Plastic Synaptic Networks of the Amygdala for the Acquisition, Expression, and Extinction of Conditioned Fear

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Abstract

The last ten years have witnessed a surge of interest for the mechanisms underlying the acquisition and extinction of classically conditioned fear responses. In part, this results from the realization that abnormalities in fear learning mechanisms likely participate to the development and/or maintenance of human anxiety disorders. The simplicity and robustness of this learning paradigm, coupled to the fact that the underlying circuitry is evolutionarily well conserved makes it an ideal model to study the basic biology of memory and identify genetic factors and neuronal systems that regulate the normal and pathological expressions of learned fear. Critical advances have been made in determining how modified neuronal functions upon fear acquisition become stabilized during fear memory consolidation and how these processes are controlled in the course of fear memory extinction. With these advances, came the realization that activity in remote neuronal networks must be coordinated for these events to take place. In this paper, we review these mechanisms of coordinated network activity and the molecular cascades leading to enduring fear memory, and allowing for their extinction. We will focus on Pavlovian fear conditioning as a model and the amygdala as a key component for the acquisition and extinction of fear responses.

Keywords

Pavlovian fear conditioning; extinction; prefrontal cortex; hippocampus; synaptic plasticity; oscillations

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I. Introduction: The Case for an Animal Model of Fear and Anxiety

Fear and anxiety are adaptive responses generated in anticipation or in the presence of stimuli that threaten to perturb homeostasis. While fear is generally elicited by particular cues or contexts, anxiety can occur in the absence of these triggers (88). Fear and anxiety are exhibited by all mammals, including humans, and appear to be part of a universal survival strategy. Not surprisingly, these states are controlled by a hierarchy of neural systems, which determine the efficacy of the responses and permit dynamic adaptations, thereby ensuring appropriate emotional responses and return to baseline activity once the threat has passed. Extreme variations or perturbations of these mechanisms can lead to prolonged (even irreversible) and disproportional states with respect to the triggering stimulus, persistence of anxiety following withdrawal of the stimulus, or omnipresent generalized anxiety. In their extreme or pathological forms, these states include panic disorders, phobias, and

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posttraumatic stress disorders (510,523). These are common diseases with an estimated lifetime prevalence of up to 18% (8,200), imposing a major challenge to health providers and burden on the economy. A large body of evidence indicates that these states are under genetic and environmental control, during early development as well as later in life, determining inter-individual variations (for review see (143)). Genome-wide linkage analysis and association studies have indeed led to identification of a number of genetic factors that determine the heritability of anxiety disorders, although the wide spectrum of symptoms and restricted sample sizes have limited success so far (143,163).

The motivation for developing animal models of fear and anxiety is thus twofold. First, animal models allow the study of single-gene modifications in a well-defined genetic background and under controlled environmental conditions, thereby partly overcoming problems inherent to human genomic studies. Second, because fear is well conserved throughout evolution, it is a near-ideal model system to study interactions between genetic factors, operating brain circuits, and behavior, allowing one to unveil the principles regulating the impact of environmental influences, learning and memory.

Of the various models used to investigate emotional behaviors (review in (124), classical *"Pavlovian" fear conditioning* has proven particularly useful and successful (reviewed in (239)). In this task, subjects learn to associate a previously neutral sensory stimulus [*conditioned stimulus (CS)*, such as a tone, light or odor] or context with a coinciding aversive stimulus [*unconditioned stimulus (US)*, such as a brief electric stimulus]. A memory is formed, so that subsequent exposure to the CS or conditioned context will elicit conditioned fear responses (CRs). These responses involve autonomic components (like hypertension, tachycardia, and hypoalgesia), an overall endocrine arousal, as well as species-specific defensive behaviors, such as freezing and flight (239). Of particular advantage is the possibility to use this task in various species, including humans (369). Furthermore, learning on this task is rapid, robust, readily quantified, and allows for a precise control of major fear memory-modulating parameters, as, for instance, stimulus specificity and predictability, or stress level (for review see (410,417)). These features make Pavlovian fear conditioning a near-ideal experimental model for identifying critical genetic factors and neuronal systems that drive fear responses and studying how they are regulated by environmental influences. In fact, the last two decades have witnessed an explosion of interest for the mechanisms underlying this relatively simple form of learning. The number of yearly citations returned by PubMed searches using the keywords "Fear Conditioning" rose from ≈50 in the late 80s, to ≈200 at the turn of the century, to ≈1400 in 2006 and 2007. One contributing factor behind this upsurge in interest is the realization that fear learning mechanisms may participate in the etiology of human anxiety disorders. Indeed, the findings of lesion and physiological studies in animals have been confirmed in human work (24,53,224,525). Moreover, human subjects with anxiety disorders exhibit abnormalities in the acquisition and extinction of conditioned fear responses (144,306,343). While it remains controversial whether anxiety disorders represent pathological manifestations of normal fear learning mechanisms (302,312,313,383), there is consensus that the structures normally involved in such learning display abnormal activity patterns in anxious subjects (49,467). Another factor fuelling this sustained level of interest for fear conditioning is the realization that this task is perfectly suited for studying learning and memory formation. Indeed, this model has allowed the identification of key neuronal circuits, neurochemical components, and synaptic events underlying fear memory formation. As a result, the amygdala has been identified as a key region for the processing of aversive signals and fear learning in various species including humans (for reviews see (37,274,299,369,464,473)). This knowledge, in turn, provides a strong basis to test the role of particular gene products in a functional context (for review see (486)). For instance, there is consensus now that memory *consolidation*, the process whereby a memory shifts from a transient state (referred to as

short-term memory) to a stable form (referred to as *long-term memory*), requires gene expression and *de novo* protein synthesis (193). However, long-term memories are not consolidated in a formal sense, but remain in a labile state, or become labile again after consolidation, susceptible to change and disruption, as for instance after memory retrieval, and therefore require "*re-consolidation*" (as recently reviewed in (331)). Research on fear conditioning has also paved the way for a better understanding of *extinction*, a simple form of fear behavior regulation, in which conditioned fear responses decrease when the CS is presented repeatedly in the absence of the US (as reviewed in (274,327,389)). The mechanisms of fear extinction have attracted significant interest because of their potential clinical significance (327,457)).

In recent years, critical advances have been made in determining how the transient synaptic modifications induced during fear conditioning become stabilized during fear memory consolidation (412) and how these processes can be controlled in the course of fear memory extinction (327,457). With these advances, came the realization that activity in remote neuronal networks must be coordinated for these events to take place. In the present paper, we will review these mechanisms of coordinated network activity and the molecular cascades leading to enduring fear memory on the one hand, and allowing for extinction of these memories on the other. We will focus on Pavlovian fear conditioning as a model and the amygdala as a key component of conditioned fear responses. The reader is referred to a number of excellent reviews for theoretical and behavioral accounts of fear conditioning and extinction (239,274,299,327,369,389,457), the impact of contextual influences (180,431), the re-consolidation of fear memories (331), the role of the GABAergic system (105) or neuromodulatory systems such as monoamines and stress hormones (299,410,417), the neurobiology of anxiety states and disorders (152,310,484), experimental models (124,472) and genetic approaches to these disorders (143,163,486).

II. Structure and connectivity of the amygdala

Located in the anterior portion of the temporal lobe, the amygdala is comprised of a dozen or so nuclei and cortex-like structures. Most of these components have been divided in two or more subnuclei that exhibit significant differences in connectivity. Since many comprehensive reviews on the structure and connectivity of the amygdala have been published before (9,371), we will limit the following account to components of the amygdala that are thought to be involved in the acquisition and extinction of conditioned fear responses. These include the basolateral complex (BLA), the central nucleus (CE), and the intercalated (ITC) cell masses (Fig. 1). Below, we first provide an overview of the structure and cellular composition of these three components and then summarize their connectivity.

A. Structure and cell types

1. Basolateral complex (BLA)—The BLA is comprised of three nuclei: the lateral (LA), basolateral (BL), and basomedial (BM) nuclei. The latter is also known as the accessory basal (AB) nucleus. Moreover, BL and BM are sometimes referred to as the basal nuclei. Morphologically, the neuronal composition of the BLA is similar to that of the cerebral cortex except for the fact that neurons are randomly oriented in the BLA. As in cortex, BLA contains two classes of neurons (reviewed in (285)). The dominant group (≈80%) are glutamatergic projection cells with multipolar dendritic trees covered with spines and axons contributing multiple collaterals to neighboring BLA cells, amygdala nuclei, or other structures of the brain (146,147,191,289). As in cortex, most BLA projection cells express a regular spiking phenotype, with marked cell-to-cell variations in the amount of spike frequency adaptation they exhibit (70,107,110,111,[118],[229],[231],[279],354,358,394,517).

The second class of BLA neurons consists of local-circuit GABAergic cells with short axons and aspiny to sparsely spiny dendrites (≈20% of the cells). Again as in cortex, local-circuit neurons are heterogeneous morphologically (146,147,191,289), electrophysiologically, and neurochemically, with different subgroups of local-circuit cells expressing neuropeptide Y (NPY), somatostatin (SOM), vasoactive intestinal peptide, or cholecystokinin (CCK; (177,198,291-295,372-374)). In addition, as in cortex, GABA co-localizes with calcium-binding proteins, such as parvalbumin (PV) and calbindin in a high proportion of interneurons (≈ 50-60%; (198,291-295,372-374,478,479)). Moreover, there is evidence that as in cortex, different sub-types of BLA interneurons target different compartments of projection cells. For instance, PV-immunoreactive interneurons of the BLA tend to contact the soma, initial axonal segment, and/or proximal dendrites of projections cells (298,325,477) whereas SOM immunoreactive interneurons preferentially contact their distal dendrites (324). On the input side, there is also evidence that BLA afferents target different subsets of interneurons. For instance, PV interneurons receive few if any cortical inputs but are massively innervated by BLA projection cells (475), suggesting a prevalent involvement in feedback inhibition. At odds with this however, a physiological study (496) reported that most fast-spiking interneurons receive convergent monosynaptic inputs from the cortex and thalamus. Finally, there is physiological and ultrastructural evidence that interneurons belonging to the same neurochemical class are coupled by gap junctions (323,528), in PV neurons at least.

Compared to cortex, far less data is available on the physiological properties of BLA interneurons but the results obtained so far are generally consistent with the cortical literature. Indeed, the repetitive firing properties of local-circuit cells are extremely diverse, even among neurochemically-homogeneous subgroups (177,396,479,528). For instance, in one study (528), four different subtypes of PV interneurons were observed (fast-spiking, stuttering, delayed firing, and accommodating). Similarly, three subtypes of CCK interneurons were described (177).

2. Central nucleus (CE)—Early accounts identified two divisions in the CE nucleus: lateral (CEl) and medial (CEm; (26,51,127,183,216). However, the rat CEl was later subdivided further with significant variations between investigators (65,185,287,367,493). From lateral to medial, these subdivisions include an amygdalostriatal transition area, a lateral sector proper, and interposed between CEl and CEm, an intermediate subnucleus. Because there is scant data indicating that these different subdivisions of CEl form distinct connections, this review will adhere to the initial division of CE in lateral and medial sectors. Finally, a capsular region of CE was identified; it encapsulates CE ventrolaterally (287) and appears to overlap with ITC cell clusters. We will therefore use the latter term for the capsular region.

CEl and CEm each contain one main cell type (64,65,146,191,287,500). Although these cells are thought to be GABAergic (288,290,359), some might use a different neurotransmitter as many do not stain positively for the GABA synthesis enzyme (glutamic acid decarboxylase-GAD; (373,491)). In CEl, the main cell type is indistinguishable from medium spiny striatal neurons. Indeed, these cells have multiple primary dendrites that branch profusely and bear a high density of spines. By comparison, the main neuronal type in CEm has a larger soma, dendrites that branch more sparingly, and bear a lower density of dendritic spines. In addition, CEm and CEl contain a low number of aspiny GABAergic local-circuit neurons. Here, it should be mentioned that whereas the GABAergic innervation of the BLA mostly has an intrinsic origin, that of CE includes a significant extrinsic component. This statement is based on a neurochemical study where interruption of the main pathways linking the amygdala with the rest of the brain decreases GAD levels in CE, but not BLA (236).

In terms of electroresponsive properties, the prevalent types of CEl and CEm neurons express a regular spiking firing pattern with variable degrees of spike frequency adaptation and a hyperpolarization-activated cation current (102,260). Moreover, a proportion of CE neurons are endowed with a t-type calcium current, giving rise to low-threshold spike bursts (102). Because retrograde tracing studies indicate that the vast majority of CEm cells are projection neurons (162), it is likely that these cells are output neurons. Finally, CE also contains a small subgroup of cells with comparatively depolarized resting potentials, higher input resistances, and fast-spiking or burst-firing patterns. These neurons likely correspond to local-circuit cells (102,260).

3. Intercalated (ITC) cell masses—As a group, ITC cells form a reticulated sheet of neurons that spans the entire rostrocaudal extent of the amygdala (311). ITC neurons occur as small densely packed cell clusters distributed in the main fiber bundles found in and around the amygdala. They are marked by arrows in Fig. 1B. These include the external capsule that borders the BLA laterally as well as the intermediate capsule, the fiber bundle separating the BLA from CE. ITC clusters located in the external and intermediate capsules will hereafter be termed ITC-L and ITC-M, respectively. In addition, in most species, there is a larger ITC cell mass: in cats, it caps the amygdala rostrally (359) whereas in rats is it located dorsomedial to the basal nuclei (339). This larger ITC cluster is labeled with an asterisk in Fig. 1B.

There are two types of ITC neurons. The prevalent type is characterized by a small soma (8-19 μm in diameter), a flattened dendritic tree that mostly remains within the confines of the fiber bundle where its soma is located, and a high density of dendritic spines. These cells are GABAergic (Fig. 1B1; (288,290,339,359)) and express an extremely high density of μ opioid and dopamine type-1 receptors (Fig. 1B2; (156,176,381)). In addition, a minute proportion of ITC cells have extremely large somata (>40 μm in diameter) and exceptionally long aspiny dendrites. Little is known about these cells except that they are not GABAergic but perhaps cholinergic (340). They will not be discussed further in this review.

Compared to principal neurons of the BLA and CE, principal ITC cells have a very high input resistance (500-900 MΩ), and can sustain higher firing rates with only modest spike frequency accommodation (137,277,426). In guinea pigs, ITC cells exhibit a bistable behavior because they express an unusual voltage-dependent K$^+$ current termed I_{SD} (SD for slowly deinactivating; (426)). I_{SD} activates at subthreshold membrane potentials, inactivates with depolarizations beyond spike threshold, and de-inactivates very slowly upon return to rest. Thus, following periods of firing, ITC cells assume a state of augmented excitability characterized by a sustained membrane depolarization and reduced conductance, thereby increasing the probability that synaptic inputs will trigger spiking.

B. Intrinsic Connectivity

1. Synaptic interactions within the BLA—The BLA is endowed with an extremely divergent system of intrinsic connections. Indeed, principal cells contribute multiple axon collaterals that bear varicosities (146,147,191,289) forming en passant excitatory synapses, usually with other principal neurons (476). Based on the length of the intervaricose segments, it was estimated (476) that each principal cell forms 100-200 excitatory synapses per millimeter of axon, most with other principal cells. Given the presence of a profusely divergent system of excitatory connections between principal BLA neurons, one would expect them to exhibit high firing rates. Yet, single unit recordings in unanesthetized animals have consistently emphasized the opposite (43,136,357). As we shall see below, the solution to this paradox resides in the spatial heterogeneity of connections formed by principal cells with interneurons.

Previous work has revealed that several factors reduce the excitability of principal cells. First, they express a calcium-dependent K+ conductance (gKCa) that can be activated when glutamatergic synapses cause Ca^{2+} entry via NMDA receptors, thereby shunting EPSPs (70,87,109,230). Second, the spontaneous activity of projection cells *in vivo* is dominated by large amplitude IPSPs mediated by GABA-A and B receptors following GABA release by local-circuit cells (87,279,395,518). We discuss these two mechanisms here in some detail because they interfere with induction of long-term potentiation (LTP) and, as we shall see in section IV, this suppressing effect is relieved by neuromodulators that are released in emotionally arousing conditions (35,109,504).

The first clue to the participation of intrinsic gKCa conductances to synaptically evoked inhibition came from intracellular recording studies where it was observed that cortical stimulation triggered EPSPs that were curtailed by large amplitude IPSPs with a reversal potential negative to that expected for chloride mediated GABA-A IPSPs (87,229). This observation implied that overlapping chloride and K conductances participated to the IPSP. However, this effect was seen at too short a latency for a mediation by GABA-B IPSPs. Furthermore, dialysis of principal cells with a calcium chelator produced a gradual positive shift in IPSP reversal potential toward that expected for pure GABA-A IPSPs, implying a mediation by gKCa (70,87,230). Moreover, Ca^{2+} chelation altered evoked responses within 5 ms of their onset, suggesting that the Ca^{2+} source (NMDA receptors; (87)) and gKCa channels were in close proximity, possibly in the same dendritic spines or branches (70,87,230). Subsequent studies yielded inconsistent results regarding the identity of the gKCa channels involved ((70) IK; (109) SK channels).

The second mechanism reducing the excitability of principal cells, namely GABA-A and B receptor-mediated inhibition, is similar to that seen in neurons throughout the prosencephalon. However, it is expressed differently in principal cells and interneurons of the BLA. Indeed, fast-spiking interneurons are subjected to less inhibition than BLA projection cells. First, they receive a markedly lower proportion of inhibitory synapses (477). Second, IPSPs in BLA interneurons lack a GABA-B component (279). They are comprised of apparently pure GABA-A IPSPs that reverse at more depolarized potentials than in projection cells (by > 15 mV; just under spike threshold). Pharmacological analyses *in vitro* suggest that this is secondary to a contrasting regulation of intracellular chloride in the two cell types. In projection cells, the main regulators of intracellular chloride are cation-chloride cotransporters that extrude chloride whereas in local-circuit neurons, transporters that accumulate chloride predominate (279).

The various factors listed above should contribute to make interneurons more excitable than projection cells. However, given the extremely divergent excitatory connections that exist between projection cells, their low spontaneous firing rates remains surprising. The key to this paradox resides in the spatial heterogeneity of connections formed by projection cells with each other and interneurons (438,440). By antidromically activating the axons of LA projection cells ending in the BM nucleus, one study inferred the intra-LA targets of projection cells (438). BM stimuli evoked markedly different synaptic responses depending on the slice orientation with inhibition dominating in coronal slices and excitation in horizontal slices. These results implied that the axon collaterals of projection cells contact different cell types depending on the rostrocaudal position of their targets: inhibitory interneurons at proximity and other projection cells at a distance. A subsequent study (440), using local pressure application of glutamate, revealed that the spatial heterogeneity of connections was not limited to feedback interneurons. Indeed, glutamate application at a distance from the recorded projection cells evoked only inhibitory responses in coronal slices. By contrast, in horizontal slices, the character of the responses depended on the lateromedial position of the glutamate ejection site with respect to the recorded cell. Ejection

sites located laterally to the recorded cells evoked mostly excitation whereas inhibition was typically elicited from medial sites. Overall, the ubiquity of inhibition in coronal slices combined with the predominance of excitatory responses in horizontal slices imply that the LA network is designed to allow associative interactions within the rostrocaudal plane while preventing runaway excitation locally.

