Molecular Neurobiology

ISSN0893-7648/96/13(1): 1–22/$10.50

Synaptic Transmission and Plasticity in the Amygdala

An Emerging Physiology of Fear Conditioning Circuits

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Abstract

Numerous studies in both rats and humans indicate the importance of the amygdala in the acquisition and expression of learned fear. The identification of the amygdala as an essential neural substrate for fear conditioning has permitted neurophysiological examinations of synaptic processes in the amygdala that may mediate fear conditioning. One candidate cellular mechanism for fear conditioning is long-term potentiation (LTP), an enduring increase in synaptic transmission induced by high-frequency stimulation of excitatory afferents. At present, the mechanisms underlying the induction and expression of amygdaloid LTP are only beginning to be understood, and probably involve both the *N*-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) subclasses of glutamate receptors. This article will examine recent studies of synaptic transmission and plasticity in the amygdala in an effort to understand the relationships of these processes to aversive learning and memory.

Index Entries: Amygdala; long-term potentiation; glutamate receptors; learning; memory; rats.

Introduction

One memorable morning in January of 1995, I was awakened at 4 AM by a truly frightening experience: My bedroom, all of its contents, and the ground underneath me were heaving and shaking uncontrollably. To my chagrin, I had found myself in the middle of the now infamous Northridge earthquake—a powerful temblor that killed over 50 people and struck fear into the hearts of the Los Angeles residents who survived. In the days and weeks following the quake, it became apparent that the fear evoked by the shaking was not short-lived. Indeed, thousands of Angelenos refused to sleep in their homes following the earthquake, and those who braved their bedrooms did not sleep restfully. Apparently, many people who experienced the earthquake had come to associate their fear of the shaking with the stimuli and places that coincided with the quake. In fact, the earthquake had conditioned Angelenos to fear their own homes!

Besides illustrating one of the pitfalls of living in Southern California, this anecdote illustrates a ubiquitous and simple form of learning

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that is exceptionally robust and rapidly acquired: Pavlovian fear conditioning. Although earthquake victims might prove to be the ideal experimental subjects for laboratory studies of Pavlovian fear conditioning, this form of learning is typically studied in rats. In a typical fear conditioning experiment, a rat is placed in a small observation chamber and presented with an innocuous stimulus (conditional stimulus or CS), such as a tone, that is immediately followed by an aversive stimulus (unconditional stimulus or US), such as an electric footshock. After a few pairings, the CS begins to elicit a constellation of conditional responses (CRs) that are characteristic of fear, such as increases in arterial blood pressure, potentiated startle, pupillary dilation, urination and defecation, and somatomotor immobility or freezing (e.g, Davis, 1992). Thus, the associative relationship between the CS and US permits the CS to generate responses that it did not elicit prior to training.

In the past 40 yr, great strides have been made in elucidating the neural circuitry required for Pavlovian fear conditioning. Collectively, this work points to the amygdala, a group of nuclei buried deep within each temporal lobe, as a critical neural substrate for both the acquisition and expression of learned fear in mammals, including humans (Brady et al., 1954; Kellicutt and Schwartzbaum, 1963; Blanchard and Blanchard, 1972; Sarter and Markowitsch, 1985; McGaugh, 1989; Davis, 1992; Kapp et al., 1992; Bechara et al., 1995; LeDoux, 1995; Maren and Fanselow, 1996). The identification of the amygdala as an essential neural substrate for fear conditioning has generated a great deal of interest in the neuroanatomy and neurophysiology of amygdaloid circuits. As a consequence, there has been an emergence of exciting new research concerning synaptic connectivity, transmission, and plasticity within the amygdala. Not surprisingly, this area of research is beginning to shed light on how neurons in the amygdala encode and store conditional fear memories. The purpose of this article is to review recent studies that have examined the anatomy, pharmacology, and physiology of synaptic connections in the amygdala. Particular emphasis will be placed on the properties and mechanisms of synaptic plasticity at amygdaloid synapses and the relationship of synaptic plasticity in the amygdala to fear conditioning in rats.

Anatomical Connections of the Amygdala

In the rat, the amygdala consists of several anatomically and functionally distinct nuclei, including the lateral, basolateral, basomedial, and central amygdaloid nuclei (Brodal, 1947; Krettek and Price, 1978b). Anatomical and behavioral evidence indicates that these nuclei are components of two distinct subsystems within the amygdala that are important for fear conditioning (see LeDoux, 1995). The first subsystem of the amygdala is comprised of the lateral, basolateral, and basomedial nuclei. Collectively referred to as the basolateral complex, these nuclei form the primary sensory interface of the amygdala. Thus, selective lesions of the basolateral complex produce severe deficits in both the acquisition and expression of Pavlovian fear conditioning independent of the stimulus modality used to train fear responses (LeDoux et al., 1990a; Sananes and Davis, 1992; Campeau and Davis, 1995; Maren et al., 1996). The second subsystem of the amygdala consists of the central nucleus, and it appears to be the amygdala's interface to fear response systems. For example, electrical stimulation of the central nucleus produces responses similar to those evoked by stimuli paired with shock (Kapp et al., 1982; Iwata et al., 1987). Lesions of the central nucleus also produce profound deficits in both the acquisition and expression of conditional fear (e.g., Hitchcock and Davis, 1986; Iwata et al., 1986). Moreover, lesions placed in structures efferent to the central nucleus, such as the lateral hypothalamus or periaqueductal gray, produce selective deficits in either cardiovascular or somatic conditional fear responses, respectively (LeDoux et al., 1988). This suggests that

