highest density of synaptic contacts close to the action potential initiation site (51), which puts them in an ideal position to overwrite general dendritic input and suppress principal neuron output at

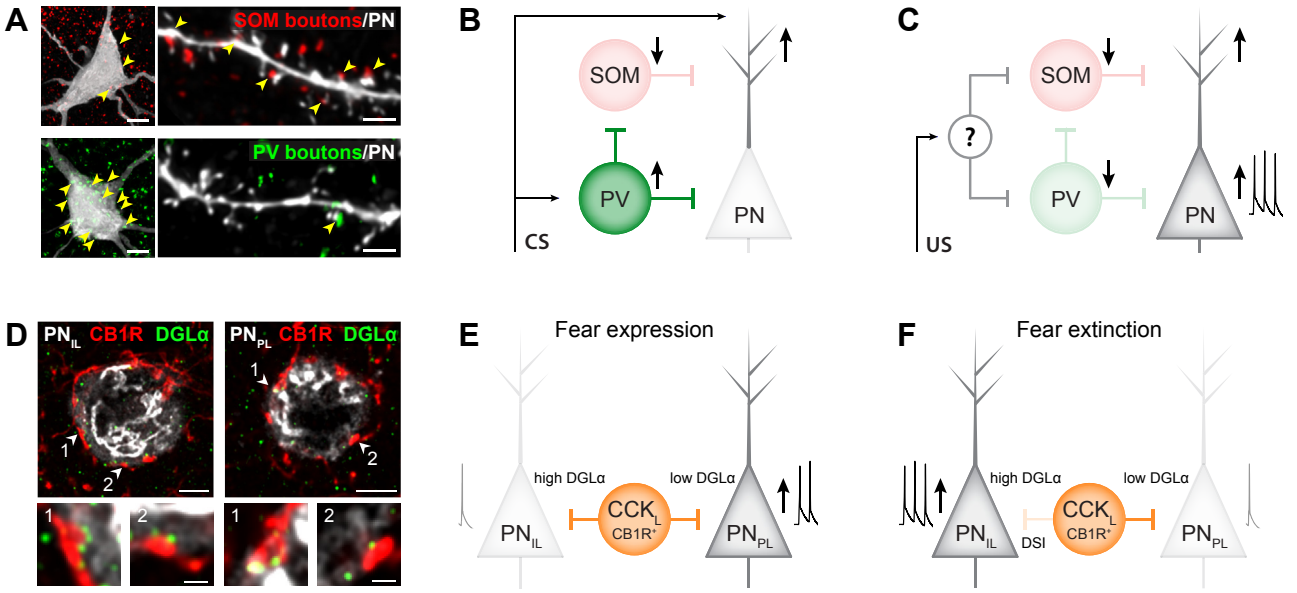

Figure 2. Inhibitory control of fear learning and extinction in amygdala microcircuits. **(A–C)** Compartment-specific inhibitory control of basolateral amygdala (BLA) principal neurons (PNs) during fear learning. **(A)** Conditional expression of synaptophysin tagged with green fluorescent protein in somatostatin (SOM) (top panels) or parvalbumin (PV) (bottom panels) interneurons labels their presynaptic terminals. SOM interneurons preferentially target the dendrites of BLA projection neurons (yellow arrowheads). In contrast, PV interneurons mainly target the perisomatic region. Adapted with permission from Wolff *et al.* (49). Scale bar = 5 μm (left panels), 2 μm (right panels). **(B)** During fear conditioning, BLA PV interneurons are excited by the auditory conditioned stimulus (CS) and inhibit SOM interneurons. This leads to a dendritic disinhibition of BLA PNs and enables dendritic processing of the CS. **(C)** Both PV and SOM BLA interneurons are on average rapidly inhibited during the presentation of the aversive unconditioned stimulus (US). The resulting disinhibition of the entire somatodendritic axis of BLA PNs increases their US-induced activity and enhances associative fear learning. **(D–F)** Projection-specific inhibitory control of BLA PNs during fear extinction. **(D)** Somata of retrogradely labeled BLA PNs projecting to infralimbic (IL) (left panels) or prelimbic (PL) (right) subdivisions of the medial prefrontal cortex are equally surrounded by cannabinoid receptor type 1 (CB_1R)–positive terminals from large cholecystokinin interneurons (CCK_L), but IL projectors display higher levels of the cannabinoid-synthesizing enzyme diacylglycerol lipase α (DGLα). Adapted with permission from Vogel *et al.* (46). Scale bars = 5 μm (top panels), 1 μm (bottom). **(E)** During fear expression, PL-projecting BLA principal cells are activated by the auditory CS. **(F)** In contrast, during fear extinction, IL projectors will strongly increase their activity. Owing to their high DGLα levels, this depolarization leads to the release of endocannabinoids and suppresses CCK_L-mediated inhibition (depolarization-induced suppression of inhibition [DSI]), which enhances the contrast between BLA fear and extinction pathways to promote behavioral adaptations.