2. Synaptic interactions within CE—Far less data is available on intrinsic synaptic interactions in CE. As mentioned above, Golgi studies (reviewed in (285)) suggest that CE contains a much lower proportion of local-circuit cells than the BLA. However, projection cells are GABAergic (288,290) and may inhibit each other via their local axon collaterals. Consistent with this, one study reported that local pressure application of glutamate in CEl evoked IPSPs in CEl neurons (260). In contrast, the same stimuli applied in CEm elicited no responses in CEl cells, in keeping with the lack of connections form CEm to CEl (185). Interestingly, BLA stimulation was reported to elicit an EPSP-IPSP sequence in CE neurons (260,427,428). However, local pressure application of glutamate receptor antagonists close to the recorded CE cells (to prevent the excitation of CE interneurons) had little effect on this inhibition (427). This suggests that a significant portion of inhibitory inputs to CE neurons have an extrinsic origin, most likely, ITC and BNST neurons. Finally, it should be mentioned that CE neurons express two types of ionotropic GABA receptors: GABA-A receptors that are blocked by low concentrations of bicuculline and GABA-C receptors that are less sensitive to bicuculline (90,91). These receptors appear to be expressed differentially at somatic vs. dendritic GABAergic inputs (91).

3. Synaptic interactions within and between ITC cell clusters—Experiments in mice and guinea pigs have revealed that ITC cells are interconnected. Within ITC cell clusters, one study reported that 14% of ITC cell pairs were connected unidirectionally and a much lower proportion bidirectionally (137). These GABAergic synapses exhibited heterogeneous short-term plasticity when presynaptic ITC cells were repeatedly activated with current injection at 0.1-10 Hz. In a roughly equal proportion of cell pairs, release probability increased, decreased, or remained constant. This variability was determined by the properties of the presynaptic neurons since sequential paired recordings revealed that the same presynaptic neuron formed the same type of synaptic connections with different postsynaptic neurons and conversely, that the same postsynaptic neuron was contacted by different types of synapses from different presynaptic neurons (137).

There are also connections between different ITCm clusters (Fig. 2A). So far, this question has only been investigated in guinea pigs (428). In this species, CE is dorsomedial to BLA such that the lateromedial axis in the guinea pig amygdala corresponds to the dorsoventral axis in the rat amygdala. Using local pressure applications of glutamate, it was found that laterally located ITC cell clusters inhibit more medial ones. The same study revealed that this directionality originated from the morphological properties of ITC neurons with their dendrites extending over longer distances in the lateral than the medial direction whereas their axons showed the opposite asymmetry. We will return to the significance of these observations when discussing the interactions between the BLA and CE.

C. Internuclear connections

A prominent feature of amygdala organization is the existence of strong and directionally polarized inter-nuclear connections (Fig. 2B; (362,377)). Within the BLA, there are strong glutamatergic projections from LA to the basal nuclei, particularly massive to BM (216,360,375,378). Some projections from the basal nuclei to LA exist but they are weaker and confined to the most ventral sector of LA (363,448). Thus, in the rat BLA, the prevalent directionality of inter-nuclear connections is from dorsal to ventral.

Principal BLA cells also project to CE, a projection that is not reciprocated (216,363,378,446,447,476). Here, it should be noted that whereas the basal amygdala nuclei project to CEl and CEm, LA only projects to CEl. Given the contrasting projections of CEl and CEm to the brainstem (162,368), this point will become critical when considering the intra-amygdala pathways participating in fear conditioning.

As BLA axons course toward CE, they form excitatory synapses with ITCm cells (Fig. 2A-B; (189, 427)). In turn, ITCm cells project to CE (361, 427) where they generate feed-forward inhibition (361, 427, 428). Physiological studies in guinea pigs indicate that there is a lateromedial correspondence between the position of ITCm cells, where they derive inputs from BLA, and where they project in CE (427). Assuming that these findings hold in rats, given the differing relative position of BLA and CE in the two species, this would mean a dorsoventral correspondence between the position of rat ITC cells, their BLA inputs and CE outputs. Because this topographical arrangement overlaps with dorsoventral connections between ITC cell clusters, the impact of ITCm activity of different parts of CE will depend on the distribution of activity in the BLA. For instance, even though LA does not project to CEm, it could indirectly affect CEm neurons by exciting laterally located ITCm clusters, which in turn would inhibit more medial ones, leading to a disinhibition of CEm cells.

D. Extrinsic Connectivity

1. Basic organizing principles of amygdala connectivity—The amygdala forms connections with an extremely diverse array of structures including cortex, striatum, some thalamic and hypothalamic nuclei, as well as various basal forebrain structures and brainstem nuclei (reviewed in (9,371)). As a result, the amygdala is in a position to influence a wide variety of processes from autonomic and motor control to memory formation and neuromodulation. Here, we first highlight basic organizing principles of amygdala connectivity and then consider in more detail the extrinsic and intrinsic pathways thought to participate in the acquisition and expression of conditioned fear responses.

Different amygdala nuclei project to different classes of CNS structures: There is a clear segregation of target structures depending on the amygdala nuclei originating the projections. Indeed, cortical and striatal projections of the amygdala originate from the BLA, not from CE (215,217,218). Conversely, BLA has little if any brainstem outputs whereas CE sends strong projections to various brainstem structures (162) involved in generating the behavioral and autonomic correlates of fear (88). However, BLA and CE do send overlapping projections to the lateral hypothalamus, basal forebrain regions containing cholinergic corticopetal neurons as well as to the bed nucleus of the stria terminalis (BNST). The latter target is of particular interest because BNST and CE are reciprocally connected and their brainstem projections overlap extensively (94-99,162). As to ITC cells, they do not project outside the amygdala, except for a projection from the main ITC group to the substantia innominata and diagonal band of Broca (horizontal limb) (360).

The amygdala receives information about all sensory modalities: Depending on the modality, sensory information can reach the amygdala via the thalamus, cortex, or more direct subcortical routes. Generally, sensory inputs from cortex do not originate from primary sensory areas but reach the amygdala after a cascade of corticocortical projections involving one or more associative cortical areas (286). Consistent with this, sensory information from the thalamus does not originate from specific thalamic nuclei, such as the lateral geniculate or ventrobasal nucleus, but from components of the posterior thalamic complex that tend to receive divergent and typically multisensory sensory inputs (186,240,241,257,505). We will consider the origin and termination of sensory inputs to the amygdala in more detail below, in the context of fear conditioning.

Many more cortical areas project to the amygdala than targeted by the amygdala:
Indeed, a diverse array of associative and polymodal cortical areas project to the amygdala
(286,436). In contrast, the BLA has no cortical projections other than the medial prefrontal
cortex (mPFC), insula, rhinal cortices, and a few hippocampal fields (217,218). Importantly,
the latter statement is only valid for lower species (mouse, rat, cat, rabbit). In primates, there
is a tremendous expansion of cortical projections including primary sensory and motor areas
as well as a number of associative cortical areas (2,6,130,380).

**Cortical inputs to the amygdala originate from different layers depending on the target
nucleus:** Paralleling the cortex-like nature of BLA and striatal-like properties of CE, cortical
inputs to BLA and CE mainly originate from layer III and layer V pyramidal cells,
respectively (52,436). Yet, even though cortical cells projecting to BLA and CE tend to be
located in different layers, most cortical areas that send axons to BLA also project to CEl
(286). In contrast, CEm receives very few cortical inputs, suggesting that inhibition and
disinhibition are major determinants of CEm outputs.

**The amygdala sends robust projections to neuromodulatory cell groups of the
brainstem and basal forebrain:** While most prosencephalic structures, including the
amygdala (112), receive inputs from neuromodulatory systems (485), relatively few
contribute dense projections to these cell groups. The amygdala is a notable exception to this
general rule. Via these projections, the amygdala can influence the general excitability of
much of the brain, even of structures it is not directly connected to. In turn, because the
neuromodulatory inputs often exert facilitating influences on synaptic plasticity (1,150),
these pathways likely enhance the formation of Pavlovian associations and may partly
explain how the amygdala facilitates memory formation for emotionally arousing
experiences (299). With the exception of substantial BLA projections to the substantia
innominata and diagonal band of Broca (184,215), most amygdala projections to
neuromodulatory cell groups originate in CE. These include projections to cholinergic and
noradrenergic cell groups located at the junction of the pons and mesencephalon, as well as
dopaminergic cells groups of the ventral tegmental area and substantia nigra pars compacta
(162,384).

E. Input and output pathways involved in fear conditioning

Because most data on the cellular and molecular substrates of fear conditioning was
obtained using auditory CSs paired with footshocks as USs, the following will focus on
sensory pathways relaying auditory and nociceptive inputs to the amygdala. As we shall see,
CS and US information can reach the amygdala through multiple routes (Fig. 2C).

CS and US input pathways—First, LA receives auditory inputs from the posterior
intralaminar nucleus (PIN) and the medial sector of the medial geniculate nucleus (MGm)
(244,257,469,505,529). Auditory inputs to PIN and MGm originate in the inferior colliculus
(IC; (241,256)). Auditory inputs also reach LA via thalamic projections to temporal auditory
cortical fields that innervate LA (280,415,416,466). Importantly, the same posterior thalamic
regions that relay auditory information to LA also receive inputs from the spinothalamic
tract (243) and may therefore send convergent CS and US inputs to LA.

The above routes of CS and US communication to the amygdala have been studied
extensively and figure prominently in most models of auditory fear conditioning. As
reviewed in section IV, convergence of CS and US in LA was shown to produce long-term
changes in the efficacy of synapses conveying CS information (274). Reversible inactivation
of LA during conditioning was found to prevent the acquisition of conditioned fear
responses (275,322,527), and animals with excitotoxic lesions of the BLA could learn

normal contextual fear, but showed substantial forgetting 30 days after training compared to intact controls (382). As a result, LA is thought to be the primary storage site of conditioned CS-US associations (239) and the BLA is thought to be critical for remote fear memories (382). However, other paths exist for the transfer of CS information to the amygdala, but they have received little attention so far. For instance, medial to PIN is the posterior thalamic nucleus (PO). PO could relay CS information to the amygdala. Indeed, PO receives auditory inputs (3) from the external and pericentral nuclei of the IC (221,256), the dorsal nucleus of the lateral lemniscus (220) and the nucleus of the brachium of the IC (222). However, in contrast with the pathways reviewed above, PO does not project to LA but to CEm and BM (244,257,505).

Similarly, there are other routes for US information to reach the amygdala and they too bypass LA. For instance, nociceptive inputs from the spinal cord and trigeminal complex can reach CE (particularly CEl) via the parabrachial nuclear complex of the pons (27-30,338). In keeping with this, physiological studies have revealed that CE cells respond to both mechanical and thermal noxious stimuli, but rarely to innocuous stimuli (337). Finally, there is evidence that PO relays nociceptive signals from the spinal cord to CEm and BM (186).

Amygdala outputs generating conditioned fear—There is general consensus that the main output station of the amygdala for conditioned fear responses to cues is CE (reviewed in (88); however see (213)). First, CE lesions block or reduce the expression of conditioned fear responses (60,141). Second, distinct conditioned fear responses can be selectively attenuated by lesioning different targets of CE. For instance, lateral hypothalamic lesions interfere with conditioned changes in arterial pressure, but not conditioned freezing. In contrast, lesions of the periaqueductal gray (PAG) suppress conditioned freezing but not conditioned changes in blood pressure (242). However, not all conditioned fear responses are completely dependent on CE. In contextual fear conditioning for instance, BNST lesions also interfere with conditioned freezing (490). Also, some conditioned avoidance responses do not depend on CE but on BLA outputs (202).

Links between the input and output stations of the amygdala—Behavioral freezing is the most commonly monitored measure of conditioned fear. Importantly, amygdala projections to the brainstem site mediating freezing (PAG) originate exclusively in CEm. This is significant because LA, the presumed storage site of CS-US associations, has no direct projections to CEm (216,378,476). However, there are three possible routes for LA activity to influence CEm (Fig. 2D). Indeed, CEl, the basal nuclei, and ITC cells all receive inputs from LA and in turn project to CEm.

Evaluating these various possibilities is complicated by the fact that there is uncertainty regarding the nature of CEm control over conditioned fear. Indeed, CE output cells are thought to use GABA as a transmitter (288,290) raising the following question: are conditioned fear responses generated by an increase or a decrease in the CS-evoked responses of CEm neurons? Insights in this question can be obtained by considering the effects of CE stimulation and conditioning-induced changes in CE activity. These two lines of evidence are considered in turn below.

Studies that examined the effects of CE stimulation or inactivation yielded somewhat inconsistent results (reviewed in (88)). Yet, the overall pattern of results suggests that an increase in CE activity causes an enhancement in fear expression, as expected given the effects of CE lesions (60,141). As to conditioning induced changes in CS responsiveness, only three studies have addressed this question. The first, in rabbits (364), reported that the CS-responsiveness of brainstem projecting CE neurons (presumably CEm cells) decreased

as a result of fear conditioning. In contrast, the other two studies, in rats (67) and mice (77), reported the opposite, consistent with the effects of lesion and stimulation studies. Therefore, the following will assume that an increase CEm output underlies expression of conditioned fear.

Since CEl activation is expected to inhibit CEm (260), and LA sends glutamatergic projection to CEl (216,378,476), it seems unlikely that CEl is the relay station between LA and CEm. Indeed, by enhancing the CS responsiveness of LA neurons, and therefore CEl cells, fear conditioning would be expected to cause a reduction in CEm output.

On the other hand, the two other candidate routes for transmitting LA outputs to CEm appear viable. Indeed, LA sends glutamatergic projections to laterally located ITCm cells (427), which inhibit medially-located ITCm cells (428), therefore causing a disinhibition of CEm output neurons (427). Similarly, LA sends glutamatergic projections to the basal nuclei (363,476), which form excitatory synapses with CEm output neurons (363). Therefore, when the CS responsiveness of LA neurons increases, both routes are expected to cause an increase in CEm activity, albeit through different mechanisms (disinhibition vs. excitation, respectively).

Consistent with the involvement of the basal nuclei in relaying LA activity to CEm, it was observed that post-training lesions of the basal nuclei abolish conditioned fear responses (12). However, pre-training lesions did not prevent the acquisition of conditioned fear responses (11,141,332). This suggests that in an intact brain, the basal nuclei constitute an essential relay of potentiated LA activity to CEm.

However, the fact that animals can learn conditioned fear responses despite pre-training lesions of the basal nuclei indicates that another path exist for the transfer of LA outputs to CEm (ITC cells) or that CEm is not a simple relay station for potentiated LA outputs to the brainstem. Indeed, there is evidence that CE is also a critical site of plasticity for fear conditioning. In particular, local infusions of drugs that affect CE only during fear conditioning are sufficient to prevent the formation of long-term fear memory (526).

Overall, the evidence reviewed above suggest that fear conditioning depends on distributed plasticity in the amygdala. The fact that inactivation of LA or CE during training prevents the acquisition of conditioned fear indicates that both nuclei are essential sites of plasticity but that neither is sufficient. Also, the fact that post-training lesions of basal nuclei block the expression of conditioned fear indicates that, in an intact brain, the basal nuclei are at least required for relaying CS information from LA to CE.

III. Oscillatory Activity During Fear Learning and Emotional Arousal

As mentioned above, LA is thought to be the storage site of CS-US associations. According to this view, fear memory storage would involve an activity-dependent potentiation of synapses conveying CS information to LA neurons (see section IV). This potentiation would result from converging depolarizing inputs about the CS and US during fear conditioning. While *in vitro* studies have emphasized that tightly correlated pre- and postsynaptic activity is most effective for LTP induction, the paradigm typically used during fear conditioning is not optimal to meet this requirement. Indeed, most fear conditioning experiments involve long tone (CS) presentations (20-30 s) co-terminating with brief (≤ 1 s) footshocks. This is perplexing because the tone responses of LA neurons are strongest at tone onset and quickly diminish with time, nearing pre-tone firing rates toward the end of the CS (for instance see (390)). As a result, it would seem that LA neurons experience comparatively little tone-evoked depolarization when the US occurs, a conclusion that is in apparent contradiction with the findings of *in vitro* studies on LTP induction mechanisms.

A possible solution to this paradox resides in the ability of BLA neurons to express oscillatory activity (Figs. 3-4). By generating short recurring periods of depolarization during which the activity of pools of BLA neurons is synchronized with that of afferent neurons, oscillations might allow for the facilitated induction of synaptic plasticity with little increases in firing rates. As we shall see below, accumulating evidence indicate that BLA neurons do engage in such oscillatory activity and that these oscillations tend to synchronize BLA neurons with each other and with afferent neurons, with no change in discharge rates.

A. Theta oscillations

Previous *in vitro* (351,354) and *in vivo* (358) intracellular recordings studies have revealed that BLA neurons have an intrinsic propensity to generate voltage-dependent membrane potential oscillations in the theta frequency range. Two types of intrinsic theta oscillations were identified. The first (Fig. 3A), seen at membrane potentials near firing threshold (354,358), results from the interplay between a tetrodotoxin-sensitive persistent Na$^+$ conductance and the M-type K$^+$ current (351). The second, seen at supra-threshold membrane potentials, results from the rhythmically alternating influence of high-voltage activated Ca^{2+} conductances and Ca^{2+}-dependent K$^+$ currents (351). Theta oscillations are regulated by the intracellular AC-cAMP system, in that an increase in intracellular cAMP concentration facilitates generation of oscillatory activity via modulation of SK-type K$^+$ channels (353).

In keeping with this, local field potential (LFP) oscillations and rhythmic unit activity at the theta frequency were seen in the BLA during paradoxical sleep (Fig. 3B; (357)) and periods of intense arousal caused by the anticipation of noxious stimuli (356). Although the intrinsic propensity of principal BLA neurons to oscillate or reverberate at the theta frequency likely played a role in these phenomena, another important contributing factor is the generation of theta oscillations by cortical fields that are reciprocally connected with the BLA such as the hippocampal formation (55), and the rhinal cortices (Fig. 3C; (7,79,315)).

In fact, the synchrony of hippocampal CA1 and LA theta increases during consolidation (458) and reconsolidation (336) of fear memories, while theta synchrony decreases at remote memory stages (Fig. 3D,E (335)), and during fear memory extinction (352). Theta activity recorded as LFPs in LA is not likely to be volume conducted from neighboring regions due to the following reasons. First, theta synchrony occurs between LA and CA1 during specific stages of fear memory, but not with CA1 theta during exploratory behavior (335,458). Second, theta phase relations between regions vary characteristically during different states of fear memory (352). Third, the firing probability of LA neurons fluctuates rhythmically with theta oscillations in LFPs (352). These findings are in line with studies indicating that hippocampal circuits are engaged in the early stages of learning and show only limited activation as memory progresses at remote stages, while the reverse gradient has been documented for prefrontal cortical circuits (42,128,129,283). Theta-entrained activity has indeed been recorded across widespread prefrontal cortical-hippocampal circuits (471,474). In keeping with this, infralimbic prefrontal cortical activity was phase-locked to CA1-LA theta during retrieval and extinction of fear memory (352). In conclusion, theta synchronization appears to be an important organizing principle for creating time windows of fear memory consolidation within extended hippocampal-amygdala-prefrontal cortical networks.

B. Gamma oscillations

Another type of oscillatory activity that synchronizes principal BLA neurons with each other and with target cells is gamma (35-45 Hz; Fig. 4A). There is reason to believe that theta and gamma oscillations are related in the BLA. Indeed, the theta oscillations seen in the

hippocampal formation (47) as well as in the entorhinal (75,76) and perirhinal (79) cortices are associated with cyclical amplitude modulations of gamma activity at the theta frequency. Given the existence of strong reciprocal connections between these cortical areas and the BLA, it is likely that the two oscillations are similarly related in the BLA. However, this remains to be tested.