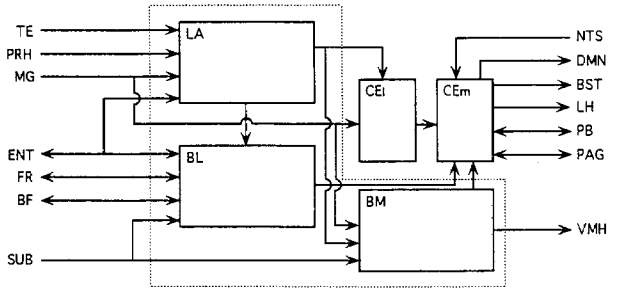

Fig. 1. Schematic representation of amygdaloid efferents and afferents. Nuclei of the amygdala are depicted as rectangular boxes (LA, lateral nucleus; BL, basolateral nucleus; BM, basomedial nucleus; CEl, lateral division of the central nucleus; CEm, medial division of the central nucleus). The basolateral complex is bounded by the dotted line. Arrows indicate the direction of orthodromic projections. The schematic is not intended to be a complete representation of amygdaloid projections. Rather, it illustrates the convergence of sensory information in the basolateral complex and the divergent projections of the central nucleus to response structures in the hypothalamus and brainstem. Abbreviations: TE, temporal cortex; PRH, perirhinal cortex; MG, medial geniculate body; ENT, entorhinal cortex; FR, frontal cortex; BF, basal forebrain; SUB, ventral subiculum; NTS, nucleus of the solitary tract; DMN, dorsal motor nucleus of the vagus; BST, bed nucleus of the stria terminalis; LH, lateral hypothalamus; PB, parabrachial area; PAG, periaqueductal gray; VMH, ventromedial hypothalamus.

the central nucleus is the final common pathway for the generation of learned fear responses. The anatomical connections of these subsystems and the morphology of neurons in these nuclei will be considered below.

Basolateral Complex

As illustrated in Fig. 1, neurons in the basolateral complex receive afferents from both cortical and subcortical brain areas, and the distribution of these afferents to each nucleus is unique (for a review *see* Turner and Herkenham, 1991). For example, the lateral and basomedial nuclei receive a prominent projection from the medial geniculate body, which transmits both auditory and somatosensory (e.g., nociceptive) information to the amygdala (Ottersen and Ben-Ari, 1979; LeDoux et al., 1990b; Turner and Herkenham, 1991; Romanski et al., 1993). Auditory information also reaches the lateral nucleus by way of projections from temporal neocortical areas (Ottersen, 1982; LeDoux et al., 1991). In contrast, the basolateral nucleus receives projections from frontal cortical areas (e.g., the anterior cingulate, insular, and orbitofrontal cortices) (Ottersen, 1982), the basal forebrain (Ottersen, 1980; Kelley et al., 1982), and midline thalamic nuclei (e.g., the interanteromedial, parataenial, and paraventricular nuclei) (Krettek and Price, 1974; Ottersen and Ben-Ari, 1979; Turner and Herkenham, 1991; Groenewegen and Berendse, 1994). These projections may carry viscerosensory information to the amygdala (e.g., Turner and Herkenham, 1991). Structures in the hippocampal formation, particularly the ventral subiculum and lateral entorhinal cortex, also project to all nuclei of the basolateral complex (Wyss, 1981; Ottersen, 1982; Van Groen and Wyss, 1990; Canteras and Swanson, 1992). Additionally, cortical areas associated with the hippocampus, such as the perirhinal cortex, project heavily to the basolateral complex (Ottersen, 1982). These projections form the route by which highly processed polymodal and visual information reach the amygdala.

The efferents of the basolateral complex are similarly diverse. For instance, the lateral and basolateral nuclei reciprocate their projections from the hippocampal formation and associated cortical areas (Krettek and Price, 1977). In addition, the basolateral nucleus projects to striatal areas (e.g., the caudate-putamen and nucleus accumbens) (Krettek and Price, 1978a; Kelley et al., 1982) and reciprocates its frontal cortex projections (Krettek and Price, 1977; Sripanidkulchai et al., 1984). The basomedial nucleus sends a robust projection to the medial hypothalamus. Within the basolateral complex, the lateral nucleus projects strongly to both the basolateral and basomedial nuclei (Stefanacci et al., 1992; Smith and Pare, 1994), and these nuclei project, in turn, to the central nucleus of the amygdala (Pare et al., 1995;

Krettek and Price, 1978b). As will be described below, the central nucleus is the primary route by which the basolateral complex influences structures involved in autonomic regulation. Thus, the basolateral complex is anatomically situated to integrate information from a variety of uni- and polymodal sensory areas, and much of the information processed by the basolateral complex is either relayed back to afferent structures or sent to the central nucleus of the amygdala and relayed to the brainstem.

Regarding the morphology of basolateral amygdaloid neurons, anatomical studies have revealed three classes of neurons. Class I neurons are large, spiny pyramidal cells (McDonald, 1984) that are immunoreactive for glutamate (LeDoux and Farb, 1991) and glutamate receptors (McDonald, 1994; Farb et al., 1995). Class II and III neurons are smaller, spine-sparse stellate cells and neurogliaform cells, respectively, that are immunoreactive for both γ-aminobutyric acid (GABA) and a variety of neuropeptides (McDonald, 1984, 1985a,b; McDonald and Pearson, 1989). Combined morphological and electrophysiological studies suggest that the spiny neurons are glutamatergic projection cells, whereas the aspiny neurons are GABAergic interneurons (Washburn and Moises, 1992a; Rainnie et al., 1993; Sugita et al., 1993). For example, class I and II neurons differ in both passive membrane properties and firing frequency. Compared to class I cells, class II neurons tend to have higher input impedances, greater firing rates, and less spike accommodation (i.e., their firing rate does not decrease appreciably during an extended membrane depolarization). The high, non-accommodating pattern of spike firing in class II neurons may be because of the absence of a slow afterhyperpolarization (sAHP) following the action potential in class II cells (Washburn and Moises, 1992a). Collectively, the properties exhibited by class I and class II neurons are typical of those exhibited by pyramidal neurons and inhibitory interneurons, respectively, in other brain areas.

Central Nucleus

The central nucleus subsystem of the amygdala appears to be the primary route by which the basolateral complex influences hypothalamic, pontine, and medullary regions involved in autonomic regulation during fear conditioning. Consisting of medial and lateral areas, the anatomy of the central nucleus is fundamentally different from that of the nuclei in the basolateral complex. Neurons in the lateral central nucleus are medium-sized, spiny neurons, exhibiting substantial immunoreactivity for GABA and neuropeptides (Cassell et al., 1986; Cassell and Gray, 1989; McDonald, 1989; Sun and Cassell, 1993). These neurons project to large output neurons in the medial central nucleus (Sun et al., 1994). In general, neurons in the central nucleus exhibit higher input impedances than those in the basolateral complex (Davis et al., 1994). Additionally, medial, but not lateral, central nucleus neurons exhibit a sAHP following spike firing (Schiess et al., 1993).