the site of spike generation. PV-expressing cells also target other GABAergic interneurons such as SOM cells (49) and form extensive connections among themselves, which supports synchronized activity within PV and principal cell ensembles (36,53–55). Owing to strong glutamatergic inputs from neighboring BLA principal cells, PV interneurons can provide feedback and lateral inhibition (56–58). Most PV cells fire narrow action potentials at high frequencies that can reach up to 200 to 350 Hz (36,53,55,59). Although PV basket cells and PV axoaxonic cells are equally potent in suppressing action potentials in postsynaptic principal neurons, the short-term dynamics of their synapses show a different frequency dependence, which points to a diverging role in temporal control of postsynaptic activity (50,59).

SOM Interneurons

SOM interneurons preferentially target principal cells at their distal dendrites, and to a lesser degree at the perisomatic region (49,60) (Figure 2A). Therefore, they are in an ideal position to regulate synaptic transmission and plasticity at excitatory inputs onto principal neuron dendrites. SOM interneurons also target PV and VIP interneurons (60,61), and a specialized subset of SOM- and neuropeptide Y–expressing GABAergic cells projects out of the BLA to other brain regions (38,39). Different in vitro activity patterns of SOM interneurons have been described, and based on electrophysiological criteria, they cannot be reliably distinguished from other interneuron groups or principal cells (62).

CCK Interneurons

CCK-expressing interneurons can be divided into two groups: 1) large CCK interneurons (CCK_L), which coexpress the calcium-binding protein CB or vesicular glutamate transporter type 3, and which are the only BLA interneuron class expressing cannabinoid receptor type 1 (45,63,64); and 2) small CCK interneurons, which often coexpress VIP or calretinin and lack cannabinoid receptor type 1 receptors (45,63). CCK_L and small CCK interneurons display differential biophysical properties and electrophysiological response patterns (46). Nevertheless, some in vitro studies further suggest that there are at least three physiologically distinct types of CCK interneurons in the BLA (65). Similar to PV basket cells, CCK interneurons form basket-like synapses around the somata of principal neurons and innervate their proximal dendrites, which enables them to reliably suppress spiking in the postsynaptic cells (45,50).

VIP Interneurons

VIP interneurons in the BLA are partially overlapping with the small CCK interneuron group. They mainly target CB-expressing BLA interneurons and occasionally other VIP interneurons (61). However, VIP^+ axons have also been shown to form basket-like synapses around principal neurons (45,61).

So far, little is known about the activity patterns and function of BLA interneurons in the awake, behaving animal. Depending on their inputs and connectivity onto neighboring principal neurons, individual classes of interneurons might exert distinct, highly specialized functions during the acquisition, expression, and extinction of conditioned fear responses. Although most studies do not differentiate between LA and BA interneuron populations, region-specific interneuron function during aversive learning is likely. Given that sensory brain areas preferentially target the LA (12,13,66), interneurons in this subnucleus are in an ideal position to control plasticity during CS-US associations. In contrast, based on the interconnectivity of the BA with brain regions such as the prefrontal cortex or ventral hippocampus (12,14–17), interneurons in the BA are likely involved in higher-order contextualized behavior including fear extinction. In the following sections, we only refer to the specific subnuclei if region-specific interneuron function has been described.