Several observations suggest that gamma activity plays a critical role in synchronizing BLA neurons with each other and with target cells. For instance, fluctuations in the power of LFPs recorded simultaneously in the BLA and rhinal cortices are more strongly correlated in the gamma range than other frequencies (Fig. 4B1; (21)). Similarly, the coherence of BLA and rhinal (Fig. 4B2) or striatal LFPs is highest in the gamma range compared to all other frequencies (21,379). In contrast, other major sources of inputs to the striatum such as intralaminar thalamic nuclei and cortex do not show a preferential coupling at the gamma frequency (379). Thus, there results suggest that coherent gamma activity represents a physiological signature of BLA interactions with target structures.

Two types of evidence indicate that the gamma activity seen in the BLA is not volume conducted from neighboring regions and is perhaps generated within the BLA. First, the firing probability of BLA neurons fluctuates rhythmically with gamma oscillations (Fig. 4D; (21,379)). Second, local intra-BLA infusions of the GABA$_A$ receptor agonist muscimol produce a pronounced and frequency-selective reduction of gamma power in the LFP of target structures (Fig. 4C; (379)). In the BLA, gamma activity typically occurs is short bursts of 2-6 consecutive high amplitude cycles during which there is no overall increase in firing rate, only a change in spike timing (21,379). Importantly, functional coupling among BLA neurons as well as between BLA and target neurons was shown to increase when gamma power augments (Fig. 4F; (21,379)).

Although the implication of BLA gamma oscillations in fear conditioning has not been examined so far, these oscillations were shown to coordinate the activity of BLA neurons with target structures during various forms of appetitive learning paradigms. For instance, in an appetitive trace conditioning task, thought to be dependent on the hippocampus, the power of CS-evoked gamma oscillations increased in the BLA and rhinal cortices, in parallel with improvements in behavioral performance (21). Similarly, in a discriminative stimulus-response task, thought to be dependent on the striatum, BLA-striatal gamma coupling increased selectively in relation to the rewarded CS (379), paralleling learning improvements.

Overall, these results suggest that the generation of coherent oscillatory activity in the BLA and related structures might be involved in fear conditioning and extinction. By generating short, recurring time windows during which pools of BLA cells and target neurons, fire synchronously, these oscillations may facilitate the induction of synaptic plasticity, with little or no change in firing rates. Moreover, the fact that coding in the BLA does not necessarily involve global increases in activity but changes in neuronal synchrony, highlight the importance of simultaneously recording multiple neurons to gain insights in the mechanisms that support fear memory and extinction.

IV. Synaptic plasticity in the amygdala related to conditioned fear

Central to the mechanisms of learning and memory are changes in synaptic efficacy, which take place during learning and are stabilized during memory consolidation. The Hebbian postulate (151) and the subsequent discovery of *long-term potentiation* (*LTP*) in the hippocampus (38,39) paved the way for a widely accepted concept of synaptic plasticity, in which temporally correlated pre- and postsynaptic activity results in presynaptic release of glutamate and postsynaptic depolarization. Provided presynaptic activity coincides with a

sufficient level of postsynaptic depolarization, postsynaptic NMDA receptors with bound glutamate are relieved from their Mg^{2+}-dependent block and allow a Ca^{2+} influx into postsynaptic compartments, such as dendritic spines, thereby inducing a lasting increase in synaptic efficacy referred to as LTP (267). NMDA receptors thereby act as coincidence detectors that transform correlated neuronal activity into changes in synaptic strength. A large number of subsequent studies have yielded information on intracellular transduction and signalling pathways related to LTP in unforeseen detail (266). These transient molecular changes must be stabilized in order for the memory to persist (300). There is consensus now that the shift from the transient state of memory (referred to a *short-term memory*) to the stable form of memory (referred to as *long-term memory*) requires gene expression and *de novo* protein synthesis (193), which correlates with structural changes in synaptic morphologies (referred to as *structural plasticity*; (227)). In analogy to short- and long-term memory in behavioral studies, different phases of LTP have been distinguished based upon the transition from labile to more stable changes in synaptic efficacy. In fact, the maintenance of LTP, like memory storage, depends on intact protein synthesis and thus consists of at least two temporal phases, referred to as transient early-LTP (E-LTP) and protein synthesis-dependent late-LTP (L-LTP; for a review see (131)). Although the two phases of plasticity do not fully match in temporal characteristics at the synaptic and behavioral levels, they seem to share a common set of molecular mechanisms.

In an attempt to link changes in synaptic efficacy to specific learned behaviors, *Pavlovian fear conditioning* has proven particularly attractive for a number of reasons: a) the training paradigm is relatively simple and results in associative learning, which is rapidly acquired and long-lasting; b) this model allows one to control the induction, expression, and extinction of the memory; and c) the behavioral and autonomic fear-like responses can be reliably measured. While initial studies focused on the thalamus and cortex as possible sites of fear memory storage, subsequent lesion and electrophysiological studies indicated that the amygdala is a site of associative plasticity for Pavlovian fear memories (14,194,364). Converging evidence over the last three decades has supported the hypothesis that LTP of synaptic inputs that transmit CS information to the amygdala underlies the increase in fear responsiveness to the CS. Core support for this view comes from three major lines of evidence: a) fear conditioning causes a facilitation of responses to afferents relaying CS information to the amygdala, b) LTP occurs at these afferent inputs, and c) fear conditioning and LTP share a common set of mechanisms affected similarly by a range of experimental manipulations. The extensive literature on these themes is covered by a number of review articles (37,93,114,142,[207],[239],270,274,409,473). Recently, critical advances have been made in determining how the transient synaptic modifications induced by NMDA receptor activation become stabilized during fear memory consolidation, and how different neuronal input systems must be coordinated for theses events to take place. Here, we will briefly summarize the findings that have laid the groundwork for understanding conditioned fear on a synaptic level, followed by a more extensive review of the molecular cascades of memory stabilization. An overview about the molecular mechanisms is provided in figure 5. The various forms of long-term synaptic plasticity described in amygdala neurons are schematically illustrated in figure 6.

A. A classical view

Most of the knowledge about the circuits involved in conditioned fear was derived from experiments on auditory fear conditioning in rodents. The major sensory input station to the amygdala is LA. Therefore, the majority of studies have focused on auditory pathways to LA, and particularly on thalamic inputs to the dorsal part of the LA (LAd). The central idea underlying the cellular hypothesis of fear conditioning is that the convergence of CS and US inputs onto principal LA neurons during Pavlovian fear conditioning results in a lasting

increase in synaptic strength at CS inputs, recorded as LTP. This increased activity is relayed to the central amygdala (CE), the main output station for fear responses. This hypothesis is based upon three major assumptions, all of which underwent ample experimental examination, as described below (see also ref (473)).

First, fear conditioning induces changes in efficacy at afferent synaptic inputs to the amygdala—This has been shown, mostly in LAd, by extra- and intracellular recordings of CS-evoked firing *in vivo* (80,139,390,404,414,419) and by recordings of synaptic responses to afferent stimulation in brain slices *in vitro* obtained from fear-conditioned animals (301,502,538). These studies demonstrated the associative nature of the plasticity, established LA as the site of plasticity, and provided support for a causal relationship between LA plasticity and fear memory (reviewed by (274)). For instance, LA responses to the CS^+ following conditioning were greater than those after explicitly unpaired presentations of the CS^+ and US (390) and were opposite to those evoked by a non-conditioned stimulus (CS^-) in a discriminative auditory fear training paradigm (80). These results indicated that LA plasticity is of an associative nature rather than being dominated by non-associative processes, such as sensitization. Importantly, the plastic changes recorded in LA upon fear conditioning preceded increases in responsiveness observed in the auditory thalamus (303) or auditory cortex (386). Moreover, local manipulations of the LA known to interfere with fear conditioning had either no effect on neuronal activity in the auditory thalamus (451) or impaired the development of plasticity in auditory cortex or thalamus (15,275). These data ruled out the possibility that changes in LA responsiveness simply mirror plasticity occurring upstream of LA, as for instance in the thalamus or cortex (56), and further supported the notion that the LA is a site of associative plasticity.

As fear conditioning gives rise to behavioral changes that could affect CS processing in LA, and fear responses often outlast the stimuli that induce them, it is important to determine whether plastic changes in LA activity are a cause or consequence of conditioned fear behavior. In an elegant study apt to dissociate LA plasticity and fear expression, Maren and colleagues (139) performed discriminative fear conditioning in rats using distinct auditory CSs (CS^+ versus CS-), which were then presented in a neutral context and, in a different group of animals, in a context that had been conditioned with an aversive US. Fear conditioning increased both CS^+-evoked LA responsiveness and fear behavior, whereas presentation of the CS^- did not result in changes in LA responsiveness, even though it evoked high fear behavior in the conditioned context. Further and importantly, inhibiting the behavioral expression of conditioned fear through pharmacological inactivation of CE had no effect on CS^+-evoked increases in LA responsiveness. Together these data indicated that LA neurons signal the CS^+-US association irrespective of the behavioral expression of fear (as reviewed in (274)).

Second, LTP occurs at synaptic inputs to the amygdala—This has been demonstrated *in vivo* in anesthetized (78,413,531) and freely behaving animals (101), as well as *in vitro* in slice preparations (69,164,166,170,497,503,519). The focus has been on postsynaptic LTP at thalamic inputs to LA, which was induced by a high frequency train of stimuli allowing summation of depolarizing postsynaptic potentials to unblock NMDA receptors (Fig. 6A). To better model the temporal pattern of CS-US pairing, single presynaptic stimuli have been paired with postsynaptic depolarization *in vitro* (166,170,503,524). These studies revealed that LTP occurred only at those inputs that underwent paired stimulation, thereby demonstrating input specificity of LA plasticity. More recently, Kwon and Choi (223) in a very clever approach probed a conditioning paradigm in which tetanic microstimulation of the auditory thalamus (MGm) rather than a sensory CS^+ was used. Pairing of tetanic stimulation with a US resulted in conditioned fear behavior and LTP-like increases in evoked field potentials in LA, whereas explicitly unpaired protocols or

microstimulation of a neighboring thalamic region (MGv) had no effect on behavior or LA responsiveness. These results indicate that LTP induction and associated changes in synaptic efficacy at thalamo-LA inputs are involved in fear learning. Associative LTP has also been shown upon stimulation of both thalamic and cortical inputs to LA in awake rats, with characteristic asymmetries occurring in LTP magnitude and duration between the two inputs (101). Furthermore, paired afferent input or pre- and postsynaptic stimulation revealed the existence of a presynaptic form of LTP at cortical inputs to LA (Fig. 6A) (166,172,502). There is agreement that LTP induction at thalamic and cortical inputs to LA involves NMDA receptors, which are predominantly located at postsynaptic and presynaptic sites, respectively (but see (13)). Thalamic and cortical inputs fibres converge onto both projection neurons and local interneurons (496), where they may even converge onto the same dendrites. The question thus arose as to how the two input systems are functionally segregated in a non-layered structure like LA. One answer was provided by Humeau and colleagues (170) who showed that the two inputs contact functionally and morphologically distinct types of dendritic spines, and that this heterogeneity determines Ca^{2+} influx and thereby the afferent-specific Hebbian plasticity.

Third, fear conditioning and LTP share a common set of mechanisms—The demonstration that intra-amygdala infusion of NMDA receptor antagonists blocks the induction (but not expression) of conditioned fear *in vivo* and of LTP *in vitro* provided the basis for the hypothesis that NMDA receptor-mediated LTP represents a cellular substrate of fear conditioning (22,61,166,206,314). Early studies yielded evidence for the additional contribution of L-type voltage-gated Ca^{2+} channels (166,468,524) or questioned the involvement of NMDA receptors in amygdala LTP (69). Currently, the consensus is that postsynaptic LTP induced by weak stimulation protocols is dependent on NMDA receptors, while stronger induction protocols, such as sustained pre- and postsynaptic pairing, may also require the activation of voltage-gated Ca^{2+} channels (22,170,455) (Fig. 6A). Native NMDA receptors are formed by the heteromeric expression of the NR1 subunit, which is required for the ion channel pore, and one type or a combination of NR2 subunits, which determine the kinetics of the NMDA-mediated currents (reviewed in (350)). In particular, NMDA receptors with NR2B subunits have slow decay kinetics, promoting Ca^{2+} entry and induction of synaptic plasticity (499). That these receptor subunits are important for conditioned fear is supported by the finding that intra-amygdala infusion of ifenprodil, a NR2B receptor antagonist, disrupts the acquisition – but not the expression - of conditioned fear (411). In keeping with this, NMDA receptors present on principal amygdala neurons (259) and GABAergic interneurons (498) contain NR2B subunits, particularly at thalamo-amygdala synapses (391), and application of ifenprodil blocks LTP at thalamic input pathways to principal LA neurons *in vitro* (22). These findings do not rule out, however, a contribution of NR2A receptors to synaptic plasticity in LA neurons (320). Inspired by these findings, many pharmacological and genetic studies have targeted molecular processes involved in cellular and behavioral plasticity in the amygdala (reviewed by (412)) and shed light on the mechanisms underlying long-term plasticity in the amygdala. These mechanisms will be reviewed below.

B. Molecular cascades of memory stabilization

As outlined above, induction of synaptic plasticity in the LA involves activation of NMDA receptors, with a critical role played by NR2B receptor subtypes, and voltage-gated Ca^{2+} channels, both of which mediate an influx of Ca^{2+} ions into LA neurons. An additional source of Ca^{2+} is the release from intracellular stores triggered by second messenger systems secondary to stimulation of membrane bound G protein-coupled receptors. Of particular interest here are metabotropic glutamate receptors (mGluRs), of which the group I receptor subtype mGluR5 plays a key role in the modulation of synaptic plasticity.

Activation of group I mGluRs may alter the potential for plasticity, a phenomenon referred to as *metaplasticity* (1). Receptors of the mGluR5 subtype are localized to dendritic shafts and spines in LA neurons, are postsynaptic to thalamic inputs (408), and are blocked through specific antagonists, such as 2-methy-6-(phenyle-ethynyl)-pyridine (MPEP). MPEP impairs the induction of L-LTP at thalamo-LA synapses and the acquisition, but not expression or consolidation, of conditioned fear (119,246,408). In keeping with the concept of metaplasticity, infusion into the BLA of a group I mGluR agonist, (R.S.)-3,5-dihydroxyphenylglycine (DHPG), was found to enhance the acquisition of conditioned freezing normally supported by a weak footshock (432). Furthermore, activation of group II mGluRs evokes long-term depression (LTD) of synaptic transmission in the amygdala (153,255). mGluRs are coupled to Ca^{2+}-cAMP pathways, located postsynaptically at thalamic inputs to principal LA neurons (153), or presynaptically at LA-BLA connections (255) (Fig. 6B). Their significance for conditioned fear remains unclear to date.

The overall rise in intracellular Ca^{2+} concentration triggers a plethora of signalling steps. There are three major, mutually interconnected signalling routes, which involve Ca^{2+}/calmodulin-dependent protein kinases II and IV (CaMKII, IV), the protein kinase (PK) family of enzymes, and tyrosine kinase (TK) pathways. These signalling cascades eventually can reach the nucleus to induce macromolecular synthesis or control translational processes. Consequently, they can act on cytoskeletal and adhesion molecules to re-organize and stabilize synaptic structures, or target membrane transport systems. These mechanisms may act separately or in concert to consolidate transient changes in synaptic efficacy. They provide the intracellular framework, upon which neuromodulatory systems, such as monoamines and stress hormones, act to regulate memory formation (reviewed in (299,410)). An overview of these molecular mechanisms is provided in figure 5.

1. Initial protein kinase pathways—One important target of Ca^{2+} is CaMKII. The α isoform of CaMKII is considered a key mediator of synaptic plasticity and associative learning in a variety of brain regions and species (520). Critical to this function is CaMKII's ability to shift to a constitutively active form, even after Ca^{2+} has declined to baseline levels, following autophosphorylation of a specific threonine residue (Thr^{286}). Interaction with NMDA receptors, particularly the NR2B subunit, can lock the molecule in this active form (23). Mouse mutants with inducible CaMKII deficiency restricted to the forebrain are impaired at acquiring cued and contextual fear (516). In LA, α CaMKII is postsynaptic to auditory thalamic inputs, and co-localizes with NR2B subunits (409). Fifteen minutes after fear conditioning, CaMKII shifts to the autophosphorylated (active) form, and a CaMKII inhibitor, KN-62, impairs both thalamic-LA LTP *in vitro* and the acquisition, but not the expression, of auditory cued and contextual fear conditioning (409).

Another route of Ca^{2+}-dependent signalling for stabilization of synaptic plasticity involves the protein kinase family of enzymes. An early study found that infusion into the BLA of H7, a potent albeit rather unspecific blocker of cAMP-dependent protein kinase A (PKA) and protein kinase C (PKC) activity, interfered with long-term but not short-term conditioned fear memory responses (140). These findings were supported by the use of a more specific PKA inhibitor (Rp-cAMPS), which attenuated long-term conditioned fear if administered shortly after fear training into LA (452). Furthermore, a mouse mutant with a deficiency for the β isoform of PKC displayed normal brain anatomy and hippocampal-based electrophysiological responses, but a deficit in cued and contextual fear conditioning (521).

2. Towards protein trafficking—Of eminent importance for synaptic plasticity is the brain-specific, atypical isoform of PKC, termed protein kinase Mzeta (PKMζ; for recent review see (437)). So far, PKMζ is the only molecule identified that is both necessary and

sufficient for maintaining LTP. PKMζ consists of the independent catalytic subunit of PKC and is autonomously active to sustain LTP maintenance. LTP induction triggers the synthesis of new PKMζ and the transport of new PKMζ to dendrites, where it increases the number of the AMPA subtype (AMPA-Rs) of glutamate receptors through GluR2 subunit-mediated trafficking to the synapses (for recent review see (106,199)).

Two lines of evidence support the notion that PKMζ and AMPA-R trafficking are also critical for synaptic plasticity in the amygdala and conditioned fear. First, Serrano and colleagues (462) examined the effects of zeta inhibitory peptide (ZIP), a specific blocker of PKMζ activity. PKMζ inhibition in the BLA, but not in the hippocampus, impaired retention of conditioned associations for both contextual and auditory fear, as well as instrumentally conditioned inhibitory avoidance. Postshock freezing was not affected, indicating that fear expression mediated by the BLA remained intact. Second, Rumpel and colleagues (435) showed that AMPA-R trafficking in LA is essential for cued conditioned fear. They constructed three amplicon vectors to either monitor or perturb AMPA-R trafficking. The first encoded GluR1 fused with green fluorescent protein (GFP) to drive expression of homomeric AMPA-Rs that display electrophysiological properties different from those of endogenous AMPA-Rs, and could be used to tag modified synapses with incorporated GluR1 ("plasticity tag vector"). The second vector encoded the carboxyl cytoplasmic tail of GluR1 fused with GFP that functions as a dominant-negative construct to prevent synaptic incorporation of endogenous GluR1, and which was thus used to block synaptic plasticity ("plasticity block vector"). The third vector drove expression of only GFP and was used as a control ("infection control vector"). After transfection through localized injection into the amygdala, animals were fear-conditioned, and plasticity was examined at the behavioral and synaptic levels *in vivo* and *in vitro*, respectively. It was observed that auditory fear conditioning drives GluR1 receptors into synapses onto LA neurons, that this trafficking is specific to thalamic inputs, and that blockade of AMPA receptor incorporation blocks both LTP at thalamo-LA inputs *in vitro* and retention of conditioned fear *in vivo* (tested 3 or 24 hours after training). Only about a third of the LA neurons were found to undergo this type of plasticity, thereby supporting the notion that fear memory formation requires coordinated changes in synaptic strength in distributed networks, and perturbing a few plastic units may corrupt integrated function. Of further interest is that the conditioning-induced increase in surface expression of GluR1 depended on the activation of NMDA receptors and protein kinases, and required the synthesis of new proteins (534). Indeed, mice with a genetic deficiency in GluR1 displayed an impairment of both conditioned fear and LTP at thalamo-LA synapses, whereas GluR3-/- mice showed no alteration in conditioned fear, thereby contributing to the view that GluR1-dependent synaptic plasticity predominates in conditioned fear (171). The regulated transport of AMPA-Rs towards exocytosis and endocytosis at synaptic sites seems to be important for balanced plasticity in the amygdala. Blockade of vesicle-mediated exocytosis and endocytosis of AMPA-Rs indeed prevents LTP and LTD at thalamic inputs (535). Conversely, AMPA-R endocytosis is critical for fear extinction (208)(see section V.D).