Unlike the nuclei of the basolateral complex, the central nucleus receives most of its afferent input from the midbrain (e.g., parabrachial nucleus and periaqueductal gray) (Veenig, 1978b; Ottersen, 1981; Rizvi et al., 1991; Bernard et al., 1993) and hindbrain (nucleus of the solitary tract) (Norgren, 1976; Ottersen, 1981), although the central nucleus also receives a input from frontal cortical areas (Veenig, 1978a; Ottersen, 1982). The mid- and hindbrain pathways primarily carry autonomic and nociceptive information to the central nucleus (e.g., Bernard and Besson, 1990). However, this information is not conveyed to other amygdaloid nuclei because the central nucleus lacks such intra-amygdaloid projections (Krettek and Price, 1978b). The primary efferent projections of the central nucleus are directed rostrally to the bed nucleus of the stria terminalis, frontal cortex, and lateral hypothalamus, and caudally to reciprocate projections from mid- and hindbrain areas (e.g., Cassell et al., 1986). Thus, the central nucleus sends and receives projections from areas that are involved in

generating cardiovascular, respiratory, and somatic responses to fear-eliciting stimuli (Kapp et al., 1982; LeDoux et al., 1988). Collectively, these data reveal two distinct amygdaloid subsystems that represent areas of sensory convergence (basolateral complex) and response divergence (central nucleus), respectively.

Synaptic Transmission in the Amygdala

The neuroanatomical work described above reveals an array of synaptic input to the basolateral and central amygdala. Insofar as these connections are required for the acquisition and expression of conditional fear, it is important to understand the physiology and pharmacology of synaptic transmission in these circuits. Indeed, important details concerning the nature of synaptic transmission in the amygdala are now beginning to emerge.

The functional nature of synaptic connections in the amygdala has now been demonstrated in a number of studies using electrophysiological recording techniques in vivo. For example, action potential discharge (hereafter referred to as "unit activity") in basolateral complex neurons can be driven by electrical stimulation of a variety of amygdaloid afferents, including the medial geniculate body (Clugnet et al., 1990; Mello et al., 1992a; Romanski et al., 1993), basal forebrain (Mello et al., 1992a), hippocampal formation (Morrison and Poletti, 1980; Brothers and Finch, 1985; Mello et al., 1992a; Maren and Fanselow, 1995), and temporal neocortex (Le Gal La Salle and Ben-Ari, 1981; Prelevic et al., 1976). In addition to exciting amygdaloid neurons, afferent stimulation has also been noted to inhibit unit activity in the basolateral amygdala (Morrison and Poletti, 1980; Le Gal La Salle and Ben-Ari, 1981; Mello et al., 1992b). Stimulation of central nucleus afferents produces similar effects on unit activity (e.g., Prelevic et al., 1976; Bernard and Besson, 1990).

The ability of afferent electrical stimulation to modulate neuronal activity in the amygdala suggests the existence of functional synaptic transmission in amygdaloid circuits. In support of this, Finch and colleagues have used intracellular recording techniques to measure stimulus-evoked synaptic potentials in amygdaloid neurons in vivo (Brothers and Finch, 1985; Mello et al., 1992a). Consistent with the anatomical work described above, it was found that single neurons in the basolateral complex received convergent input from the thalamus, basal forebrain, and hippocampal formation. Stimulation of the hippocampal formation, for example, produced both excitatory and inhibitory postsynaptic potentials (EPSPs and IPSPs) in basolateral amygdaloid neurons. Typically, the responses occurred in EPSP-IPSP sequences. Excitatory responses were evoked at a short latency and were presumably evoked by monosynaptic projections. Recordings in candidate inhibitory interneurons suggested that the longer latency IPSPs were mediated by feed-forward inhibition. Corresponding pharmacological work confirmed that hippocampal projections to amygdaloid inhibitory interneurons and principal cells were glutamatergic, and that the feed-forward projections from interneurons to principal cells were GABAergic (Mello et al., 1992b).

Amino Acid Neurotransmitters in the Amygdala

Although intracellular recordings in vivo have provided insight into the mechanisms of synaptic transmission in the amygdala, this technique is not optimal for fine-grained studies of synaptic physiology and pharmacology. However, the recent development of in vitro amygdala slice preparations (e.g., Gean and Shinnick-Gallagher, 1987; Chapman et al., 1990) has provided the necessary tools to further elucidate the mechanisms of amygdaloid synaptic transmission. Confirming the earlier in vivo work, intracellular recordings in the basolateral nucleus in vitro have revealed both excitatory and inhibitory synaptic transmission following afferent stimulation (Chapman et al., 1990; Rainnie et al., 1991a,b; Gean and

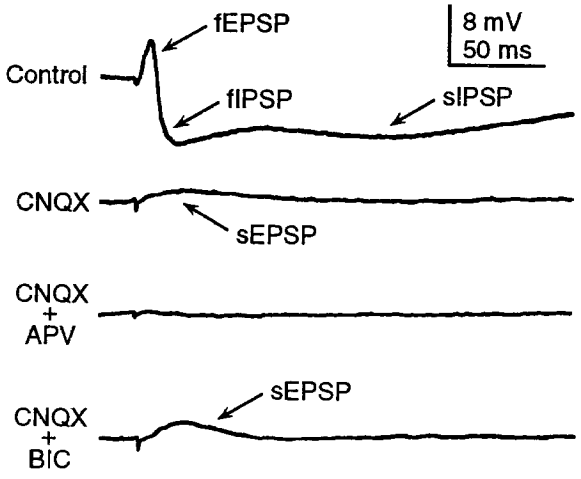

Fig. 2. Synaptic responses recorded in amygdala neurons in vitro. **(A)** Under control conditions, stria terminalis stimulation evokes a multiphasic response in amygdaloid neurons consisting of excitatory and inhibitory components. **(B)** Application of CNQX (an AMPA receptor antagonist) to the bathing medium eliminates the fast excitatory postsynaptic potential (EPSP), both the fast and slow inhibitory postsynaptic potentials (IPSPs), and reveals the existence of a slow EPSP. The elimination of the IPSPs by CNQX suggests that they are generated by feed-forward inhibition. **(C)** Both the fast and slow EPSPs are eliminated by a combination CNQX and APV (an NMDA receptor antagonist). **(D)** The slow EPSP is more prominent in the presence of both CNQX and bicuculline (a $GABA_A$ receptor antagonist). These data indicate that fast and slow EPSPs are mediated by AMPA and NMDA receptors, respectively (adapted from Rainnie et al. [1991]).