ACQUISITION OF CONDITIONED FEAR: COMPARTMENT-SPECIFIC INHIBITORY CONTROL OF BLA PRINCIPAL NEURONS

During auditory fear conditioning, CS and US information converges in the LA, which is a major site of neuronal plasticity (67–71). Behavioral changes upon fear conditioning are thought to rely on synaptic plasticity at sensory afferents onto principal neurons, causing enhanced neuronal responses to the auditory CS (71–76). According to the classical Hebbian learning model, these synaptic changes are induced by converging and temporally coincident CS and US inputs to the same postsynaptic cells (67,77). While the auditory CS alone would elicit only a weak postsynaptic response, the US induces a strong postsynaptic depolarization, thereby triggering associative, activity-dependent synaptic plasticity mechanisms leading to the induction of long-term potentiation (LTP) at coactive CS inputs. This suggests that the US could act as a teaching signal, instructing associative plasticity at CS-activated synapses (78). Accordingly, pairing an auditory CS with artificial depolarization of LA neurons in vivo induces, albeit only weak, fear learning (79). Consistent with this finding, additional inputs including neuromodulatory transmitters have been implicated (27,80–83). A recent study using a deep brain imaging approach of large neuronal ensembles in the BLA found that only a fraction of principal neurons with potentiated CS responses displayed somatic US responses, and that fear conditioning–induced changes in the encoding of the CS involved both up- and downregulation of CS responses (31). Together, these studies support more complex scenarios involving additional learning rules and/or plasticity of inhibitory circuit elements. Importantly, understanding the function of cell type– and compartment-specific inhibitory circuits, and their dynamic regulation through synaptic and neuromodulatory mechanisms, will be key for obtaining a mechanistic model of neuronal circuit plasticity underlying associative fear conditioning.

CS Responses in BLA Interneurons

Inhibition is a powerful regulator of plasticity in the LA, and neither fear learning nor LTP can be induced without disinhibition (25,27,80,84,85). Until recently, little was known about how individual classes of interneurons might regulate neuronal plasticity in BLA circuits. Using single-unit recordings of optogenetically identified cells in freely behaving mice (33), Wolff *et al.* (49) could show that PV and SOM BLA interneurons display opposing responses during the CS presentation in an auditory fear-conditioning paradigm. While the majority of PV interneurons were excited by the auditory cue, SOM interneurons were on average inhibited. Moreover, optogenetic enhancement or suppression of these physiological CS responses improved or impaired fear learning, respectively. Thus, during the CS, PV interneurons may inhibit SOM interneurons, and as a consequence disinhibit principal neuron dendrites, a process that could be required to open a permissive temporal gate for the induction of synaptic plasticity at auditory input synapses. Consistent with such a disinhibitory circuit module, PV interneurons directly target SOM cells (49). Furthermore, a direct input from auditory regions onto PV interneurons has recently been demonstrated using monosynaptic rabies tracing (66). Experiments addressing the functional connectivity revealed that thalamic inputs specifically project onto LA PV interneurons, while cortical auditory projections target both LA and BA PV interneurons (66). This ideally positions both LA and BA PV interneurons to mediate CS-induced dendritic disinhibition in principal neurons (Figure 2B).

SOM interneurons preferentially target spines located on distal branches of the dendrites of BLA principal neurons (49,60). This anatomical configuration is consistent with the notion that SOM interneurons are key regulators of plasticity at auditory synaptic inputs and plasticity during fear learning. Dendritic spines receiving presynaptic inputs from thalamic afferent fibers were previously identified as sites of Hebbian plasticity in the LA (72,86). Consistently, activation of SOM interneurons in ex vivo slice preparations can suppress thalamic inputs to principal cells (49). In prefrontal cortex, SOM interneurons exert a highly compartmentalized influence on postsynaptic calcium signals in neighboring spines, enabling them to regulate the dendritic integration of individual excitatory inputs (87). It is thus conceivable that SOM interneurons in the BLA could regulate plasticity in an input-specific manner. However, it remains unknown whether SOM interneurons specifically control thalamic synaptic inputs, or whether they provide more global dendritic inhibition that could also affect cortical afferent synapses on the same dendritic branches (86). Furthermore, in motor cortex, SOM interneurons interfere with spine reorganization during motor learning (88). Indeed, spine size and numbers can change after fear learning in BLA principal neurons (89,90). Yet, how these synaptic plasticity mechanisms in the BLA are influenced by SOM interneurons during fear learning is so far unknown.