Recent evidence suggests that regulated trafficking in the amygdala is not restricted to AMPA-Rs. NR2B subunits can be tyrosine-phosphorylated, and mice with a knock-in mutation of the major phosphorylation site (Tyr-1472) show impaired fear learning and reduced amygdala LTP, accompanied by improper localization of the NR2B subunits at amygdala synapses (334). NR2B subunits are downregulated after fear conditioning (539), suggesting that the plastic synaptic events supporting fear learning involve the regulation of NMDA receptor proteins through phosphorylation and/or transport (for review on NMDA-R trafficking see (232)). Moreover, the trafficking of functional molecules at synaptic sites may not be limited to ligand-gated ion channels. One example are small-conductance Ca^{2+}-activated potassium channels (SK channels), which limit postsynaptic responses and

plasticity of principal LA neurons (108). Stimulation of β–drenoceptors, known to facilitate fear memory formation (299), results in a PKA-mediated reduction in SK channel activity and their removal from the postsynaptic membrane, thereby enhancing synaptic transmission and facilitating induction of synaptic plasticity (108,109).

In conclusion, the available evidence suggests that the acquisition of Pavlovian fear involves enduring changes in glutamatergic transmission at thalamic synapses onto LA neurons. These changes are likely maintained by the insertion of AMPA-Rs and other types of ion channels into thalamo-LA synapses. Consistent with this idea, A-kinase anchoring proteins (AKAPs), a family of scaffolding proteins that bind the regulatory subunits of PKA and target PKA to GluR1, are essential for the consolidation of Pavlovian auditory fear memories (316).

3. Towards transcriptional control—The protein kinase signals, including CaMKII and IV, PKA and PKC, are known to converge on the mitogen-activated protein kinase (MAPK) signal transduction pathway, one of the most widespread mechanisms of cell regulation (reviewed in (219)). Six distinct groups of MAPKs have been characterized in mammals, of which the extracellular regulated kinases (ERK) are the best understood. Typical of MAPK is a central three-tiered signalling molecule, consisting of a set of three sequentially acting kinases: an MAPK, an MAPK kinase (MAPKK or MEK) and an MAPKK kinase (MAP3K or MEKK). The ERK/MAPK pathway can be activated by a large number of upstream extracellular and intracellular stimuli, including growth factors, cytokine, and ligands of G-protein-coupled receptors. Their signals are usually transduced to small GTPases, such as RAS, which transmit the signal by recruiting the MAP3K tier-like RAF kinases. Activated RAF binds to and phosphorylates down-stream kinases MEK, which in turn phosphorylate ERK. Of particular importance is that scaffolding proteins of MAPK pathways can dictate the specificity of activation as well as entry in the nucleus. MAPKs translocated into the nucleus phosphorylate transcription factors, such as cAMP response element binding protein (CREB), thereby regulating gene expression and new macromolecular synthesis (mRNA and protein). Examples include the immediate early genes c-jun and c-fos. In fact, tagging of c-fos active neurons allowed the identification of a neuronal subpopulation in BLA that are activated during fear conditioning and are reactivated after during memory retrieval (403).

What evidence indicates that these pathways are involved in long-term synaptic plasticity in the amygdala and conditioned fear? Early studies indicated that pharmacological interference with PKA, MAPK activity, and protein synthesis interferes with the late phase of LTP (L-LTP) at afferent inputs to LA *in vitro* and with the consolidation of Pavlovian fear *in vivo*. In contrast, early LTP and short-term fear memory were spared (165,167,449,452). Furthermore, ERK/MAPK is transiently activated/phosphorylated in LA following auditory fear conditioning or high-frequency stimulation of the auditory thalamus (449,453). Infusions of a MEK (MAPK kinase) inhibitor or of an mRNA synthesis inhibitor into the auditory thalamus before or after fear training yielded impaired long-term memory of conditioned fear and thalamo-LA (13), in line with previous suggestions that thalamic neurons contribute to memory formation by promoting protein-synthesis-dependent plasticity in the LA (272). Of the two ERK isoforms (ERK1, 2), ERK2 seems to contribute critically to conditioned fear, as ERK1 null-mutant mice did not display deficits in the acquisition or retention of either contextual or cued fear (459).

Upstream of ERK/MAPK is the RAS signalling pathway, which has been implicated in fear memory and synaptic plasticity in the amygdala. Mice lacking RAS-GRF, a neuronal-specific factor inducing RAS signalling in response to Ca^{2+} influx, show impaired consolidation of conditioned fear and BLA LTP, whereas spatial memory tasks and hippocampal LTP were unaffected (48). Mice with a null mutation of RIN1, a RAS effector

that competitively inhibits the RAF-MEK-ERK pathway and is preferentially expressed in dendrites, show an enhancement of amygdala LTP and amygdala-dependent aversive memories like fear conditioning (92). Of particular interest here is STEP (for striatal-enriched protein-tyrosine-phosphatase), a molecule that is colocalized with ERK in LA neurons and can prevent their nuclear translocation (366). Fear conditioning induced activation of ERK1/2 in the amygdala as well as a *de novo* translation of STEP, whereas infusion of a substrate-trapping STEP protein prevented translocation to the nucleus, disrupted LTP in LA, and impaired fear memory consolidation. By contrast, blockade of phosphatidylinositol 3-kinase (PI3-kinase) activity, preventing MAPK activation, CREB phosphorylation and LA LTP, leads to a decrease in conditioned fear (252). Also SRC kinases, nonreceptor kinases downstream to a rise in intracellular Ca^{2+}, seem to be required for the acquisition of conditioned fear (34), particularly upon stimulation of the NR2B subunit (212).

Together, these data support the hypothesis that ERK1/2 signalling and translocation to the nucleus play an important role in the maintenance of synaptic plasticity and consolidation of conditioned fear in the amygdala. Downstream of ERK/MAPK, CREB has been implicated in fear conditioning based upon findings in mice with null mutation in different CREB isoforms or with overexpression of the dominant negative CREB[133A] (44,135,201,397,522). In line with this, an increase in phosphorylated CREB and transcription from CRE motifs occur after fear conditioning (174,483). Expression of a constitutively active form of CREB (VP16-CREB) lowered the induction threshold for late LTP in hippocampal CA1 neurons and increased the intrinsic excitability of CA1 and BA neurons (511). These effects were accompanied by resistance of both cued and contextual fear conditioning to the protein biosynthesis blocker anisomycin, suggesting that *de novo* protein synthesis can be bypassed by constitutive CREB function (511). Using virus-mediated gene transfer, the critical CREB activity was located to the BLA region and correlated with the strength of the memory trace (187,513). In particular, LA neurons with increased levels of CREB were preferentially activated by auditory fear memory during training or testing (148). Specific ablation of CREB-overexpressing LA neurons by diphtheria toxin-mediated apoptosis after fear learning abolished the fear memory. These results indicate that CREB function in a subset of LA neurons is critical for the formation and maintenance of the fear memory trace (149). In keeping with this, CREB activation is also linked to histone acetylation through the CREB-binding protein CBP (214), which itself is required for the acquisition of conditioned fear (342). The importance of this mechanism is indicated by the finding that chromatin modifications through increased histone-tail acetylation induce dendritic sprouting, increase the number of synapses, and reinstate hippocampal-dependent learning and access to long-term memories upon exposure to an enriched environment (123). Other rapidly activated transcription factors, like nuclear factor-κB (532,533), or the potassium channel interacting protein 3 (KChIP3; also known as calsenilin and as the transcription factor DREAM; (5)) also seem to be involved in fear conditioning. However, CREB is the most intensively studied one, found to be bound to at least 6000 genomic loci and to regulate expression of about 1600 transcripts (for review see (173,258)).

Genes that are transcriptionally regulated upon fear conditioning include immediate early genes, like c-fos (418,456). As with CREB, a relation has been proposed between expression level and memory strength (393,483), including an influence of novelty, context, and stress. Other important targets of CREB transcriptional activity are nerve growth factors (NGF) and brain-derived neurotrophic factors (BDNF). A convergent line of evidence indicates that BDNF plays a role in amygdala-dependent learning and memory (reviewed by (36,346,400)). BDNF mRNA is elevated during the consolidation of conditioned fear memory (401), and BDNF blockade in the amygdala through expression of a dominant negative isoform or antagonism of the tyrosine kinase receptor B (TrkB) interferes with

long-term fear memory (399). Upon fear conditioning, the level of TrkB receptor immunostaining declines in the amygdala, whereas the level of phosphorylated TrK receptors increases, suggesting TrK activation and internalization by BDNF binding (400). The two phosphorylation docking sites of TrkB receptors are specifically linked to the acquisition of cued fear and CaMKII signalling, and to memory consolidation and Akt signalling, respectively (326). Furthermore, in concert with developmental processing of BDNF, cleavage of pro-BDNF by tissue plasminogen activator (tPA) seems to be essential for hippocampal LTP and the formation of contextual fear memory, as tPA null mutation interferes with both processes (10,349). Particularly interesting are BDNF/TrkB-dependent mechanisms of neuronal plasticitiy that may bypass NMDA-dependent processes (400). One route is via PI3-kinase, a critical intracellular mediator of synaptic plasticity during fear conditioning (253). Another route involves the RAS-RAF-MEK-ERK pathway (reviewed in (400)), thereby suggesting that these intracellular signalling mechanisms likely act in parallel. A recent study in knock-out mice has provided evidence that the immediate early gene vesl-1S (VASP/Ena-related gene upregulated during seizure and LTP, also termed homer-1a) is required for contextual fear memory consolidation and re-consolidation (175). Vesl-1S is the alternatively spliced, short isoform of the vesl-1 gene, the long isoform of which encodes a scaffolding protein modulating intracellular Ca^{2+} dynamics via metabotropic glutamate receptors, IP3 receptors, and ryanodine receptors. In any case, both fear memory consolidation and re-consolidation were impaired upon vesl-1S knock-out, thereby supporting the view that symmetrical signalling cascades are involved in these two stages of memory stabilization (see (100,104); reviewed in (331)).

4. Towards post-transcriptional and translational control—Although the transcriptional control of gene expression has received much attention, post-transcriptional and translational mechanisms also participate in memory formation (for recent review see (85)). One of these mechanisms involves the regulation of mRNA stability. The Hu family of RNA-binding proteins is perhaps the most important group of mRNA-stabilizers described so far (196). Recent studies indicate that they are also involved in synaptic plasticity (40,385), including acquisition and retention of both cued and contextual fear, although their exact role remains unclear (41). One hypothesis is that consolidation involves proteins that are translated from existing mRNA stores, as for instance at synaptic sites in dendrites. One particular example for conditioned fear involves mTOR (155,355), the mammalian target of rapamycin kinase, which regulates protein synthesis in neurons at the translational level through intracellular phosphorylation. One of its targets, p70s6 kinase, is upregulated after fear training, and prevention of this upregulation by post-training injection of rapamycin into the amygdala, blocked the fear memory formation (155). Interestingly, when rapamycin was infused in the amygdala after fear memory recall, subsequent retention was disrupted, suggesting that local translational control is required for the formation as well as the stability of long-term fear memories. A study in chicks (309) lends support to the hypothesis that re-consolidation is also dependent on dendritically synthesized proteins.

While prevailing models of memory identify transcriptional regulation or post-transcriptional RNA editing as necessary for enduring information storage, consolidation of long-term memory may also occur in the virtual absence of new macromolecular synthesis. The above-mentioned trafficking of AMPA receptors to and from synapses, the processing of BDNF, and the constitutive activity of enzymes at various steps in the intracellular signalling pathways exemplify such a scenario. In fact, an alternative model of long lasting information storage has been proposed (424,425). According to this model, pre-existing synaptic proteins are modified at a post-translational level upon learning experience, supporting memory formation. One important feature of this model is endogenous, reverberant activity at the respective synaptic interconnections, providing a positive feedback rehearsal mechanism by which proteins are increasingly modified and thereby

functionally up-dated for enduring information storage. In this model, protein synthesis is thus a permissive step for the subtle modification of synaptic proteins to occur. The spatiotemporal segregation of the various forms of memory may then be explained through correlated activity in the involved neuronal assemblies. While it is currently unclear how the various transcriptional and post-translational entities interact, it is interesting to note that both types of models require coordinated activity in synaptic networks – for coincidence detection in the Hebbian sense (151) and for rehearsal processes in maintaining memory longevity. The significance of correlated activity in circuits of the amygdala and beyond is discussed in section III of the present review.

5. Towards structural plasticity—How are synaptic changes structurally stabilized? Most excitatory synapses in the mammalian brain end on dendritic spines, which provide an isolated functional compartment for coupling synaptic activity with postsynaptic intracellular signalling pathways. It was proposed that enduring alterations in synaptic transmission depend on changes in the number and/or morphology of spines (as reviewed in (536)), and that spine architecture is an important parameter for the specificity of Hebbian plasticity at thalamic and cortical inputs to LA neurons (170). Spine architecture and spinogenesis, in turn, depend on cytoskeletal filaments, in particular on the dynamics and polymerization of one of their major constituents, actin (103,398). It was hypothesized that re-organization of actin contributes to the stabilization of spines, thereby providing a mechanism of structural plasticity for memory stabilization. In keeping with this, LTP induces a lasting increase in polymerized actin in dendritic spines (132), and a reduction in actin-based spine motility underlies spine stabilization (282). In fact, fear conditioning alters the expression of cytoskeletal proteins including actin and *a*-actinin (406,488) Furthermore, actin dynamics regulate NMDA receptor function, AMPA receptor trafficking, and spinogenesis after contextual fear conditioning in the hippocampus (122). Anchored to the actin cytoskeleton are cadherins, including neuronal (N)-cadherin, which are associated with docking proteins to intracellular pathways and are regulated by extracellular domains mediating cell-cell adhesion (for review see (188,402)). Much of our current knowledge on N-cadherin involvement in fear conditioning is derived from studies of contextual fear and related hippocampal mechanisms. An N-cadherin antagonistic peptide containing the His-Ala-Val motif (HAV-N) disrupted N-cadherin dimerization in the hippocampus and impaired the formation of long-term contextual fear memory while sparing short-term memory, retrieval, and extinction (454). At the molecular level, HAV-N impaired learning-induced phosphorylation of the cytoskeletally associated fraction of ERK-1/2 in the hippocampus, prevented NMDA-induced dendritic ERK-1/2 phosphorylation *in vitro*, and caused a relocation of IQGAP1, a scaffold protein linking cadherin-mediated cell adhesion to the cytoskeleton. The N-cadherins may thus enable the translation of cell adhesion signals into long-term cellular responses required for contextual fear in the hippocampus through signalling pathways involving cytoskeletal IQGAP1/ERK signalling.

Actin rearrangement, in turn, is under the control of RhoGTPases, intracellular molecules that can be activated via G protein-coupled receptors, Ca^{2+} or kinase pathways, and that switch between an active (GTP-bound) and inactive (GDP-bound) form. Indeed, fear conditioning causes the formation of a molecular complex that contains the tyrosine-phosphorylated RhoGTPase-activating protein (RhoGAP), which is located in the dendrites of LA neurons (225). RhoGTPases regulate activity of the Rho-associated kinases (ROCK), whose inhibition in LA impairs long- but not short-term conditioned fear (225). ROCK, in turn, is a key molecule for regulation of the cytoskeleton (reviewed in (262)). A number of other cytoskeletal-regulatory proteins also contribute to synaptic plasticity and fear learning in the amygdala. They include myosin light chain kinase (228), stathmin, an inhibitor of microtubulin formation (470), LIMK-1, a member of a kinase family (LIMK) that induces actin polymerization through the phosphorylation and cofilin, a protein that facilitates de-

polymerization of actin (305). Another example is profilin, an actin polymerization-regulatory protein (226). For instance, fear conditioning drives profilin into LA dendritic spines with enlarged postsynaptic densities (226). In line with this, the number of dendritic spines increases in LA after fear conditioning (392).

At the level of cell-cell interactions, various cell recognition molecules seem to translate such cytoskeletal re-arrangements into altered cell-cell and cell-matrix interactions. Fear conditioning-induced expression changes were found for the mRNA of the extracellular matrix molecule tenascin and the cell adhesion molecule neuroligin (406,488). Persistent expression of neuroligin-1 is indeed required for maintenance of NMDA-R mediated synaptic transmission, enabling normal development of synaptic plasticity and long-term memory in the amygdala (203). Furthermore, interfering with the integrity of the extracellular matrix through null mutation for specific tissue inhibitor of matrix metalloproteinases (TIMPs) interfered with fear-potentiated startle responses (178). One of the most intensively studied cell recognition molecule is the neural cell adhesion molecule (NCAM), which mediates neuromodulatory and hormonal effects on conditioned and unconditioned fear (442,489). NCAM function is regulated by polysialic acid (PSA). Injection of PSA-NCAM and PSA, but not NCAM, into the hippocampus impaired the formation and consolidation of hippocampus-dependent contextual fear memory (461). The expression of PSA-NCAM increased 24 h after fear conditioning in the amygdala, but only in animals subjected to the highest shock intensity, and intra-amygdala cleavage of PSA-NCAM affected fear extinction rather than acquisition or consolidation of cued fear memory (276). Studies in null mutant mice suggest that NCAM contributes to the stress modulation of long-term context fear memory (4). In any case, many adhesion molecules can initiate signalling pathways that couple the dynamics of extracellular and intracellular events, particularly those that regulate cytoskeletal processes and spine architecture. Together, these processes may then form an interlinked molecular network that regulate structural re-arrangements and morphology between pre- and postsynaptic sites, concomitant with the stabilization of the fear memory trace.

C. Emerging views on distributed synaptic plasticity

In the previous sections, we described converging lines of evidence indicating that Pavlovian fear conditioning depends on mechanisms of enduring synaptic plasticity in the amygdala. However, most studies focused on LTP of thalamic inputs to LA neurons. Although these studies captured synaptic features critical for fear conditioning, it is clear that the underlying molecular changes occur at multiple sites rather than at a single location, a principle referred to as "*distributed plasticity*". For instance, studies mapping changes in protein expression, metabolism or electrophysiological activity at multiple sites indicate that learning initiates coordinated patterns of activity in distributed brain areas, reflecting fear memory stabilization (see section IV.B). Furthermore, the induction of synaptic plasticity requires correlated activity to occur in a relatively narrow time window, for instance between pre- and postsynaptic sites or between two afferent input pathways. Fear conditioning, however, does not necessarily require such precise timing, as the US can be applied at the end of the CS with no temporal overlap. This suggests that longer time windows are created for induction of conditioned fear behaviour. One possible solution resides in the ability of BLA neurons to generate oscillatory patterns of activity. These oscillations provide recurring time windows during which groups of BLA neurons are synchronized with afferent inputs signals, thereby facilitating synaptic plasticity with no major increases in activity per se in spatially distributed networks (see section III). These time windows may then facilitate synaptic plasticity in distributed networks involving local neuronal circuits within the amygdala, or neuromodulatory input systems (reviewed in (299)). Outstanding questions therefore relate to the fine-scale organization of these synaptic

networks, and the mechanisms of synaptic plasticity within these circuits. Although the detailed mechanisms remain to be identified, some principles have emerged recently, which we discuss in the following section. An overview of the forms of long-term synaptic plasticity detected at the various inputs to types of neurons in the amygdala is provided in figure 6.