Chang, 1992; Washburn and Moises, 1992b). Specifically, electrical stimulation of the lateral nucleus, external capsule, endopiriform nucleus, or stria terminalis was shown to produce both EPSPs and IPSPs in neurons of the basolateral amygdala. As shown in Fig. 2, both types of synaptic response contained fast and slow components. Pharmacological experiments indicated that these responses were mediated by glutamate and GABA receptors. Thus, fast EPSPs were blocked by 6-cyano-7-nitro-quinoxaline-2, 3-dione (CNQX), an antagonist of the AMPA subclass of glutamate receptors, and slow EPSPs were blocked by D,L-2-amino-5-phosphonovalerate (APV), an antagonist of the NMDA subclass of glutamate receptors. In contrast, fast IPSPs were blocked by a $GABA_A$ receptor antagonist (bicuculline) and slow IPSPs were blocked by a $GABA_B$ receptor antagonists (saclofen). Pharmacological experiments in vivo have confirmed that excitatory responses in the basolateral complex are mediated by glutamate receptors (Mello et al., 1992b; Li et al., 1995; Maren and Fanselow, 1995) and that inhibitory responses are mediated by GABA receptors (Mello et al., 1992b). Similar results have been reported for excitatory and inhibitory synaptic responses evoked in the central nucleus following stimulation of the basolateral nucleus (Nose et al., 1991). Altogether, these data indicate that glutamatergic projections synapse on both principal neurons (class I) and inhibitory interneurons (class II), and inhibitory interneurons, in turn, send feed-forward GABAergic projections to principal neurons. This type of feed-forward inhibitory circuit is typical of that found in both the neocortex and hippocampus.

In addition to generating fast excitatory responses in amygdaloid neurons, glutamate receptors have also been reported to generate inhibitory responses in the amygdala. Specifically, membrane hyperpolarization has been reported following application of (±)*trans*-1-aminocyclopentane-1,3-dicarboxylic acid (ACPD), an agonist of metabotropic glutamate receptors (mGluRs) (Rainnie et al., 1994). Metabotropic glutamate receptors differ from ionotropic glutamate receptors (e.g., AMPA and NMDA receptors) insofar as the former are coupled to G-protein-mediated second messenger systems, whereas the latter directly gate transmembrane ionic conductances. The inhibitory effects of ACPD occurred in the presence of both GABA and glutamate receptor antagonists, suggesting that postsynaptic mGluRs mediated the hyperpolarization. In addition to generating postsynaptic hyperpolarization, ACPD has also been reported to inhibit presynaptic glutamatergic transmission, presumably through activation of a presynaptic autoreceptor (Rainnie and Shinnick-Gallagher, 1992). Thus,

glutamate receptors can produce both excitatory and inhibitory actions in the amygdala, and the degree of ionotropic and metabotropic receptor activation is likely to be an important determinant of amygdaloid cell excitability.

Other Neurotransmitters and Neuromodulators in the Amygdala

Although glutamate and GABA provide the principal sources of synaptic transmission in the amygdala, other neurotransmitter systems have been reported to influence amygdala neurons. For instance, membrane hyperpolarization in basolateral complex neurons has been reported following the application of μ opioid receptor agonists (Sugita and North, 1993). Similarly, inhibition of presynaptic transmission in the basolateral complex has been reported following application of the cytokine interleukin-1β (Yu and Shinnick-Gallagher, 1994), μ and δ opioid receptor agonists (Sugita and North, 1993; Sugita et al., 1993), $GABA_B$ antagonists (Asprodini et al., 1992), and the acetylcholinesterase inhibitor tetrahydro-9-aminoacridine (Wang et al., 1995).

Other neurotransmitters have been found to increase the excitability of neurons in the amygdala. For example, muscarinic acetylcholine receptor agonists (e.g., carbachol) have been reported to produce membrane depolarizations through an inhibition of muscarinic-sensitive M-currents (I_M) and potassium leak conductances (Womble and Moises, 1992). Carbachol also decreases spike accommodation in basolateral complex neurons, an effect that is a result of the inhibition of the sAHP (Womble and Moises, 1993a,b). Similar inhibition of the sAHP has been reported in both basolateral and central nucleus neurons following application of corticotropin releasing factor (CRF) (Rainnie et al., 1992). In the central nucleus, however, the increased cell excitability produced by CRF-induced sAHP inhibition was offset by a commensurate membrane hyperpolarization (Rainnie et al., 1992). Noradrenergic transmission has also been implicated in modulating amygdaloid cell excitability. Specifically, β-adrenergic receptor agonists (e.g., isoproterenol) decrease sAHPs and produce consequent reductions in spike accommodation in basolateral amygdaloid neurons (Huang et al., 1994, 1996). The actions of β-adrenergic receptor agonists were not limited to the postsynaptic membrane, because isoproterenol also increased synaptic transmission by enhancing presynaptic calcium influx (Gean et al., 1992; Huang et al., 1996). In other work, serotonin has been reported to act as a fast neurotransmitter in the amygdala (Sugita et al., 1992). In sum, pre- and postsynaptic activity in the amygdala is modulated by a number of compounds, including acetylcholine, GABA, opioids, neuropeptides, norepinephrine, and serotonin.

The elucidation of the pharmacology of synaptic transmission in the amygdala has provided important information regarding the pharmacology of fear conditioning (e.g., Davis et al., 1994). For example, as will be discussed in more detail below, it has recently been demonstrated that glutamate receptor antagonists attenuate the acquisition and expression of fear conditioning (Miserendino et al., 1990; Campeau et al., 1992; Jerusalinsky et al., 1992; Fanselow and Kim, 1994; Liang et al., 1994). Moreover, modulation of GABA, opioid, noradrenergic, and cholinergic systems in the amygdala can either enhance or impair aversive learning (for an excellent review *see* McGaugh, 1989). Studies of synaptic transmission in the amygdala have, therefore, provided critical information regarding the pre- and postsynaptic loci for memory–modulating drug effects.