US Responses in BLA Interneurons

Several studies investigated the activity of BLA interneurons upon aversive stimuli. In freely moving animals, both PV and SOM interneurons were on average inhibited by the US during an auditory fear-conditioning paradigm (49) (Figure 2C). Yet, similar to their CS responses, the response profile was diverse, with subsets of US excited cells in both interneuron types. Bienvenu *et al.* (91) recorded BLA interneuron activity in response to foot shocks or hind paw pinches in anesthetized rats and used juxtacellular labeling to identify interneuron subtypes depending on molecular marker expression and morphology. In contrast to PV axoaxonic cells, which were uniformly activated by noxious stimuli, PV basket cells were heterogeneous and displayed both excitatory and inhibitory responses. A net inactivation of both PV and SOM interneurons leading to principal neuron disinhibition during the aversive US would be in accordance with a Hebbian learning rule that requires strong postsynaptic depolarization to induce LTP at CS inputs. Consistently, optogenetic activation of the entire BLA PV population during the aversive US impairs fear learning, while their inhibition has the opposite effect (49). However, conventional optogenetic manipulations suffer from the limitations that they are indifferent to cellular heterogeneity and the precise physiological timing of neuronal activity. Indeed, potentiation of CS responses does not necessarily require somatic US activation in LA principal cells (31), and rapidly increased inhibition at the perisomatic level by excited PV interneurons could even be beneficial to support mechanisms of spike-timing-dependent plasticity (86,92). Thus, more detailed studies are required to address the precise and possibly diverse roles of PV interneurons during US exposure.

What could be the source of US-induced inhibition of PV and SOM interneurons? Considering its rapid time course, US-induced inhibition may be mediated by fast neuromodulation and/or by GABAergic inhibition (93,94). In the cortex, VIP interneurons are strongly activated by aversive stimuli (95). Furthermore, they preferentially connect to SOM and to a lesser degree to PV interneurons, thereby disinhibiting cortical pyramidal neurons (95–97). In the BLA, VIP interneurons predominantly target CB interneurons, which include PV, SOM, and CCK_L groups (61). However, a functional connectivity has not yet been demonstrated, and the in vivo activity pattern of BLA VIP interneurons remains so far unknown. Alternatively, the US induced inhibition of PV and SOM neurons could be mediated by long-range GABAergic or cholinergic inputs from the basal forebrain (98–101), or by recently described specialized intercalated neurons, located in the lateral and medial clusters of the ITCs (40). In response to noxious stimuli, these cells are rapidly activated and target, among other brain regions, PV interneurons in the BLA. Furthermore, additional neuromodulatory inputs to the BLA such as dopamine or noradrenaline have been shown to be crucial for cued fear learning and LTP induction via suppression of inhibition (27,80,81,102–104). Indeed, subsets of dopaminergic and noradrenergic neurons are activated by aversive stimuli (105–109). Within the BLA, dopamine not only reduces feedforward inhibition from local interneurons in support of associative plasticity (21,27), but also leads to target-specific suppression of GABA release selectively at synapses from PV to principal neurons, but not to other interneurons (110).

Notably, BLA principal neurons are also involved in associative appetitive conditioning (111–115), and evidence suggests that learning instructed by aversive or rewarding stimuli might be mediated by distinct, antagonistic groups of projection neurons (116–119). So far, it is unknown how BLA interneurons contribute to appetitive learning, and if separate populations could selectively control the formation of conditioned fear or appetitive memories, respectively. Intriguingly, cortical VIP interneurons are uniformly activated by both aversive and rewarding stimuli (95), and a similar activation pattern has been observed for a subset of dopaminergic midbrain neurons (105–107). This indicates that the same disinhibitory mechanisms could gate associative learning irrespective of the valence of the US, but might rather respond to stimulus salience. Future studies will need to show how these signals are integrated in BLA microcircuits.