1. Long-term pre- and postsynaptic plasticity in principal amygdala neurons— In addition to thalamic inputs, principal LA neurons receive inputs from the cerebral cortex. Postsynaptic NMDA-Rs are expressed at both, thalamic and cortical inputs (116,117,265,498,524). However, the properties of synaptic plasticity differ considerably at the two inputs, particularly the temporal precision needed for induction of synaptic plasticity. Recent studies have emphasized that the polarity of synaptic plasticity depends on the precise order of pre- and postsynaptic activity, in the millisecond range, a phenomenon referred to as *spike-timing-dependent synaptic plasticity* (reviewed in (63)). In LA, the standard protocol used to induce spike-timing dependent LTP (presynaptic firing closely followed by postsynaptic depolarization) induces long-term plasticity at thalamic but not cortical afferents *in vitro* (170). This is in line with previous *in vivo* findings of a greater LTP magnitude at thalamic compared to cortical inputs (101,473). Interestingly, the two inputs contact neighbouring but functionally and morphologically distinct types of dendritic spines (170). Spines receiving thalamic inputs are bigger, display larger Ca^{2+} transients, and express R-type Ca^{2+} channels, thereby providing reliable Ca^{2+} influx for postsynaptic LTP induction and expression (170).

In addition to LTP dependent on postsynaptic NMDA receptors, some forms of LTP depend on presynaptic NMDA receptors in the amygdala. For instance, Humeau and colleagues (172) reported an associative form of LTP at cortical inputs to LA neurons that is induced by simultaneous Poisson-train stimulation of thalamic and cortical afferents (Fig. 6A). This LTP is of an associative nature, in that its induction requires simultaneous activation of converging cortical and thalamic inputs to principal LA neurons, whereas stimulation of either input system alone evokes no plasticity (172). Consistent with earlier immuncytochemical observations (115), presynaptic NMDA-Rs, mediate this form of LTP through a persistent increase in transmitter release probability. The intracellular mechanisms involve the cAMP/PKA signalling pathway and a change in the Ca^{2+} coupling of vesicle release mediated via the active-zone protein and PKA target RIM1α (126). In addition to LA, a presynaptically induced and expressed form of homosynaptic LTP has been discovered at thalamic afferents to CEm neurons (439). Induction was dependent on presynaptic NMDA-Rs since hyperpolarization, chelation of Ca^{2+} or blockade of NMDA-Rs in the postsynaptic neurons, had no effect.

Consistent with presynaptic sites of plasticity, expression of the synaptic vesicle protein, synaptophysin, increases in the BLA following auditory fear conditioning (341). The gaseous molecule nitric oxide (NO), thought to serve as a retrograde messenger to presynaptic sites of LTP expression, has been shown to contribute to both LTP and consolidation of auditory fear conditioning (450), in part by activating the ERK/MAPK signalling cascade via the cyclicGMP-protein kinase G pathway (344,365), although this influence has been localized to thalamic rather than cortical inputs.

Overall, the above indicates that thalamic and cortical inputs to LA neurons express different types of plasticity associated with contrasting forms of coincidence detection. The homosynaptic form of thalamo-LA LTP requires pre-synaptic activity coinciding with strong postsynaptic activation and associated Ca^{2+} influx, thereby apt to detect coincidence at individual inputs in an input-specific manner. By comparison, cortico-LA LTP does not rely on postsynaptic activity, but might be induced by subthreshold activity generated by

thalamic and cortical afferents. Through this presynaptic mechanism of coincidence detection, relatively weak cortical inputs may be primed for subsequent induction of homosynaptic Hebbian plasticity at neighbouring synapses, which require stronger afferent activity and/or the induction of postsynaptic action potentials (172). Two observations support this conclusion. First, postsynaptic hyperpolarization reduces but does not abolish LTP in fear-conditioning (421), suggesting that LTP induction independent of postsynaptic activity also occurs *in vivo*. Second, depletion of RAP1 (a small GTPase involved in AMPA-R trafficking and LTP) in a mouse line with CaMKII-α-Cre-mediated knock-out of *rap1a* and *rap1b* genes, results in impaired synaptic plasticity and increased basal transmission of glutamate via presynaptic changes (348). Behaviorally, these mice display impaired fear learning, which could be rescued by training with a more aversive unconditioned stimulus. The gene deletion eliminates 90% of the RAP1 protein in the cortex, suggesting that the deficit in fear learning reflected an impaired interaction between the cortical and thalamic input pathways involving presynaptic priming upon weak training. The importance of network timing has been extracted more directly from patterns of polysynaptic responses within the LAd, where latencies of recurrent activity triggered by thalamic afferent stimulation were found to overlap with cortical afferent latencies (182). The spatio-temporal architecture of the intra-amygdala network may thus be tuned to facilitate coincidence of the two sensory afferent input systems, as for instance, during synaptic plasticity and fear learning (182).

2. GABAergic plasticity—There is ample evidence that GABAergic interneurons regulate signal flow through the amygdala (87,229), thereby modulating synaptic plasticity in principal cells and influencing fear learning and extinction (reviewed in (105)). The induction of LTP in principal LA neurons can thus be gated by influences that suppress inhibition from local interneurons. Examples include the dopaminergic (35) and noradrenergic (504) transmitter system. Another mechanism of GABAergic influence is via presynaptic $GABA_B$ receptors, stimulation of which dampens subsequent transmitter release and thereby mediates short-term plasticity of glutamatergic and GABAergic transmission in LA (496). While presynaptic $GABA_B$ receptors exist on glutamatergic afferents to interneurons and principal neurons in LA, they selectively inhibit glutamatergic transmission and suppress LTP in principal neurons (347). This effect is most likely due to a differential local GABA spill over from GABAergic synapses (347). When the extracellular GABA level is decreased in the BLA after fear conditioning (487), the $GABA_B$ mediated inhibition of glutamate release may be relieved. Consistent with such a balancing function of presynaptic $GABA_B$ on LTP in the amygdala, a genetic deficiency of $GABA_{B(1a)}$ receptors resulted in a shift from the associative, NMDA receptor-dependent form of LTP towards a non-associative, NMDA receptor-independent form of presynaptic LTP at cortico-amygdala afferents (465). The balancing function of the $GABA_B$ receptors is dependent on GABAergic activity, and lack of $GABA_B$ receptors is associated with generalization of conditioned fear (465). Fear generalization is also observed upon a deficiency of GAD65, the activity-dependent isoform of the GABA synthetizing enzyme (25), indicating the requirement of balanced GABAergic activity for cue specific fear responsiveness.

In addition, glutamatergic inputs to local GABAergic interneurons exhibit activity-dependent synaptic plasticity, although the evidence is sparse compared with that in principal neurons. An overview is provided in figure 6C. LA interneurons receive convergent cortical and thalamic afferents (496), and input-specific LTP can be induced at either input (264, 497). The Ca^{2+} influx required for induction of input specific LTP is mediated via Ca^{2+} permeable subtypes of AMPA receptors (264, 497), while NMDA-Rs seem to be involved in a heterosynaptic form of LTP in LA interneurons (20). Fear conditioning results in a decrease in GABAergic plasticity in the LA, reflected by a decrease in the magnitude of GABAergic LTP in principal neurons (497). Furthermore, the

extracellular GABA concentration and GAD65 mRNA level are decreased after fear conditioning (25, 487). Changes in GAD expression and decrease in GABAergic plasticity follow a similar time course (497), thereby suggesting the following scenario. Under baseline conditions, the GABAergic influence is high, resulting in dampening of activity and synaptic plasticity in principal neurons, through presynaptic $GABA_B$ receptors at afferent inputs and postsynaptic $GABA_A$ as well as $GABA_B$ receptors. Upon fear conditioning, GAD65 expression and the extracellular GABA concentration decrease, thereby relieving glutamatergic inputs from presynaptic $GABA_B$ blockade and facilitating LTP, both the postsynaptic thalamic and the heterosynaptic cortical types. Behaviorally, conditioned fear responses occur with high specificity for the conditioned stimulus. During impaired or blocked function of GAD65 or $GABA_B$ receptors (as, for instance, in the respective knockout mutants), the decreased GABA level or dysfunction of presynaptic $GABA_B$ receptors result in a shift from associative to non-associative (NMDA receptor-independent) forms of LTP at cortical inputs, while postsynaptic LTP is preserved at thalamic inputs. Conditioned fear responses occur with reduced stimulus discrimination, i.e. in a generalized manner. Through these mechanisms, GABAergic regulation of synaptic plasticity may help control both the induction of conditioned fear and the CS-specificity of the conditioned responses.

V. Synaptic Plasticity Related to Fear Extinction

Compared to the acquisition and consolidation of conditioned fear, much less is known about the mechanisms of fear extinction. However, extinction is the focus of increasing attention because of its potential clinical significance. Indeed, an approach commonly used by clinicians to treat anxiety disorders (exposure therapy) is similar to that used to extinguish conditioned fear responses in the laboratory. In both cases, the subject is repeatedly presented with the feared object or situation (*conditioned stimulus, CS*) in the absence of danger (or *unconditioned stimulus, US*). Thus, it is widely believed that understanding the networks and mechanisms of extinction might ultimately lead to improvements in the treatment of anxiety disorders. Consistent with this, it was proposed that some human anxiety disorders reflect an extinction deficit (84). In fact, this appears to be the case in post-traumatic stress disorder (306). Therefore, this section will review current knowledge and concepts regarding the behavioral properties of extinction as well as the networks and cellular mechanisms participating in extinction.

A. Behavioral properties of extinction

In the Pavlovian fear conditioning paradigm, extinction is studied by repeatedly presenting the CS in the absence of the US, resulting in the decline of CS-evoked fear responses. When considering extinction, it is important to distinguish between the reduction of conditioned fear that takes place within the extinction training session (*within-session extinction*) from that observed one day or more after extinction training (*between-session extinction, extinction retention/retrieval/recall*). Indeed, as we shall see below, much evidence suggests that the decrease in behavioral responding seen within an extinction training session depends on mechanisms that partly differ from those underlying the between-session effect.

Whereas conditioned fear responses can persist for the entire adult lifetime of rats (133,284), the expression of extinction decays with time, a process termed "*spontaneous recovery*" (407). Similarly, whereas cued conditioned fear responses are expressed even if the training and testing contexts are different, extinction is expressed in a relatively context-specific manner. Indeed, if testing occurs in a different context than the one where extinction training took place, extinction is not expressed as strongly, a phenomenon known as "*renewal*" (45,46). Another defining property of extinction is "*reinstatement*" where presentation of unsignaled USs after extinction training causes a resurgence of conditioned fear responses, provided the USs were presented in the extinction training context (405). Finally, it should

be mentioned that the impact of extinction training is relatively specific to the extinguished CS. Indeed, extinction training does not abolish the conditioned fear responses associated to a different CS (157) or with the subsequent acquisition of conditioned responses to a different CS (for instance see (248)). Moreover, extinguishing a generalization stimulus has little effect on fear responding to the CS (for instance, see (509)).

The behavioral properties of extinction suggest that it does not result from the erasure or reversal of the initial fear memory. This statement is based on the fact that conditioned fear responses can re-appear with the passage of time (spontaneous recovery), if the CS is presented in a different context than where extinction training took place (renewal), or if unsignalled USs are presented in the extinction training context prior to testing extinction recall (reinstatement). Thus, the behavioral properties of extinction indicate that this form of safety learning depends on the development of a new inhibitory memory that competes with the initial fear memory for control of behavior. However, as we shall see below, there is also evidence that weakening of the initial CS-US association is involved.

B. Cerebral networks involved in extinction

Three interconnected brain regions have been implicated in extinction: the amygdala, mPFC, and hippocampal formation. Increasing evidence suggests that the amygdala is the critical site of plasticity where the extinction memory is stored. In contrast, the infralimbic component of the mPFC is critical for the consolidation and recall of extinction (387). Finally, the hippocampal formation mediates the context specificity of extinction (180). To understand how the amygdala, mPFC, and hippocampus interact in extinction, we must first consider the connections existing between these structures.

1. Connections between the amygdala and mPFC—Two components of the mPFC are most densely interconnected with the amygdala: the infralimbic and prelimbic areas (286,436,463). In the BLA, infralimbic and prelimbic projections show minimal overlap with infralimbic axons focusing on the ventral part of LA and the BM nucleus whereas prelimbic axons mainly target BL (Fig. 7A; (286,297,508)). Projections of the mPFC to the BLA are thought to be glutamatergic with mPFC axon terminals forming only asymmetric synapses, usually with the dendritic spines of principal cells, and much less frequently with the dendrites of presumed GABAergic neurons (50,475). In addition, the infralimbic cortex sends a very dense projection to the medial ITC cell clusters and significant one to CEl (Fig. 7A1; (66,297)). Although the prelimibc cortex also projects to ITC cells, this projection is significantly weaker than the one originating in the infralimbic region (Fig. 7A2; (286,297,508)).

In the context of extinction, the infralimbic projection to ITCm cells is especially significant because electrical infralimbic stimuli that coincide with CS onset reduce conditioned fear responses and accelerate the acquisition of extinction (307). Moreover, infralimbic stimuli block the excitation of CEm neurons by BL inputs (388), an effect thought to depend on the activation of ITCm cells by infralimbic stimuli. Consistent with this, disinhibition of the infralimbic cortex with local picrotoxin infusions enhances c-fos expression by ITCm cells (31).

The amygdala sends return projections to the mPFC (218). However, these projections arise exclusively in the BLA, particularly BL, posterior part of AB and, to a lesser extent, ventral part of LA. The existence of reciprocal connections between the mPFC and BLA has complicated the interpretation of physiological studies, leading to a disagreement regarding the nature of mPFC influences (excitatory vs. inhibitory) over the BLA (247,420,422). We consider this issue in some detail as its resolution will impact on how we conceive mPFC involvement in extinction.

Because the BLA and mPFC are reciprocally connected, electrical mPFC stimulation not only recruits mPFC axons ending in the BLA but also antidromically activates BLA axons ending in the mPFC (247). It is important to disentangle the consequences of these two phenomena because the antidromic effects are an unavoidable by-product of electrical stimulation that does not accompany natural mPFC activation. Because the conduction velocity of BLA axons to the mPFC is higher than that of mPFC axons to the BLA (125,247), the arrival of antidromic impulses precedes that of orthodromic ones. Importantly, because the local axon collaterals of principal BLA neurons recruit feedback interneurons (438), the inadvertent antidromic activation of BLA projections by electrical mPFC stimuli can lead to widespread feedback inhibition in the BLA. This artefactual feedback inhibition can therefore give the impression that mPFC inputs "inhibit" the BLA, as was previously proposed (420,422). However, given that mPFC axons typically form asymmetric synapses with the dendritic spines of BLA projection cells, this conclusion is probably erroneous. Consistent with this, indirect activation of the mPFC by electrical stimulation of the mediodorsal thalamic nucleus or of the contralateral mPFC elicits a robust synaptic excitation of physiologically identified BLA projection cells (247). Moreover, behavioral studies indicate that the mPFC exerts excitatory influences over the BLA. Indeed, local inactivation of the prelimbic region reversibly inhibits the expression of previously learned cued or contextual fear responses (83,235).

Overall, the data reviewed above suggests that the impact of mPFC inputs to the amygdala depends on the cortical field at the origin of the projection and the target nuclei. Infralimbic inputs excite ITCm cells that, in turn, inhibit CE neurons and thus, the expression of conditioned fear responses. In contrast, prelimbic inputs excite BLA neurons that send a glutamatergic projection to CE. As a result, prelimbic lesions interfere with the expression of conditioned fear responses (83).

2. Hippocampal projections to the amygdala and mPFC—The results of lesion and/or reversible inactivation studies indicate that the hippocampus is required for the renewal of cued conditioned fear responses after extinction training (reviewed in (180)). However, it is currently unclear how this contextual information is relayed to the amygdala. A number of possible routes exist including direct CA1, subicular, and entorhinal projections to various components of the amygdala (Fig. 7B). In addition, it is possible that one or more of these sources influences the amygdala indirectly (Fig. 7B), via the mPFC projections described above.

The results obtained to date are compatible with all these possibilities. For instance, permanent and/or reversible interference with CA1 (81,82,160) or entorhinal activity as well as fornix lesions (181) all prevent the contextual renewal of conditioned fear responses after extinction training. Therefore, it seems that multiple parallel routes convey contextual information to the amygdala and that normal contextual gating of extinction depends on intact coding in theses multiple parallel pathways. However, an alternative interpretation is that in some of these cases at least, the lack of renewal observed following localized lesions or inactivations reflects a disfacilitation of critical amygdala targets rather than the specific signalling of information about the renewal context.

Nevertheless, since the available data is compatible with both interpretations, we now overview the various possible routes through which contextual information from the hippocampus might reach the amygdala. As in section II, we will focus on projections ending in the BLA, CE, and ITC cell clusters. See Refs (286,376) for projections to other amygdala nuclei. It should be noted that most of the projections described below are reciprocated by the amygdala.

Direct hippocampal projections to the amygdala: Most direct hippocampal projections to the amygdala originate from the temporal subiculum and, to a lesser extent, the adjacent part of CA1 (62,286,345,376,506,507). There are no dentate and CA3 outputs to the amygdala. Subicular projections are dense in AB and medial part of BL but moderate in LA and light in CE. CA1 projections to the amygdala are considerably lighter than those originating in the subiculum. They mainly end in BL, with lighter projections to LA and AB (345,507).

Entorhinal projections to the amygdala: Entorhinal efferents to the amygdala mainly originate from deep (layer V-VI) neurons. Of the various entorhinal fields, the ventrolateral and dorsolateral areas send the densest projections. These entorhinal inputs target much of the BLA but they are heaviest in BL. In contrast, the ventromedial and lateral entorhinal areas contribute the weakest projections.

MPFC transfer of hippocampal outputs to the amygdala: In addition to the direct subicular, CA1, and entorhinal projections described above, contextual information can reach the amygdala via the mPFC. Indeed, CA1 and subicular pyramidal neurons located in the temporal and mid-septotemporal portions of the hippocampus send a heavy projection to the mPFC (17,161,179,434,494). By comparison, much fewer entorhinal cells project to this region. Double retrograde tracing studies indicate that most hippocampal neurons projecting to the mPFC also have an axon collateral ending in the entorhinal cortex (494). It remains controversial whether the infralimbic cortex, prelimbic cortex or both regions are the main recipients of CA1 and subicular projections (17,161,179,434,494).