Synaptic Plasticity in the Amygdala

Anatomical, pharmacological, and physiological studies have disclosed important details concerning the intrinsic and extrinsic wiring of amygdaloid circuits. Given the involvement of these circuits in fear conditioning, it is of considerable interest to determine if synaptic transmission in the amygdala is plastic (i.e., modifiable), and, if so, whether synap-

tic plasticity in the amygdala accompanies fear conditioning. Historically, these sorts of issues have been addressed in the hippocampus where the physiology and pharmacology of synaptic transmission and synaptic plasticity are well-characterized. However, the recent anatomical, pharmacological, and physiological characterization of synaptic connections in the amygdala now permits the analysis of plasticity in these circuits and the relationship of this plasticity to behavioral learning and memory.

Before reviewing the evidence for synaptic plasticity in the amygdala, I will first provide a brief description of the nature and properties of synaptic plasticity in other neural circuits, particularly the hippocampus (for extensive reviews on these issues *see* Brown et al., 1988; Bliss and Collingridge, 1993; Maren and Baudry, 1995; Nicoll and Malenka, 1995). This brief introduction will serve to orient the reader to the sorts of plasticity mechanisms that will be examined in the amygdala.

Forms of Synaptic Plasticity

In general, synaptic plasticity in the mammalian CNS is typically observed under conditions of repetitive activation of excitatory afferents. Several forms of synaptic plasticity have been identified and are classified according to their decay time-course (*see* Zucker, 1989). Thus, facilitation and posttetanic potentiation (PTP) are relatively short-lived (<5 min) forms of synaptic enhancement that are produced by repetitive afferent stimulation. Facilitation can be induced by delivering as few as two closely spaced stimulus pulses (e.g., 50 ms interstimulus interval), whereas PTP is produced by brief trains (20 ms) of high-frequency stimulation (100–400 Hz). Repetitive high-frequency stimulation also induces another enduring form of synaptic plasticity termed LTP. In the hippocampus, LTP has been observed to last for days in vivo, and has captured considerable interest as a possible synaptic memory mechanism. The expression mechanisms for these short- and long-term plasticity mechanisms are different. Paired-pulse facilitation (PPF) and PTP are mediated by a presynaptic increase in neurotransmitter release, whereas LTP may involve both increases in neurotransmitter release and increases in postsynaptic sensitivity to that transmitter. In addition to increases in synaptic transmission, long-term decreases in synaptic transmission (i.e., long-term depression or LTD) have been reported in several brain areas following extensive low-frequency (1–5 Hz) afferent stimulation. Thus, synaptic efficacy in the CNS can be either increased or decreased by different patterns of afferent stimulation.

Synaptic Enhancement in the Amygdala

The first indication that amygdaloid circuits exhibit physiological plasticity was reported in a series of studies by Racine and colleagues (Racine and Milgram, 1983; Racine et al., 1983). These investigators used electrical stimulation and extracellular field potential recordings to measure neural transmission in a variety of forebrain pathways in vivo. The results indicated that extracellular field potentials in the amygdala (the exact region of the amygdala in which the recordings were made was not specified) evoked by stimulation of the hippocampal formation or piriform cortex exhibited both short- and long-term forms of plasticity. Thus, paired-pulses or short trains of low-frequency stimulation (10–40 Hz) produced a short-lived (<1 min) facilitation of the field potentials. In contrast, short trains of high-frequency (400 Hz) stimulation produced an LTP of the field potentials that lasted up to 24 h. A long-term enhancement of extracellular field potentials has more recently been reported in projections from the medial geniculate body to the lateral nucleus in vivo (Clugnet and LeDoux, 1990; Rogan and LeDoux, 1995).

In a similar line of work, I have examined both short- and long-term synaptic plasticity in the basolateral complex in vivo (Maren and Fanselow, 1995). Using anesthetized rats, I first characterized extracellular field potentials in the basolateral complex following single-pulse stimulation of afferents from the hippocampal

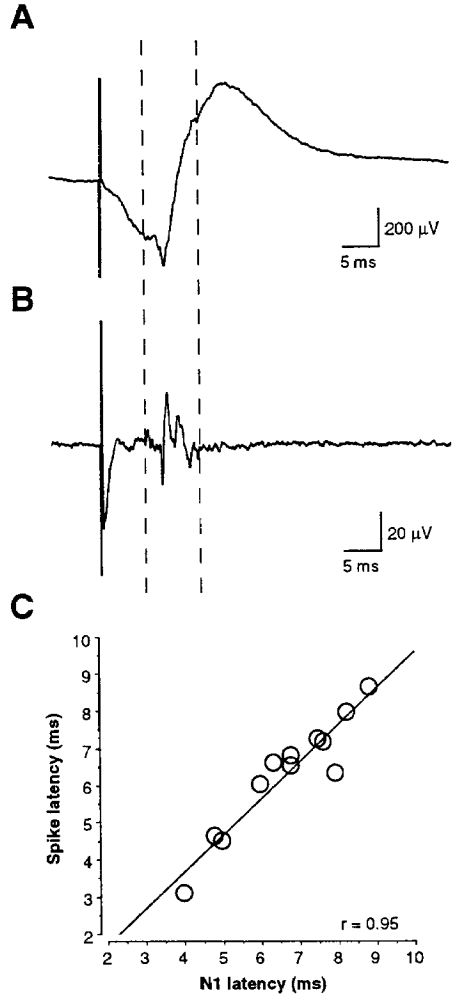

Fig. 3. Extracellular field potentials in the basolateral amygdala (BLA) evoked by hippocampal formation stimulation in vivo. **(A)** A typical field potential evoked in the BLA by single-pulse stimulation of the ventral angular bundle (VAB), and **(B)** the corresponding unit record. Waveforms are averages of five evoked responses. The dashed lines are drawn to emphasize the temporal correlation between the peak negativity of the field potential (N_1) and unit discharge. **(C)** Linear correlation between spike latency and N_1 latency in 12 rats. The Pearson correlation coefficient is displayed in the graph (adapted from Maren and Fanselow [1995]).