To date, only few studies addressed sensory responses of defined interneuron classes in the BLA. Overall, the picture of a remarkable response diversity emerges, even within a given interneuron class. This may be due to the fact that interneuron groups defined by the well-known molecular markers are still heterogeneous with regard to cell types. In addition, this diversity may also reflect the notion that sensory representations in the BLA are sparse (31,74). Only a small proportion of principal neurons exhibits increased CS responses after fear learning (31,72,74,76), and PV interneuron inhibition during fear conditioning can interfere with this sparse encoding of a memory engram (58). Consequently, altered inhibition during the acquisition or retrieval of conditioned fear memories could lead to fear generalization (26), pointing to the importance of the precise regulation of inhibition for memory specificity. Furthermore, BLA interneurons themselves undergo plastic changes during fear learning (66,120). Specifically LA PV interneurons have been shown to receive reduced excitatory inputs from auditory regions and consequently decrease their inhibitory output onto principal neurons after fear learning (66). However, future in vivo studies will be necessary to illuminate the importance of inhibitory plasticity for fear learning and expression.

MECHANISMS OF FEAR EXTINCTION: PROJECTION-SPECIFIC INHIBITORY CONTROL OF BLA PRINCIPAL NEURONS

Repeated presentations of a conditioned but nonreinforced auditory cue will gradually lead to the extinction of a conditioned fear response. Rather than forgetting, fear extinction creates a new inhibitory memory competing with the original CS-US association (5–7). The CS responsiveness of BLA principal neurons changes during extinction training, and similar to the so-called fear or CS-up neurons, which specifically increase their CS responses during fear conditioning, extinction neurons have been reported, which display enhanced activity to the auditory cue after extinction training (31,71,73,74,121). These two functional classes of BLA principal neurons preferentially project to the prelimbic or infralimbic (IL) subdivision of the medial prefrontal cortex,

respectively, two brain regions with opposite roles during fear extinction (6,122,123). The acquisition of fear extinction thus can be regulated by the balance of activity between distinct output pathways targeting the different medial prefrontal cortex subdivisions (15).

Inhibitory cells, particularly cannabinoid receptor type 1–expressing CCK_L interneurons, have been proposed to mediate the switch between high and low fear states and the concomitant changes in neuronal activity in the BLA during extinction learning (124–128). Although CCK_L interneurons connect to an equal extent with prelimbic- or IL-projecting BA principal cells, their synapses display target-specific short-term plasticity (46). CCK_L-synapses onto IL-projecting cells display stronger depolarization-induced suppression of inhibition, an endocannabinoid-dependent form of short-term plasticity (46,129). This effect was attributed to differential expression levels of the postsynaptic cannabinoid-synthesizing enzyme diacylglycerol lipase α in IL- and prelimbic-projecting cell populations (46) (Figure 2D). Therefore, it is conceivable that during extinction, when IL-projecting cells are strongly activated, CCK_L inhibitory input is rapidly suppressed, which may enhance the contrast between BLA fear and extinction pathways and promote rapid behavioral adaptations (Figure 2E, F). This endocannabinoid-mediated disinhibition could further provide a time window for integration of excitatory stimuli and synaptic plasticity in extinction cells.

Furthermore, plasticity of inhibitory interneurons has been suggested as a key mechanism in fear extinction (130). In contrast to fear learning (66), excitatory drive onto distinct subtypes of LA interneurons may be increased by LTP following fear extinction (131–133). In accordance with a shift in excitability of BLA fear and extinction pathways, it has been demonstrated that perisomatic PV^+ terminals increase around then silent BA fear cells after extinction training (134). Correspondingly, ablation of axoaxonic inhibitory synapses in the BLA impairs fear extinction (135). This implies that PV-mediated silencing of fear neurons might be needed for the expression of extinction.

In addition to BLA interneurons, the medial cluster of ITCs (mITCs) provides an inhibitory gate for the information flow between the BLA and CEA, thereby regulating fear extinction. Extinction training is associated with increased expression of immediate early genes in mITCs (136,137), and ablation of these cells interferes with extinction retrieval (138). Furthermore, extinction leads to a potentiation of excitatory BA inputs to mITCs, which in turn increases inhibition onto CEA output neurons to reduce fear responses (139). This effect depends on activity in the IL subdivision of the medial prefrontal cortex, which can directly activate cells in the mITC cluster in vivo (139–141).

Taken together, these data demonstrate the importance of BLA inhibitory circuit elements to create a competitive extinction memory suppressing fear responses. Nevertheless, in vivo studies addressing the role of distinct BLA interneurons or ITCs during and after extinction are still lacking. Therefore, further efforts investigating the precise activity patterns and recruitment of different BLA interneuron groups and ITCs with both recordings and perturbations in freely moving animals will be necessary to delineate their individual contributions to the acquisition and expression of extinction memories.