C. Mechanisms of synaptic plasticity underlying extinction learning and consolidation

Overall, the available data indicate that extinction learning and expression relies on a tripartite synaptic circuit, including the amygdala for storing of both conditioned fear and extinction, the hippocampus for processing of contextual information, and the infralimbic region of the mPFC for the consolidation and retrieval of extinction memory (190,274,308,327,389). In the extinction context, mPFC activity inhibits CE fear output neurons via the glutamatergic activation of GABAergic ITCm neurons, which results in dampening of fear expression (189,248). Outside the extinction training context, CE neurons are subjected to less inhibition and fear responses re-vive. In addition, different types of neurons in the basal amygdala signal fear memory or extinction, which may shift the balance between the context-dependent expression of fear and or extinction after conditioning (157). Two main classes of synaptic mechanisms and intracellular pathways have been identified in relation to fear extinction: (1) mechanisms underlying the reinforcement of an active inhibitory process that competes with the initial fear memory for the control of behavior; (2) mechanisms that reverse the changes in synaptic efficacy induced during fear conditioning. A most convincing piece of evidence supporting the dual mode of extinction comes from a recent study focusing on the involvement of αCaMKII in extinction (209). First, this study confirmed earlier observations that extinction training conducted 24 hours, but not 15 min, after contextual fear conditioning showed spontaneous recovery. This suggests that depending on the interval between fear conditioning and extinction training, extinction can result from the formation of a new inhibitory learning or from unlearning of the initial CS-US association. However, it should be mentioned that the effects of extinction timing on recovery effects (renewal, spontaneous recovery, reinstatement) are controversial, with contrasting and even completely opposite results between different studies (68,271,328). Next, by conducting these tests in heterozygous knock-in mice with partial reduction of αCaMKII activity, this study showed that αCaMKII is required for the formation of the new inhibitory memory, but not for the loss of conditioned fear responses during early extinction, thereby providing molecular evidence for the duality of mechanisms in fear extinction. These two sets of mechanisms seem to be developmentally regulated. In contrast to adult

animals, rats at earl postnatal stages (below 3 weeks) do not exhibit reinstatement or re-newal of conditioned fear memories, and extinction has been suggested to reflect an unlearning process leading to erasure of initial fear memories (205). Fear extinction depends on the amygdala at all postnatal stages investigated (205,274,327), whereas the mPFC is involved in fear extinction in adult but not young animals (204). In an elegant series of experiments, Gogolla and coworkers (138) have shown that erasure-resistant fear memories are mediated by the formation of perineuronal nets composed of extracellular matrix chondroitin sulphate proteoglycans in the amygdala during a postnatal critical period.

Accordingly, we will use this duality of processes when describing extinction-related synaptic mechanisms. The remainder of this section will focus on signalling pathways and network mechanisms supporting the formation of new extinction-related inhibitory memory. The following section will consider the mechanisms underlying the reversal of conditioning-evoked alterations.

1. NMDA receptors—There is ample evidence that application of NMDA-R antagonists, either systemically or locally into the BLA, just before extinction training, prevents formation of the extinction memory (18,113,245,253), with NR2B receptor subtypes playing a particularly important role (481,482). Furthermore, the NMDA-R agonist D-cycloserine, a partial agonist acting at the glycine-recognition site of the NMDA-R, facilitates extinction of fear-potentiated startle or conditioned freezing when administered shortly before or after extinction training (237,238,512,530). Importantly, several lines of evidence indicate that effects obtained with experimental manipulation of NMDA-R activity are not due to state-dependent changes in neuronal activity, but that NMDA receptors are specifically involved in learning and consolidation of extinction. *First*, systemic application of an NMDA-R antagonist during extinction training interfered with extinction recall when tested 24 hours, but not 1.5 or 48 hours later (445). A second application of the antagonist 24 hours after extinction training also affected long-term extinction recall. These results suggest that consolidation of extinction shifts from an NMDA-independent early stage to an NMDA-dependent form. *Second*, pre- or post-extinction infusion of the relatively selective NR2B antagonist ifenprodil locally into BLA or mPFC indicate that within-session extinction involved NMDA-R activation in the BLA, whereas consolidation depends on NMDA-Rs in the mPFC (445). Interestingly, re-learning of extinction recruits NMDA-Rs in both BLA and mPFC (233,234). Thus, the development of extinction seems to involve NMDA-Rs in the BLA, whereas its consolidation involves NMDA-Rs in the mPFC (Fig. 8A). Relearning to inhibit fear responses seem to involve NMDA-Rs in both the BLA and mPFC, and consolidation again involves NMDA-Rs in the mPFC. The NR2B receptor subtype is critical for these phase-dependent roles of NMDA-Rs in extinction (482). *Third*, it was shown that Ca^{2+}-mediated burst firing in infralimbic neurons predicted subsequent recall of extinction, and that this burst activity was dependent on NMDA-R activation (54). Therefore, NMDA-R mediated bursting in infralimbic neurons seems to initiate Ca^{2+}-dependent intracellular cascades that stabilize fear extinction memory.

2. Voltage gated Ca^{2+} channels—Other sources of intracellular Ca^{2+} in relation of fear extinction may include voltage-gated Ca^{2+} channels. However, the evidence remains sparse as compared to that for fear conditioning. There is some evidence for impaired extinction, involving both within-session extinction and extinction recall, upon systemic application of the Ca^{2+} channel blockers nifedipine and nimodipine (19,57,58,492). However, it was suggested that nifedipine affects fear extinction indirectly, through induction of a stress response (514).

3. Metabotropic glutamate receptors—There is also evidence that mGluRs regulate extinction. Indeed, mGluR7-/- mice exhibit an extinction deficit (59). Moreover, systemic

pre-extinction application of a novel mGluR7 allosteric agonist (AMN082) facilitates, whereas mGluR7 knockdown using siRNA prior to aversive training severely attenuates between-session extinction in fear-potentiated startle (120). In addition, acquisition of conditioned fear and thalamo-LA LTP in principal neurons were impaired by application of a mGluR agonist, whereas mGluR knockdown had not effect on the acquisition of conditioned fear. As mGluR7 is localized to presynaptic terminals of glutamatergic neurons in the amygdala and negatively coupled to the adenylyl cyclase/cAMP system (281), a decrease in presynaptic glutamate release may contribute to extinction learning, although it remains unclear how impaired fear acquisition can coincide with facilitated fear extinction. Pre- or postsynaptically located group II mGluRs positively coupled to the adenylyl cyclase/ cAMP system have been found to mediate LTD in LA/BLA, although the significance for fear extinction remains unclear to date (153,255). Further experiments using pharmacological interference with the adenylyl cyclase/cAMP system yielded a somewhat inconsistent picture. Subchronic blockade of phosphodiesterase activity (assuming to raise cAMP levels) resulted in hippocampal CREB activation and increase in freezing behavior throughout extinction training (318), while transgenic mice overexpressing type 1 adenylyl cyclase within the forebrain displayed hippocampal CREB activation and unaltered tone and context fear acquisition but delayed context extinction (515).

4. Protein kinases—Several kinase pathways are involved in fear extinction in the relevant brain regions, including PKA (319,495), MAPK (159,168,169,261,423,530), PI3-kinase (71,253,530), SRC kinases (33), and CAMK (32,495). Pharmacologically interfering with a given kinase pathway before extinction training typically had no effect on within-session extinction but impaired extinction recall, while the same treatments shortly after extinction training resulted in a deficit in extinction recall at later times. These data indicated an involvement of the respective kinase pathway in the consolidation rather than the acquisition of fear extinction. In line with this are reports of an upregulation of phosphorylated MAPK/ERK within the BLA, which occurs in a time-dependent manner at late extinction periods (159) and depends on extinction success (530). Similarly, infusion of MAPK inhibitors prior to or immediately after extinction training into the BLA (159) or the mPFC (168,169) impaired subsequent retrieval of extinction in later test sessions. A detailed account on kinase pathways comes from the work of Fischer and colleagues (121) on hippocampal ERK/MEK signalling. Both contextual fear conditioning and its extinction triggered an upregulation of phosphorylated ERK-1/2, with conditioning and extinction effects displaying a difference in time course and localization to the cytoplasmic and nuclear compartment of hippocampal neurons, respectively. Pharmacological inhibition of the ERK-activating kinase, MEK, immediately after extinction trials prevented ERK-1/2 activation and impaired extinction recall. Control procedures ruled out actions on fear memory retrieval or consolidation. Hippocampal MEK/ERK signalling may thus serve as one of the key mediators of contextual fear regulation, with specific temporal and compartmental characteristics differentiating between fear conditioning and extinction. Another critical pathway recruits Trk receptors. Blocking BDNF influence in the BLA through lentiviral-induced expression of a dominant-negative truncated TrkB receptor after fear conditioning had no effect on within session extinction, but impaired retention of extinction. This suggests that TrkB activation is required for the consolidation of stable extinction memories (74).

The engagement of kinase pathways suggests that transcriptional modulation of gene expression is involved in extinction consolidation. Indeed, induction of immediate early genes, like c-fos, has been observed in both the BLA and the mPFC following extinction training and has been related to extinction success (158,321). Increases in c-fos and ERK expression have been observed upon both conditioning and extinction of contextual fear in the hippocampal CA1 area, and have been associated with separate populations of pyramidal

neurons (501). Furthermore, infusion of protein synthesis blockers into BLA (253) or mPFC (444) lead to impaired retrieval of extinction in later sessions, suggesting that protein synthesis is required for consolidation of extinction. However, in contrast to the robust involvement of protein synthesis in the consolidation of conditioned fear, its role in extinction appears to vary depending on the conditioning and extinction paradigm. For instance, in a contextual fear paradigm, inhibition of hippocampal protein synthesis after the first extinction trial reduced freezing responses ((122); see also (89)). This effect reflected enhanced extinction rather than loss of stable fear memory, because conditioned freezing could be re-instated by a reminder shock (122). Protein synthesis counteracting extinction during brief extinction trials might thus prevent rapid extinction of conditioned freezing in situations in which the CS does not reliably predict the absence of the US. This possibility is consistent with the downregulation of immediate–early genes such as c-fos, egr-1, and arc (197,268,393) with short non-reinforced CS exposures. In fact, there has been some debate as to whether results obtained with protein synthesis blockers relate to effects on extinction or re-consolidation of conditioned fear, given the similar experimental procedures used to examine these two phenomena (as discussed in (327,331,333,389)). Which process predominates in a given retrieval session, and how do the two processes interact? The emerging consensus is that the duration of the re-exposure to the conditioned stimulus determines which process predominates: re-consolidation with very short re-exposure and extinction with long and/or repeated exposure (389). Protein synthesis is involved in both processes (327,331,333). During contextual fear conditioning, there is an increased expression of CREB and CREB-dependent Arc in the amygdala and hippocampus after short re-exposure, and in the amygdala and prefrontal cortex after long re-exposure, suggesting that re-activated contextual fear memories undergo CREB-dependent reconsoldation or extinction in distinct brain areas (269).

5. Synaptic remodelling—As discussed above (section IV.B), *de novo* protein synthesis leads to the persistent activation of a number of protein kinases, that directly, or via downstream targets, lead to synaptic remodelling. One important effector mechanisms is actin stability. Intrahippocampal injections of the actin rearrangement inhibitors cytochalasin D or latrunculin after contextual fear conditioning impaired conditioned freezing, while injection in between extinction trials prevented extinction (122), Notably, the inhibitors were not effective when applied after extinction of conditioned freezing. Supporting these conclusions is the recent finding (441) that Cdk5, a serine/threonine-kinase and important regulator of synaptic function and actin dynamics, regulates between-session extinction of contextual fear. Extinction was found to require a downregulation of Cdk5 and upregulation of p21 activated kinase-1 (PAK-1) activity, which is achieved by a reduced membrane association of the Cdk5 activator p35 and dissociation of p35 from PAK-1, mediated by the small GTPase RAC-1. Actin rearrangement, involving a molecular pathway with counteracting Cdk5, PAK-1, and RAC-1, thus seems to regulate extinction of contextual fear, predominantly during repeated extinction trials (441). As to NCAM, intra-amygdala cleavage of PSA-NCAM did not affect acquisition, consolidation or expression of remote fear memories, nor within-session extinction, but strengthened extinction memory (276). Since NCAM is thought to be involved in stress-modulated contextual fear, its specific contribution to fear extinction remains to be delineated.

6. GABA signalling—Consistent with the role of GABAergic mechanisms in extinction, mRNA and protein levels of the $GABA_A$ receptor clustering protein gephyrin are significantly upregulated in the BLA 2 hours after extinction training, together with an increase in the surface expression of $GABA_A$ receptors in the BLA (73). In contrast, gephyrin expression is reduced after fear acquisition (254,406). In fact, the expression of various GABA-related genes seems to be differentially regulated in the amygdala. Three

hours after fear training, mRNA levels of the GABA$_A$ receptor subtypes α1, α5 and the GABA-synthetizing enzyme GAD were decreased, while after extinction training the mRNA levels of α2, β2, GAD and gephyrin, as well as the GABA transporter GAT1 were increased (154). At the protein level, gephyrin, β2 and γ2 levels were decreased upon extinction of conditioned fear (254). Also, the two isoforms of GAD, GAD 65 and GAD 67, were transiently down-regulated, respectively 3 and 24 hours after fear conditioning (25,154). Supporting the idea that extinction involves the regulation of GAD65, the activity-dependent GAD isoform, GAD65-deficient mice show impaired extinction of cued fear, both within sessions and during recall (443). In contrast, extinction of contextual fear was unaltered, suggesting functionally or regionally specific differences in GABA-related contributions to fear extinction. In fact, such differences in the regulation of GABA-related genes were reported for LA, BL and CE (154) as a result of fear conditioning and extinction. However, their functional significance remains to be examined.

Together, these findings indicate that the acquisition of conditioned fear induces a downregulation of markers related to GABAergic function in the amygdala, whereas the acquisition of fear extinction produces an upregulation of GABAergic markers. In keeping with this, a decrease in the frequency and amplitude of miniature IPSCs occurring in LA projection neurons one day after fear training returned to baseline levels during retrieval of extinction (254). Furthermore, cell-permeable TAT-conjugated peptide (TAT)-GABA receptor-associated protein (GABARAP) inhibitory peptide that blocked GABA$_A$ receptor insertion in the amygdala interfered with both extinction-induced increase in miniature IPSCs and reduction of fear-potentiated startle responses. These results corroborate the view that fear extinction involves GABAergic mechanisms that functionally oppose those recruited during fear acquisition.

One population of GABAergic neurons of critical importance for fear extinction are the paracapsular ITC GABAergic neurons located between the BLA and CE (ITCm; (189,248)). These cells receive glutamatergic inputs from the BLA, and, in turn, provide GABAergic inhibition to CE neurons. Therefore, they are situated in an ideal position to control signal flow within the amygdala (427). Lesions (248) or modulation through neuropeptide S (NPS) (189) of these GABAergic ITC neurons specifically influences fear extinction with spared fear memory acquisition and consolidation (Fig. 8C). Both NMDA-dependent LTP and LTD occur at BLA inputs to these neurons, and both can be induced homo- and heterosynaptically (Fig. 8D; (429,430)). Synaptic plasticity seems to be well balanced in ITC cells, as activity-dependent potentiation or depression of particular inputs leads to opposite changes at other inputs ending at different dendritic levels, thereby keeping total synaptic weight constant, although the relative strength of inputs is modified (430). Moreover, ITC neurons display a wide range of short-term presynaptic plasticity, which, in turn, is functionally balanced through synaptic interconnectivity between subpopulations of neurons, thereby stabilizing the pattern of spike firing (137). Therefore, these results suggest that synaptic plasticity in ITCm cells is not a local event engaging a limited group of synapses or neurons, but a distributed event in which the strength of synaptic connections can be affected by the state of other inputs, while keeping the overall weight of the synaptic network and output activity in a stable range. The functional significance of these balanced interactions for conditioned fear and extinction remains to be delineated. Further evidence that GABAergic synaptic plasticity is critical for fear extinction has been obtained by manipulating endocannabinoid signalling (reviewed in (263)). The cannabinoid receptor subtype (CB1) is found presynaptically on the axon terminals of a specific subpopulation of BLA interneurons expressing the anxiogenic peptide CCK (195,294). CCK exerts a strong depolarizing effect in principal LA neurons via activation CCK2 receptors coupled to transient receptor potential (TRP) type cationic channels (304). CB1 receptor stimulation reduced GABAergic responses in principal neurons (195), and low-frequency afferent

stimulation in LA caused the release of endocannabinoids, inducing an LTD of GABAergic synaptic transmission (LTDi) (Fig. 8B; (16)). The consequence of this particular anatomical localization for conditioned fear behavior was investigated in mice with CB1 receptor deficiency (278). These CB1 receptor mutants displayed impaired short- and long-term extinction in auditory fear-conditioning, with spared fear memory acquisition and consolidation (278). Moreover, pharmacological blockade of CB1 receptors led to a similar deficit in wild-type mice (16), which was ameliorated with administration of a CCK2 receptor antagonist (72). This regulation of fear extinction through CB1 receptors was found to be mediated via habituation-like processes rather than associative learning mechanisms (192). Moreover, prior microinjection of a CB1/CB2 receptor agonist into the BLA had no effect by itself on inhibitory avoidance conditioning or extinction, but reversed both the enhancing effects of a stressor on conditioning and its imparing effects on extinction (134). Together these findings underscore the contribution of habituationlike processes and of adaptive components such as stress to fear extinction, and their control by the endocannabinoid system.

Also co-localized with GABA in local-circuit amygdala neurons is NPY (296,479). Administration of NPY or NPY Y(1) receptor agonists into the BLA inhibits expression of fear-potentiated startle and enhances within-session extinction (145). This effect most likely depends on a decreased excitability of principal neurons secondary to the activation of Y(1)-coupled inwardly rectifying K^+ channels (480).

In conclusion, extinction training is followed by a consolidation phase, which recruits much of the same molecular machinery involved in the acquisition of conditioned fear (Fig. 9), and involves a spatially distributed synaptic network including the amygdala, hippocampus, and the mPFC for storing of extinction, processing of contextual information, and determination of extinction retrieval, respectively. Important targets of mPFC influences are GABAergic ITC neurons that, in turn, are capable of synaptic plasticity themselves.

D. Reversal of conditioning-evoked alterations

The most convincing data indicating that extinction can reverse the synaptic changes induced by fear conditioning come from studies of synaptic *depotentiation*, a physiological reversal of LTP and cellular correlate of unlearning (reviewed in (537)). Depotentiation can be induced in the amygdala by low frequency stimulation *in vitro*, reverses fear training-induced LTP *ex vivo*, and is associated with a loss of acquired fear responses. As discussed below, depotentiation shares a common set of mechanisms with extinction, which, together, seem to functionally oppose or invert those underlying LTP and/or conditioned fear.

In a comprehensive set of experiments, Gean and colleagues have identified a key signal in depotentiation and fear extinction: the phosphatase calcineurin (protein phosphatase 2B), which targets and inactivates through de-phosphorylation a number of kinases critical for long-term potentiation and conditioned fear in the amygdala (249-251,253). Depotentiation *in vitro* and fear extinction were found to be associated with an upregulation of calcineurin in the BLA, presumably through a Ca^{2+}-regulated process, and both were sensitive to calcineurin inhibitors. Importantly, the fear training-induced phosphorylation of specific substrates, such as MAPK and Akt, was reduced after extinction, and this de-phosphorylation was blocked by calcineurin inhibitors. The exact mechanisms of depotentiation in the amygdala, particularly the involvement of NMDA-Rs, MAPK and protein synthesis, remain to be clarified (253). In addition, Kim and colleagues (208) have found that depotentiation at thalamo-LA synapses and fear extinction were attenuated upon blockade of regulated AMPA-R endocytosis. Indeed, interfering with regulated AMPA-R endocytosis through a GluR2-derived peptide (Tat-GluR2$_{3Y}$) during extinction training disrupted the expression and retention of fear expression, whereas the same treatment during

fear conditioning had no effect on the expression or recall of either cue or contextual conditioned fear (86). Because Tat-GluR2$_{3Y}$ interferes with LTD, and AMPA-R endocytosis is associated with LTD at thalamic inputs in the amygdala (535), the authors suggested that LTD may be a mechanism that links AMPA-R endocytosis to fear extinction (86). Whether mGluR-dependent forms of LTD in principal BLA neurons (153,255) are relevant for fear extinction remains to be tested. Furthermore, extinction may involve structural alterations opposing those induced by fear conditioning, as indicated by an increase in expression of PSA-NCAM 24 h post fear training in the amygdala (276). In keeping with this, intra-amygdala cleavage of PSA-NCAM affected fear extinction rather than acquisition or consolidation of cued fear (276).