formation. Fig. 3A shows a representative field potential recorded in the basolateral nucleus following stimulation of the ventral angular bundle (VAB), which carries efferents from the hippocampus to the amygdala. The corresponding unit recording (Fig. 3B) indicates that short-latency spike firing was temporally correlated with the negative deflection (N_1) of the extracellular field potential, suggesting that N_1 is a population spike (synchronous, stimulus-evoked spike firing). The correlation of the latencies to spike firing and peak N_1 amplitude is shown in Fig. 3C. The underlying excitatory synaptic conductances that generate population spike firing are reflected in N_1 slope. Although difficult to determine in vivo, pharmacological manipulations suggested that the VAB-evoked field potentials were generated by local synaptic activity in the amygdala. That is, infusions of either lidocaine (a local anesthetic) or glutamate receptor antagonists (DNQX and APV) substantially reduced the amplitude of the amygdaloid field potentials. Specifically, whereas lidocaine and DNQX reduced both N_1 slope and N_1 amplitude, APV only affected N_1 amplitude. This suggests that NMDA receptors are involved in regulating cell excitability in the basolateral nucleus (also *see* Rainnie et al., 1991a), whereas AMPA receptors are required for fast synaptic transmission.

Having characterized synaptic transmission between the hippocampal formation and the basolateral amygdala, I then examined the ability of this pathway to exhibit synaptic plasticity. As shown in Figs. 4A,B, VAB-evoked field potentials exhibited paired-pulse facilitation with short interpulse intervals (10–50 ms). This facilitation was short-lived and decayed in less than 20 s. In contrast, high-frequency stimulation of the VAB induced a long-term enhancement of amygdaloid field potentials that persisted for the duration of the recording session (1 h; Fig. 4C). As in the hippocampus, LTP induction in the VAB-amygdala pathway was blocked by intra-amygdala infusion of the NMDA receptor antagonist, APV (Maren and Fanselow, 1995), an effect that may have been because of the reduction in cell excitability produced by APV. These results indicate that amygdaloid neurons exhibit both short- and long-term synaptic plasticity following repetitive afferent stimulation.

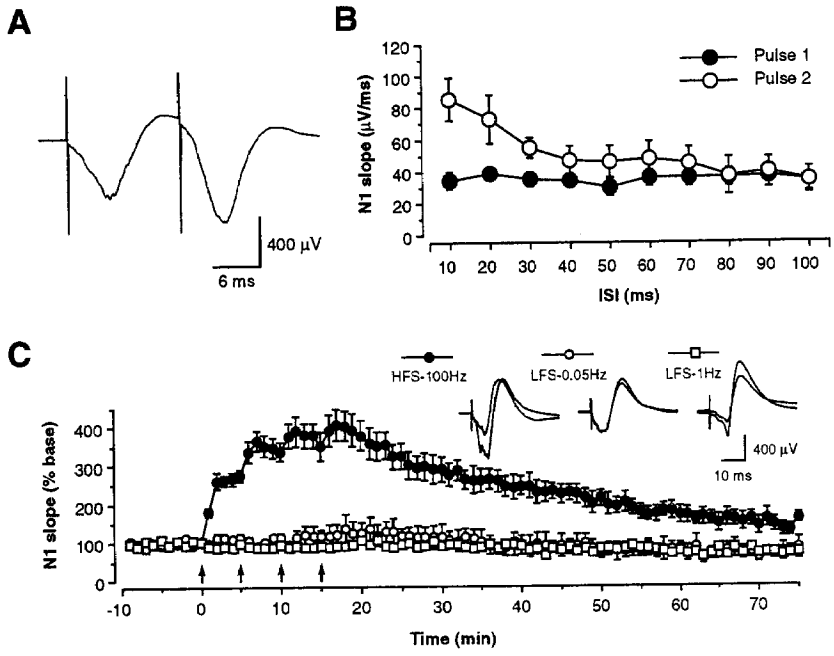

Fig. 4. Short- and long-term synaptic plasticity in the BLA *in* vivo. **(A,B)** Paired-pulse facilitation (PPF) of VAB-evoked field potentials in the BLA with an interstimulus interval (ISI) of 20 ms. The mean (± SEM) N_1 slope of field potentials evoked by each pulse of the pair (pulse 1, filled circles; pulse 2, open circles) for a series of ISIs is shown in **(B)**. PPF occurred at ISIs between 10 and 50 ms. This plasticity was short-lived, decaying during the 20 s interval between paired-pulses. **(C)** Mean (± SEM) N_1 slope (percentage of baseline) of BLA field potentials for rats receiving either high- or low-frequency stimulation. The arrowheads indicate the delivery of stimulation trains. LTP of BLA field potentials occurred in rats receiving high-frequency VAB stimulation (ten 200-ms bursts of 100 Hz stimulation at 1 Hz [a total of 200 pulses]; HF: 100 Hz, filled circles), whereas field potentials in groups receiving either test pulses alone (LF: 0.05 Hz, open circles) or 1 Hz stimulation (200 pulses; LF: 1 Hz, open squares) did not change. (Inset) Field potentials from representative subjects in each of the three groups; pre- and post-stimulation responses are superimposed. The field potentials are averages of 30 responses recorded either 10 min before or 10 min after the last stimulation train adapted from Maren and Fanselow [1995]).

Although in vivo studies indicate that repetitive afferent stimulation increases the amplitude of amygdaloid field potentials, one could argue that these changes are due an increase in neuronal excitability rather than enhanced synaptic transmission *per se*. Nonetheless, in vitro work has confirmed that amygdaloid neurons exhibit synaptic LTP. In a seminal paper, Brown and colleagues used intracellular recording techniques to isolate synaptic potentials in amygdaloid neurons in vitro (Chapman et al., 1990). These investigators then demonstrated that high-frequency stimulation of the external capsule, a fiber tract that presumably carries cortical afferents to the basolateral complex, produced a sustained enhancement of intracellular EPSPs in over 80% of the basolateral amygdaloid neurons tested. Following a rapidly decaying PTP, synaptic LTP in the amygdala persisted for the 20 min recording period following the tetanus.