CONCLUSIONS AND FUTURE DIRECTIONS

The increasing numbers of cell type-specific genetically modified mouse lines, together with technical advances in optogenetics as well as tracing and recording techniques, have led to major progress in understanding the role of defined inhibitory microcircuits in the amygdala (31,33,34). However, unequivocal identification and recording of neuronal subtypes in deep tissues during complex behavioral tasks is typically low yield. Few studies managed to reliable record and analyze BLA interneuron activity in vivo, which could reveal first general principles of the importance of inhibitory mechanisms (49,91). Nevertheless, even within a genetically defined group, individual cells exhibit an intriguing response diversity to different environmental stimuli. This presses for future studies that further investigate the functional role of interneuron classes upon learning, ideally from large populations in single animals. Furthermore, it is important to emphasize that conventional optogenetic and pharmacogenetic manipulations of genetically defined cell types override this response diversity and can thus only provide limited conclusions about causal links between neuronal activity and behavioral adaptations.

Notably, the diversity observed in interneuron populations resembles principal neuron activity. Fear acquisition induces both upregulation and downregulation of CS responses in LA principal cells, and both mechanisms are equally important to increase the similarity of CS representation to the US on the ensemble level in support of learning (31). Disinhibition of excitatory principal neurons as described above is a popular explanation for Hebbian plasticity models of learning (94), while circuit mechanisms that lead to the downregulation of CS responses, potentially involving synaptic depression and/or plasticity of inhibitory circuits, are less well defined. Furthermore, simple disinhibitory models have been challenged recently, as strong reciprocal connectivity of PV, SOM, and VIP interneurons has been described in neocortical areas (96,142). Mutually inhibitory interneuron groups can change their response patterns depending on stimulus or context, leading to differential activity in principal neuron ensembles (143–145). This reciprocal connectivity most likely also exists in BLA inhibitory circuits (49,60,61) and could be important to regulate network activity in different behavioral states or contexts.

Finally, the observed diversity of in vivo activity patterns within a genetically defined interneuron population calls for a more functionally driven definition of an interneuron subtype. Indeed, widely used marker proteins for transgenic mouse models such as PV, SOM, or VIP show little or no overlap in the BLA (44,47), and at least partially correlate with postsynaptic targets and activity patterns. However, within the same group, further subtypes with specific subcellular targeting of postsynaptic cells or with different short-term dynamics of inhibitory synapses exist (37,48,50,52), suggesting a more divergent spatial and temporal control of postsynaptic activity. Furthermore, it is unclear if the same cells target principal neurons and other groups of interneurons, or even different projection neurons as previously shown in other brain areas (146,147). It

would be crucial to test whether specific in vivo activity patterns could be assigned to distinct subtypes based on morphological features or afferent and efferent connectivity. This can now be studied with the help of additional marker proteins in combination with novel intersectional genetic tools such as Cre and Flp recombinase–driven expression systems (30,148–150).

During the past few years, we have started to better understand the role of defined inhibitory microcircuits in the BLA in associative learning. However, to achieve a mechanistic understanding of circuit plasticity underlying associative learning in amygdala circuits, further studies are required with the need to integrate population level analysis together with a more molecular and biophysical understanding of the underlying functional processes. Many open questions will soon become tractable with the help of novel genetic and imaging tools, which will foster our understanding of BLA microcircuit function in health and disease.

ACKNOWLEDGMENTS AND DISCLOSURES

This work was supported by the Novartis Research Foundation (to AL), the European Research Council under the European Union's Horizon 2020 research and innovation programme (Grant No. 669582 to AL), project grants from the Swiss National Science Foundation, a grant from the National Center of Competences in Research: "SYNAPSY - The Synaptic Bases of Mental Diseases" (financed by the Swiss National Science Foundation) (to AL), fellowships from EMBO and the Swiss National Science Foundation (Ambizione) (to JG), and a Young Investigator Award from the Brain & Behavior Research Foundation (to SK).

The authors report no biomedical financial interests or potential conflicts of interest.

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Received May 18, 2017; revised Sep 28, 2017; accepted Oct 4, 2017.

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