Together, these data suggest that fear extinction include early processes which may reset fear conditioning-induced plastic changes in the amygdala, through synaptic depotentiation or depression, distributed AMPA-R endocytosis, and kinase de-phosphorylation (Fig. 9).

VI. Conclusions: Relation Between Fear and Extinction Memories

Although it is commonly accepted that extinction training does not abolish the initial fear memory, but rather leads to the formation of a new inhibitory memory, the evidence reviewed in the previous section indicates that extinction does reverse at least some of the increases in synaptic efficacy that embody the fear memory. It is important to reconcile these two views as this may yield clues as to how extinction controls fear expression.

On the one hand, there is incontrovertible behavioral evidence that the CS can still evoke conditioned fear responses after extinction training. In other words, the fear memory is not erased after extinction. For instance, as reviewed above, presentation of unsignaled USs after extinction training causes the reinstatement of conditioned fear responses. Second, extinction memory decays with time allowing a spontaneous recovery of the fear memory. Third, after extinction training, conditioned fear responses can be elicited by the CS if the testing context is different from that used for extinction training.

On the other hand, accumulating data indicates that extinction training leads to a depotentiation of thalamic inputs about the CS in LA (208,249,535). These findings, coupled to the preserved ability of the CS to evoke conditioned fear following extinction training, raise the intriguing possibility that different pathways convey CS information to the amygdala before vs. after extinction training. Indeed, phenomena such as renewal and reinstatement are utterly incompatible with the idea that extinction only depends on a reversal of the synaptic alterations induced by fear conditioning. In order for renewal and reinstatement to exist, some pathway still has to convey enhanced CS information to the amygdala after extinction.

Consistent with this idea, single-unit studies have revealed that extinction training does not abolish the increased CS responsiveness of all BLA neurons but rather causes a shift in their spatial distribution. In LAd, where primary thalamic inputs about the CS end, extinction training causes a rapid reduction in the magnitude of CS-evoked responses (390,404). In contrast, in the ventral part of LA, a region devoid of direct thalamic inputs from PIN and MGm, CS-evoked responses typically persist after extinction training (404). Moreover, a similar situation is seen in BL where around 25% of neurons maintain an increased CS-responsiveness after extinction training and an additional 15% *acquire* an increased CS-responsiveness as a result of extinction training (157). Finally, a third group of BL neurons, accounting for 13% of the cells, express CS-evoked activity in a context-dependent manner in renewal tests (157).

While the loss of CS-evoked responses in LAd is consistent with an erasure of the fear memory, their persistence in BL and ventral LA is not. Instead, these phenomena suggest that extinction training causes a re-organization of the fear memory; a change in the networks primarily responsible for supporting CS transfer to the amygdala. Additional support for this idea comes from studies that examined the hippocampal-dependence of conditioned fear to cues before vs. after extinction training. Whereas dorsal hippocampal lesions and inactivations do not block expression of conditioned fear responses (82,370,460), the same manipulations performed after extinction training do (82,273). Indeed, dorsal hippocampal lesions and inactivations after extinction training prevented the context-dependent renewal of conditioned fear (82,273). Moreover, inactivation of the dorsal hippocampus prevented the context-dependent expression of CS-evoked responses in LAd neurons after extinction (273). As suggested by c-Fos expression patterns, the hippocampus has a role in contextual fear memory extinction and renewal, both for presentation of cues in and outside the extinction context (211).

If, as suggested by the depotentiation studies, thalamic inputs are depressed by extinction training, what pathway(s) might support the transfer of CS information to the amygdala? Auditory cortical areas are likely candidates. Indeed, these areas contribute direct projections to the amygdala as well as indirect ones, via the rhinal cortices (286). Consistent with this notion, unit recordings have revealed that many auditory cortical neurons express extinction-resistant CS-evoked responses (386).

A second area of uncertainty pertains to mechanisms supporting the contrasting hippocampal dependence of conditioned fear responses to cues before vs. after extinction training. In the model proposed here, the primary route of CS transmission shifts from the thalamus before extinction training to the auditory cortex after extinction training. In this framework, the differential connectivity of the hippocampus with the thalamus and auditory cortex would account for the changing hippocampal-dependence of fear expression before vs. after extinction training. Indeed, the hippocampus has no projections to MGm-PIN but significant indirect projections to associative auditory cortical areas via the rhinal cortices (286). Therefore, hippocampal output might allow for a contextual regulation of CS-evoked activity in the neocortex.

The view of dual representations of context is particularly interesting in this respect (for review see (431)). According to this view, context can be represented as a set of distinct features, each of which may enter into association with the aversive event via functional links to the amygdala. Alternatively, the distinct features of the situation may be bound into a new representation encoding their co-occurrence or conjunction and, for association with the aversive events, further links to the amygdala. These dual representations have been mapped onto distinct neuroanatomical substrates, in which neocortical systems represent the independent features, whereas the elaboration of features into a unitary conjunctive representation requires that the cortex interacts with the hippocampus (329,330,433). These findings raise the intriguing possibility that the two representations of context make a different contribution before versus after extinction, with neocortical/hippocampal interactions and their influence on the amygdala being critically involved in the contextual components of extinction.

From the above, it should be clear that in our view, extinction training does not result from erasure of the initial fear memory, but on its re-organization. True erasure of the fear memory only occurs in special circumstances, as when the fear memory is first reactivated and then the CS is repeatedly presented during the reconsolidation window, or when reconsolidation is disrupted by administration of a β-adrenergic receptor antagonist prior to memory reactivation (210,317), or perhaps when fear memories are formed at very early

postnatal stages and then challenged with repeated unpaired CS presentations (138,205). True erasure of the fear memory is manifested by a loss of spontaneous recovery, reinstatement, and renewal, and these conditions are not seen following conventional extinction training in adulthood.

Overall, the data reviewed here suggests that extinction training leads to distributed changes in cerebral networks. Besides the system-level alterations in the pathways supporting CS transfer to the amygdala, there are widespread changes in the expression of GABA receptors, in the rate of GABA synthesis, as well as activity-dependent potentiation of BL inputs to ITC cells, resulting in the inhibition of fear output neurons. A major challenge for future studies will be to determine how these various changes cooperate to control fear expression.

Acknowledgments

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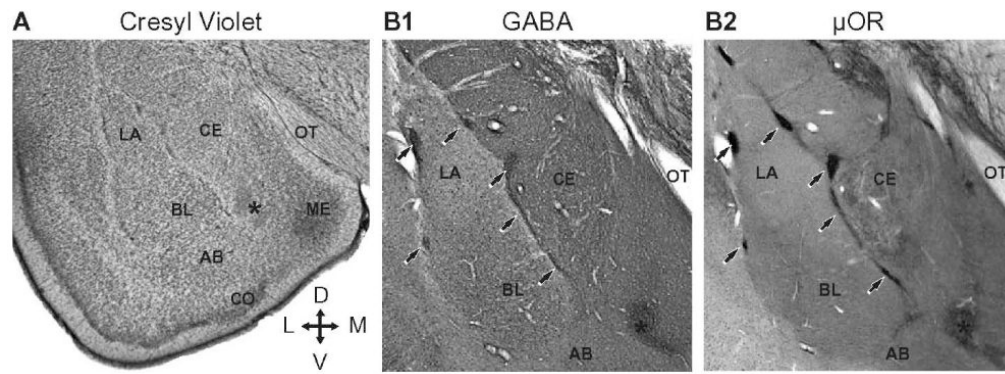
Fig. 1.
Macroscopic organization of the rat amygdala. Coronal sections. (**A**) Cresyl violet stain. (**B**) Two adjacent sections processed to reveal immunoreactivity for GABA (**B1**) or µ opioid receptors (µOR; **B2**). Note spatial correspondence between zones expressing high levels of GABA and µOR immunoreactivity. **Arrows** point to ITC cell clusters. **Asterisks** indicate main ITC cluster. **Cross** indicates orientation of the sections where D, V, L, and M respectively stand for dorsal, ventral, lateral, and medial. Abbreviations: AB, accessory basal nucleus; BL, basolateral nucleus; CE, central nucleus; CO, cortical nucleus; LA, lateral nucleus; ME, medial nucleus; OT, optic tract.
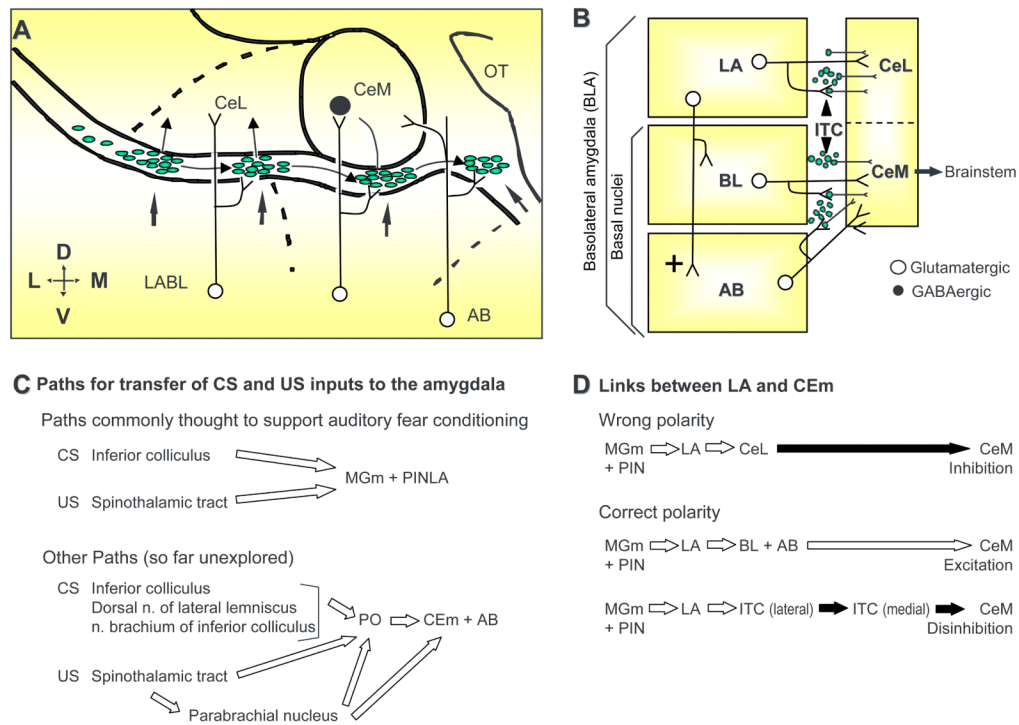
Fig. 2.

Intrinsic connectivity and CS-US input pathways of the amygdala. (**A**) Scheme showing the directionally polarized connections that exist between different ITCm cell clusters in guinea pigs. These connections prevalently run from lateral to medial. **Cross** indicates orientation of the sections where D, V, L, and M respectively stand for dorsal, ventral, lateral, and medial. (**B**) Summary of main internuclear connections between the BLA, CE, and ITC cells. Note that BL and AB also contribute projections to CeL but these were omitted from the scheme for clarity. (**C**) Scheme illustrating the various routes that exist for the transfer of CS or US information to the amygdala. Note the contrasting termination patterns of PO vs. MGm-PIN in the amygdala. (**D**) Scheme illustrating the various indirect routes that exist between LA and CeM along with their expected impact on CeM neurons (right). Abbreviations: AB, accessory basal; BL, basolateral; CeL, central lateral; CeM, central medial; ITC, intercalated; LA, lateral; MGm, medial sector of the medial geniculate nucleus; OT, optic tract; PIN, posterior intralaminar nucleus; PO, posterior thalamic nucleus.
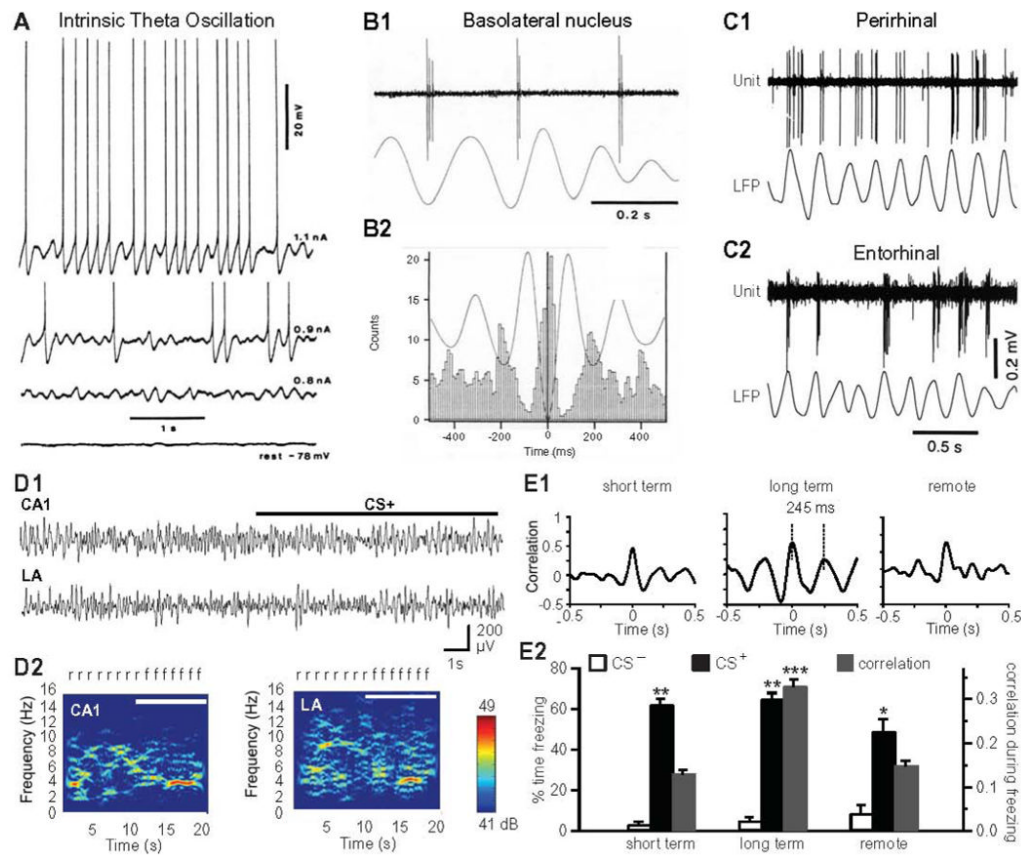
Fig. 3.
Theta oscillations in the BLA. (**A**) LA neuron recorded intracellularly *in vivo*. Near threshold membrane depolarization by intracellular current injection (numbers on right) elicits intrinsic membrane potential oscillations in the theta frequency range. (**B**) Principal BLA neuron exhibit rhythmic firing at the theta frequency during paradoxical sleep. (**B1**) Unit activity (top) and LFP (bottom) recorded by the same microelectrode and obtained by high vs. low-pass digital filtering, respectively. (**C**) Perirhinal (**C1**) and entorhinal (**C2**) neurons fire rhythmically at the theta frequency. Traces obtained as in **B**. (**D**) Synchronized theta activity in LA and CA1 during retrieval of conditioned fear. LFP recordings (**D1**) and their color-coded power spectra (**D2**) demonstrate theta activity in both LA and CA1 during CS+-evoked freezing. White bar in D1 denotes CS+ presentation; f, freezing; r, risk-assessment behavior. (**E**) LA-CA1 activity during retrieval of conditioned fear at short-term, long-term and remote stages, recorded at 2 hours, 24 hours and 30 days after fear training, respectively. (**E1**) Crosscorrelograms indicate synchronized theta during long-term (middle; obtained from recordings in D), but not short-term or remote stages. (**E2**) Significant increase in CS+-evoked freezing (black bars; compared to CS-, white bars) at short, long-term and remote stages is accompanied by synchronized theta in LA-CA1 (grey bars) only at long-term memory stages. * $P<0.01$, ** $P<0.001$, ***$P<0.0001$. Data in D, E modified from (335).
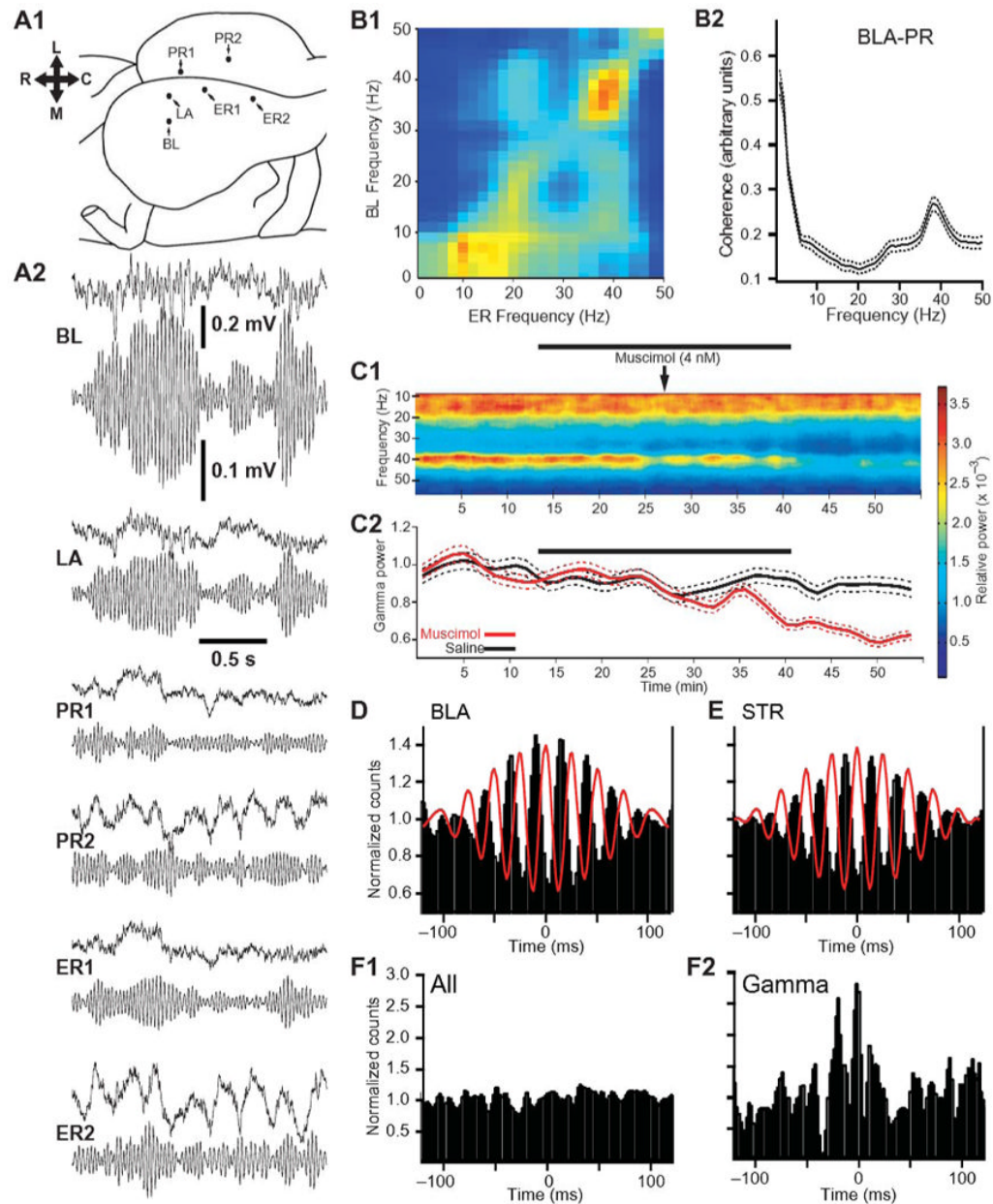
Fig. 4.