In agreement with this study, synaptic LTP in projections from the external capsule to the basolateral complex has also been demonstrated using extracellular field potential recordings in vitro (Watanabe et al., 1995a). Other experiments have confirmed the existence of LTP in projections from the endopiriform nucleus to the basolateral complex (Gean et al., 1993a,b) and stria terminalis projections to the

medial and central nuclei (Shindou et al., 1993; Watanabe et al., 1995a). Hence, the long-term enhancement of intracellular EPSPs in putative monosynaptic connections provides strong evidence that neurons in the amygdala exhibit forms of long-term synaptic plasticity that have been observed in such brain areas as the hippocampus.

Mechanisms of LTP Induction and Expression in the Amygdala

Following the initial reports of LTP in the amygdala, a number of subsequent studies have characterized the mechanisms of induction and expression of amygdaloid LTP. In the hippocampus, LTP induction requires the activation of NMDA receptors, which is brought about by coincident presynaptic activity and postsynaptic depolarization. To ascertain the role of NMDA receptors in the induction of amygdaloid LTP, Chapman and Bellavance (1992) examined the effects of APV on LTP induction in the basolateral complex in vitro. In these experiments it was found that APV (50 μM), which typically blocks LTP in the hippocampus, did not block LTP of intracellular EPSPs in the amygdala following high-frequency stimulation of the external capsule. In contrast, higher doses of APV (100 μM) did prevent LTP induction, although this effect may have been mediated by an action of APV at nonNMDA receptors. Consistent with these results, it has been reported that APV does not block LTP of extracellular field potentials in the lateral nucleus following external capsule stimulation (Watanabe et al., 1995a).

Although NMDA receptor activation is apparently not required for LTP induction in external capsule projections to the lateral nucleus, projections from the endopiriform nucleus to the basolateral nucleus do exhibit NMDA receptor-dependent LTP (Gean et al., 1993a). Similarly, APV has been found to block LTP in either the medial or central nucleus following stria terminalis stimulation (Shindou et al., 1993; Watanabe et al., 1995a). Moreover, as mentioned above, I have found that APV blocks LTP in hippocampal projections to the basolateral nucleus in vivo (Maren and Fanselow, 1995). Taken together, the extent to which LTP in the amygdala requires NMDA receptor activation seems to depend on the particular pathway and nucleus under study.

In contrast to the involvement of NMDA receptors in amygdaloid LTP, recent data indicate a more general role for cholinergic systems in this form of synaptic plasticity. Specifically, it has been reported that LTP induction in the both the lateral and medial nuclei is blocked by scopolamine, a muscarinic acetylcholine receptor antagonist (Watanabe et al., 1995a). These results are interesting insofar as LTP in the hippocampus is typically not affected by cholinergic antagonists (e.g., Abe et al., 1994; Stringer, et al., 1983). Nevertheless, the involvement of muscarinic acetylcholine receptors in amygdala LTP induction may be related to the important role these receptors have in regulating neuronal excitability in the basolateral complex (*see above*; Womble and Moises, 1992, 1993a,b).

Once LTP is induced, the mechanisms that express LTP over long periods of time are controversial (*see* Maren and Baudry, 1995; Nicoll and Malenka, 1995). In the hippocampus, evidence for both presynaptic increases in neurotransmitter release and postsynaptic changes in AMPA receptors has been reported. Thus far, the locus of expression of amygdaloid LTP has only been addressed in one experiment. To assess the possibility that amygdaloid LTP expression is associated with an increase in neurotransmitter release probability, I examined PPF before and after LTP induction in the basolateral complex in vivo. Because PPF is a result of an increase in transmitter release probability during the second pulse of the paired-pulses, a manipulation that increases release probability was expected to decrease PPF (e.g., Zalutsky and Nicoll, 1990). As shown in Fig. 5, LTP in the amygdala was associated with a sustained decrease in PPF, suggesting that amygdaloid LTP is expressed, at least in part, by an increase in presynaptic neurotransmitter release. In support of this, nitric oxide synthase

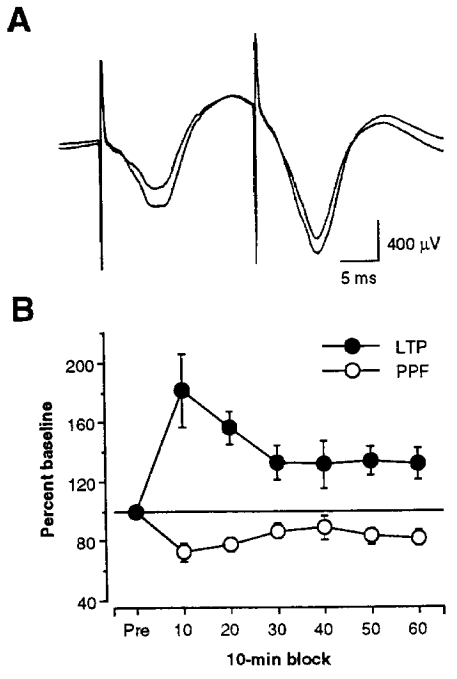

Fig. 5. Simultaneous measurement of PPF and LTP of VAB-evoked responses in the basolateral amygdala. **(A)** Representative field potentials in the BLA evoked by pairs of pulses (20 ms ISI) before and after LTP induction (pre- and post-LTP responses are superimposed). Waveforms are averages of five evoked responses. Note the relatively greater potentiation of the N_1 response to the first pulse compared to the second pulse. **(B)** Mean (± SEM) N_1 slope (percentage of baseline, solid circles) and pulse ratio (pulse 2/pulse 1 as a percentage of baseline, open circles) for the 10-min blocks during the recording session. Paired-pulses (20 ms ISI) were used as the test stimuli to permit the simultaneous assessment of both PPF and LTP. High-frequency stimulation (HFS; ten 200-ms bursts of 100 Hz stimulation at 1 Hz) was delivered following the 10 min pre-HFS period (Pre). HFS induced reliable LTP that persisted for the duration of the recording session. The induction of LTP was associated with a correlated decrease in the magnitude of PPF. This decrease in PPF was greatest in the first post-HFS block, which corresponds to a period when presynaptic posttetanic potentiation is maximal adapted from Maren and Fanselow [1995]).

inhibitors, which eliminate the production of putative retrograde messengers that are thought to increase presynaptic transmitter release, prevent LTP induction in the medial amygdaloid nucleus (Watanabe et al., 1995b). As an alternative to a presynaptic mechanism, however, the decrease in PPF may have resulted from the addition of postsynaptic AMPA receptors to previously silent high-probability synapses (Maren et al., 1993; Liao et al., 1995). Thus, although the decrease in PPF following LTP induction in the amygdala is suggestive of a presynaptic change, further experiments are required to determine the role of postsynaptic factors in amygdaloid LTP expression.