Coherent gamma oscillations in the BLA and its targets. (**A**) Simultaneous LFP recordings of gamma activity in the BLA and rhinal cortices. (**A1**) Scheme showing position of recording sites for activity depicted in **A2**. (**A2**) Top and bottom traces respectively show raw vs. digitally filtered (35-45 Hz) LFPs. (**B**) Correlated amygdalo-rhinal gamma activity. (**B1**) Power fluctuations: long periods of spontaneous field potential activity recorded during the waking state were segmented in one-second windows. Fast-Fourier Transforms were computed for each window and the power in each frequency was correlated with all others for BL and entorhinal (ER) recording sites. (**B2**) Gamma coherence. Coherence (y-axis) as a function of frequency (x-axis) for recording sites in the BLA and perirhinal cortex. (**C**) Inhibition of BLA activity by local muscimol infusions produces a selective reduction in striatal gamma activity. (**C1**) Striatal LFP power (color-coded) in different frequencies (y-axis) plotted as a function of time (x-axis) in experiments where muscimol was slowly

infused in the BLA, over a period of 25 min. (**C2**) Gamma power (y-axis) ± s.e.m. (dashed lines) as a function of time (x-axis) when either saline (black) or muscimol (red) was infused in the BLA. The thick black lines indicate infusion periods. (**D-E**) Gamma-related unit activity in the BLA (**D**) and striatum (**E**). Peri-event histograms of unit activity computed around the positive peaks of high-amplitude gamma cycles recorded by the same electrode as used to record unit activity. (**F**) Gamma oscillations increase coupling between the activity of BLA and striatal neurons. (**F1**) Crosscorrelogram that included all spikes generated by a simultaneously recorded couple of BLA and striatal neurons. (**F2**) Crosscorrelogram of unit activity for the same cell couple after excluding striatal spikes occurring during periods of low amplitude gamma.
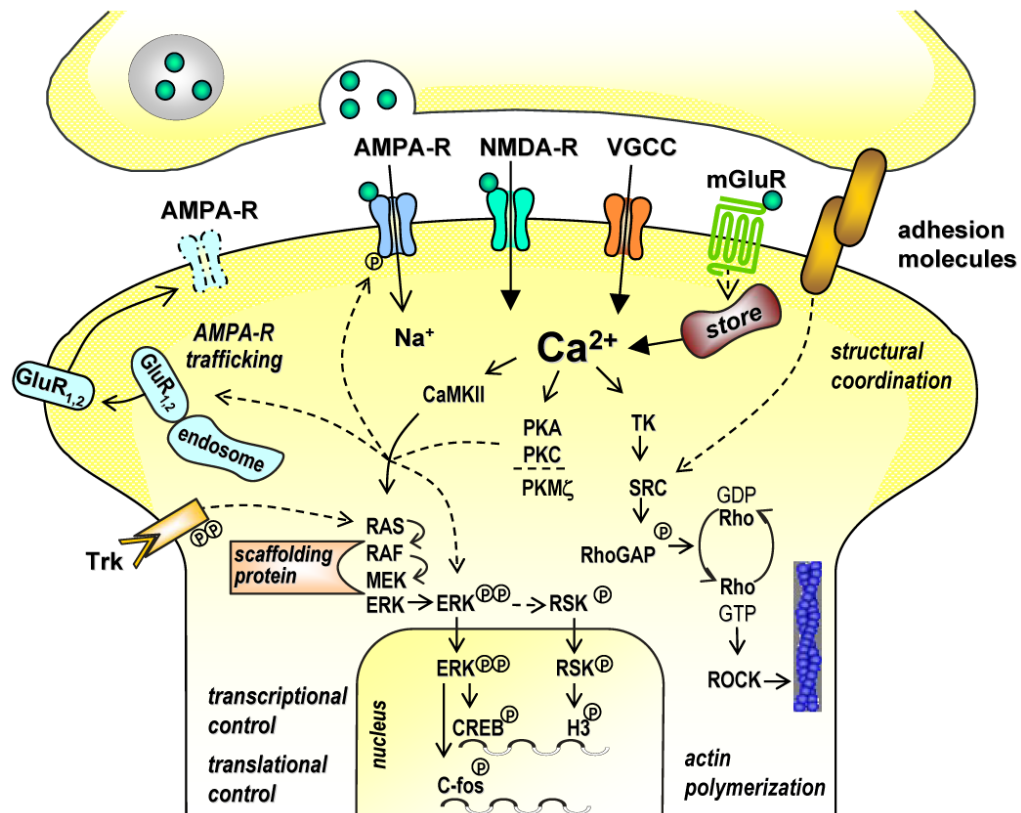
Fig. 5.
Molecular cascades of fear memory stabilization in the amygdala. A postsynaptic increase in intracellular Ca^{2+} concentration, mediated through Ca^{2+} influx via NMDA receptors and voltage-gated Ca^{2+} channels (VGCCs) and through release from intracellular stores upon activation of metabotropic glutamate receptors (mGluRs), triggers a plethora of signalling steps. Three major, mutually interconnected signalling routes involve Ca^{2+}/calmodulin-dependent protein kinases II (CaMKII), the protein kinase (PK) family of enzymes, and tyrosine kinase (TK) pathways. Signalling cascades can reach the nucleus to induce macromolecular synthesis, and they can control translational processes. Consequently, they can act on cytoskeletal and adhesion molecules to re-organize and stabilize synaptic structures, or regulate AMPA receptor trafficking to the synapse. At intermediate steps, protein kinase signals converge on the mitogen-activated protein kinase (MAPK) signal transduction pathways, including the extracellular regulated kinases (ERK). RAS, RAF, and MEK kinases transduce intra- and extracellular signals, mediated for instance through tyrosin receptor kinases (Trk), to the MAPK/ERK pathway. Scaffolding proteins dictate specificity of activation as well as entry in the nucleus. MAPKs translocated into the nucleus phosphorylate transcription factors, such as cAMP response element binding protein (CREB). Actin rearrangement is under the control of RhoGTPases, whose activation from a GDP- to a GTP-bound form is controlled via Ca^{2+} or kinase pathways, including tyrosine kinases (TK) and SRC kinases. RhoGTPases control activity of Rho-associated kinases (ROCK), a key molecule for regulation of the cytosekeleton.
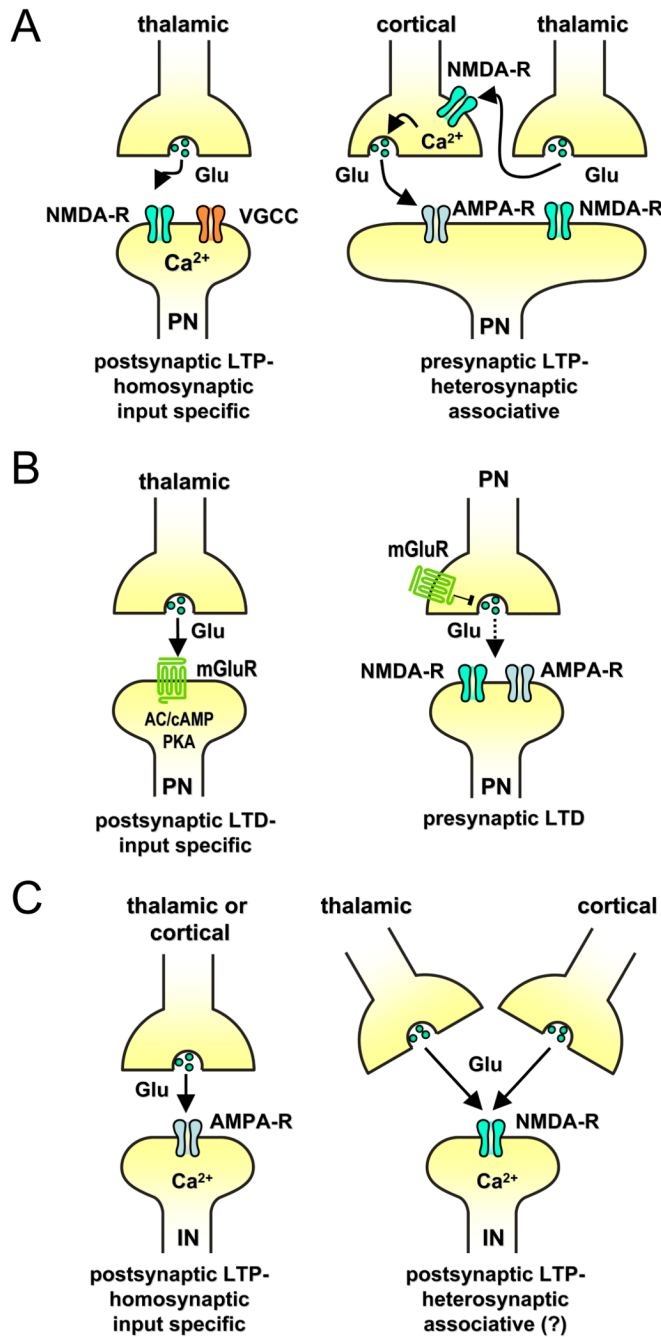
Fig. 6.
Long-term synaptic plasticity related to conditioned fear in the basolateral amygdaloid complex. **A**. Long-term potentiation (LTP) in projection neurons (PN). At thalamic inputs, LTP is homosynaptic upon stimulation of postsynaptic NMDA receptors and/or voltage-gated Ca^{2+} channels. At cortical inputs, LTP is heterosynaptic upon stimulation of presynaptic NMDA receptors through concurrent activation of thalamic inputs. **B**. Long-term depression (LTD) in PN can be mediated via stimulation of postsynaptic metabotropic glutamate receptors (mGluRs) at thalamic inputs, or via presynaptic mGluRs at LA-BLA synaptic connections. **C**. LTP in local GABAergic interneurons (IN) at thalamic and cortical

inputs can be homosynaptic upon stimulation of Ca^{2+} permeable AMPA receptors, or heterosynaptic upon stimulation of NMDA receptors.

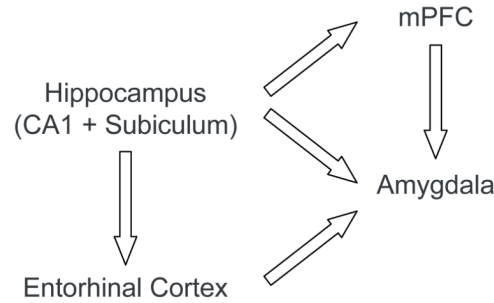**Connections between amygdala and mPF**
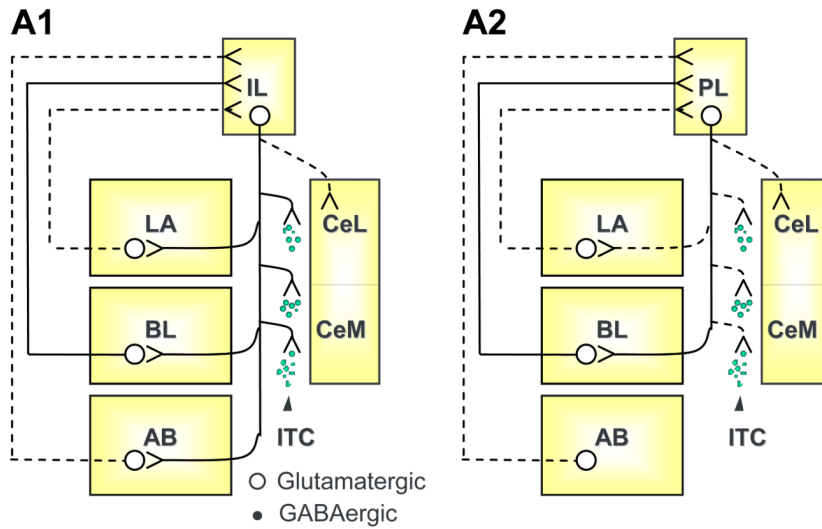
Fig. 7.
Connections between the amygdala, mPFC, and hippocampus. (**A**) Reciprocal connections of the infralimbic (**A1**) and prelimbic (**A2**) components of the mPFC with the amygdala. Solid lines indicate major projections whereas dashed lines indicate weaker ones. (**B**) Multiples direct and indirect paths for the transfer of contextual influences to the amygdala.
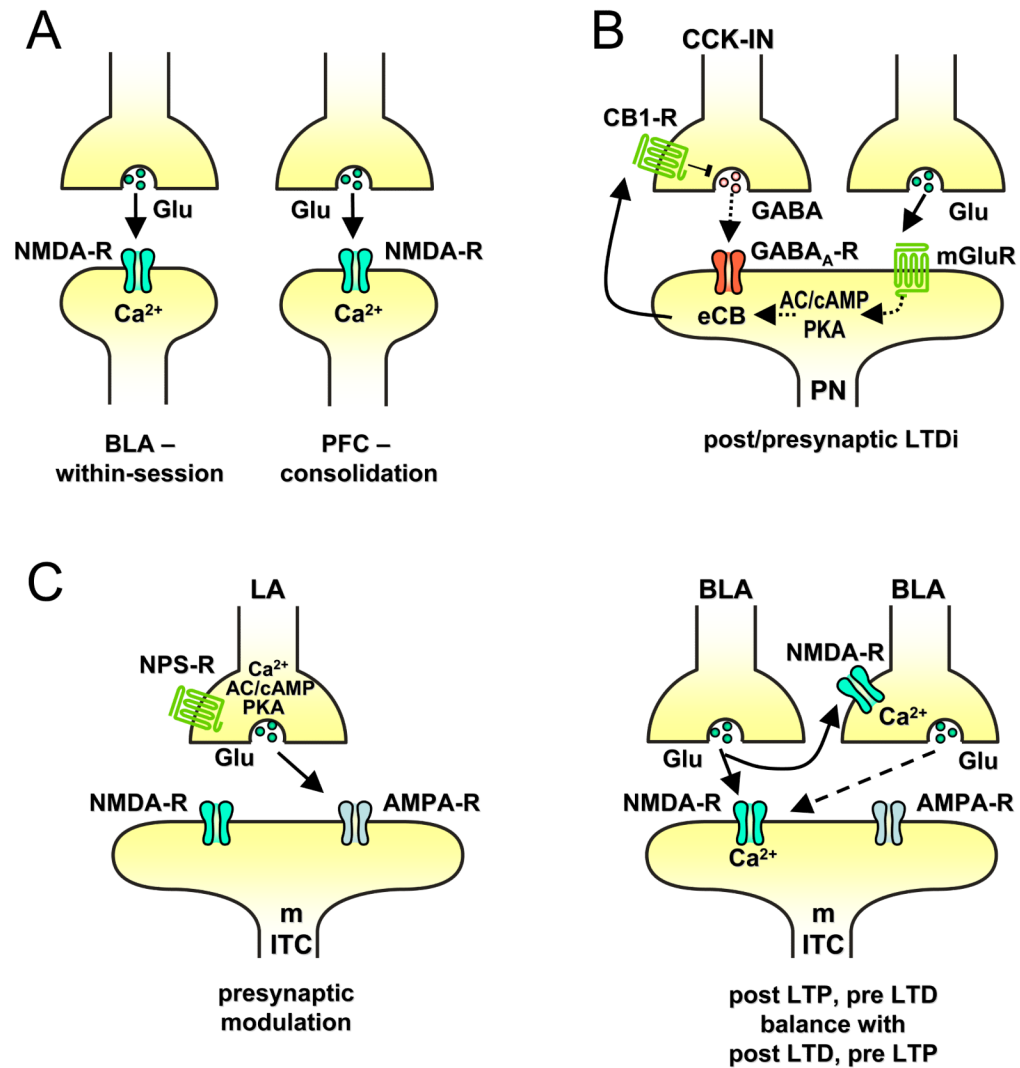
Fig. 8.
Synaptic plasticity related to fear extinction. **A**. Activation of NMDA receptors occurs in the basolateral amygdaloid complex (BLA) and the prefrontal cortex (PFC) during within-session and consolidation of extinction, respectively, most likely inducing long-term potentiation (LTP). **B**. Postsynaptic release of endocannabinoids (eCB) mediates long-term depression of GABAergic transmission (LTDi) via activation of CB1 receptors on cholecystokinin-positive interneurons (CCK-IN). Release of eCB can be stimulated via metabotropic glutamate receptors (mGluRs). **C**. Increase in glutamatergic transmission to GABAergic mITC neurons mediated through NPS receptors in presynaptic LA principal neurons. **D**. Both NMDA receptor-dependent LTP and LTD exist at BLA inputs to mITC, which can be induced homo- and heterosynaptically, and which keep the overall synaptic strength in balance.
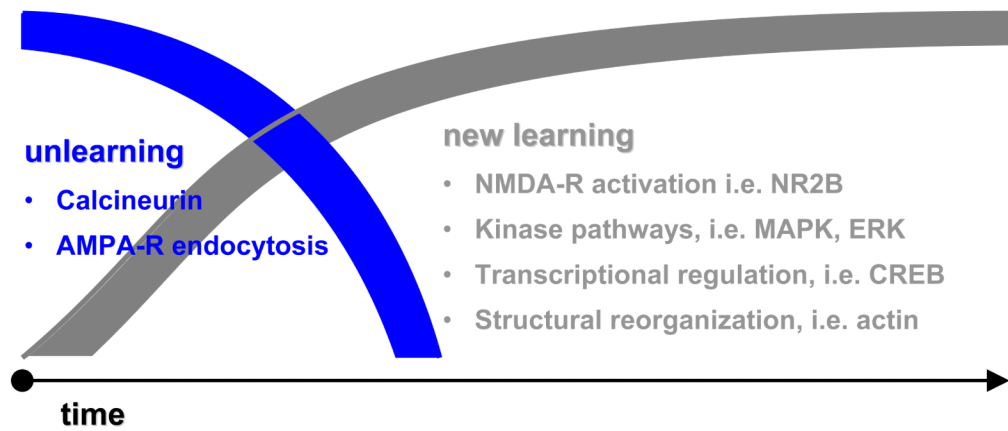
unlearning
- **Calcineurin**
- **AMPA-R endocytosis**

new learning
- NMDA-R activation i.e. NR2B
- Kinase pathways, i.e. MAPK, ERK
- Transcriptional regulation, i.e. CREB
- Structural reorganization, i.e. actin

time

Fig. 9. Molecular mechanisms of unlearning and new learning related to early and late stages of fear extinction

Reversal of conditioned fear (unlearning) involves activation of the phosphatase calcineurin and regulated AMPA receptor endocytosis. Extinction learning and consolidation (new learning) involve activation of NMDA receptors (in particular the NR2B subtype), kinase pathways (for instance the mitogen-activated protein kinase (MAPK), extracellular regulated kinase (ERK) pathway), transcriptional regulation (via transcription factors, such as cAMP response element binding protein (CREB)), and structural organization (involving cytoskeletal proteins such as actin).