Synaptic Depression in the Amygdala

Unlike potentiation phenomena, there are relatively few reports of synaptic depression in the amygdala. In the basolateral complex, I have observed that 3 min of low-frequency stimulation (1 Hz) produces a transient depression of population spike (N_1) amplitude, but has no effect on N_1 slope of VAB-evoked field potentials (Maren and Fanselow, 1995). Similarly, I have observed a short-lasting paired-pulse depression of a late component of the evoked field potential at short interpulse intervals (20 ms). Consistent with this, Huang and Gean (1994) have also observed paired-pulse depression of a slow, NMDA receptor-mediated current in the amygdala in vitro, although their depression effect was observed at interstimulus intervals ranging from 100 to 2000 ms. To date, there are no reports of LTD of synaptic transmission in the amygdala.

Amygdaloid Synaptic Plasticity and Learning

As described above, lesion studies suggest that the amygdala is a critical locus of plasticity during fear conditioning. In support of this, I have recently reported that neurotoxic lesions in the basolateral complex disrupt the expression of conditional fear when made up to 1 mo following training (Maren et al., 1996). This suggests that the basolateral complex may be the storage site for aversive memories. The view that the amygdala is a locus of plasticity

during aversive learning is further supported by electrophysiological studies of amygdala unit activity during learning. For instance, it has long been known that neurons in the amygdala preferentially respond to conditional reinforcers (Fuster and Uyeda, 1971; Sanghera et al., 1979).

Consistent with physiological plasticity in the amygdala, more recent studies have revealed that neurons in the amygdala acquire associative firing patterns during fear conditioning and other forms of aversive learning. For instance, the pioneering studies of Kapp and colleagues have revealed that the acquisition of conditional heart rate responses in rabbits is associated with associative neuronal firing in the central nucleus of the amygdala (Applegate et al., 1982; Pascoe and Kapp, 1985). In this case, multiple-unit firing in the central nucleus was greater to an auditory CS that predicted periorbital shock, compared to a different CS that did not predict shock. Similarly, I have reported that the acquisition of a conditional avoidance response in rabbits is accompanied by associative neuronal activity in the basolateral nucleus of the amygdala (Maren et al., 1991). Again, multiple-unit firing was greater to an auditory CS that was paired with footshock compared to a different CS that was not paired with shock. In a more detailed analysis, LeDoux and colleagues have shown that single-unit activity recorded from several neurons in the lateral nucleus of the amygdala exhibits learning-related activity during Pavlovian fear conditioning in rats (Quirk et al., 1995). That is, compared to a preconditioning baseline, lateral nucleus neurons exhibited robust, associative increases in firing to an auditory CS that previously had been paired with footshock. The development of cue-elicited associative unit activity in the amygdala has also been observed with appetitive reinforcers (Muramoto et al., 1993; Ono et al., 1995; Uwano et al., 1995).

Clearly, the amygdala is a locus for neuronal plasticity during fear conditioning. It is tempting to speculate that the development of learning-related patterns of neuronal firing in the amygdala and the acquisition of conditional fear require the sorts of synaptic plasticity mechanisms described above. Indeed, the existence of both short- and long-term forms of synaptic plasticity in the amygdala suggests that the amygdala possesses some of the tools one would imagine are required for learning and remembering fearful events. At present, however, there is only indirect evidence for an involvement of amygdaloid synaptic plasticity in fear conditioning. These data are described below.

Glutamate Receptor Antagonists and Aversive Learning

The most common strategy for assessing the role of LTP in learning has been to examine the effects of NMDA receptor antagonists on the behavioral task of interest. To the extent that NMDA receptor antagonists prevent LTP induction without affecting basal synaptic transmission (at least in the hippocampus), it has been assumed that those behavioral tasks that are sensitive to NMDA receptor antagonists also require LTP. Regarding fear conditioning, a number of laboratories have now demonstrated that the infusion of NMDA receptor antagonists into the amygdala prevents the acquisition of conditional fear (Miserendino et al., 1990; Campeau et al., 1992; Fanselow and Kim, 1994). Application of NMDA receptor antagonists to the amygdala also blocks the acquisition of inhibitory avoidance conditioning, another fear-motivated task (Jerusalinsky et al., 1992; Kim and McGaugh, 1992; Liang et al., 1994). In general, infusion of NMDA receptor antagonists into the amygdala does not appear to block the expression of conditional fear (Miserendino et al., 1990; Campeau et al., 1992; *see also* Kim and McGaugh, 1992; Liang et al., 1994), although infusion of AMPA receptor antagonists into the amygdala blocks both the expression of conditional fear (Kim et al., 1993) and the acquisition of inhibitory avoidance conditioning (Jerusalinsky et al., 1992).

Inasmuch as LTP in the amygdala requires NMDA receptor activation, these studies suggest that the infusion of NMDA receptor

antagonists into the amygdala disrupts fear conditioning by preventing LTP induction. However, as we have seen, LTP induction in the amygdala does not necessarily depend on NMDA receptor activation (e.g., Chapman and Bellavance, 1992). Moreover, NMDA receptors in the amygdala appear to play a fundamental role in both basal synaptic transmission and neuronal excitability (Rainnie et al., 1991a; Li et al., 1995; Maren and Fanselow, 1995). These findings suggest that the effects of intra-amygdala infusion of NMDA receptor antagonists may be mediated by an NMDA receptor-mediated reduction in basal synaptic transmission or cell excitability, rather than a disruption of LTP *per se*. Indeed, I have recently shown that intra-amygdala infusions of APV at doses sufficient to attenuate both LTP induction and normal synaptic transmission in vivo impair both the acquisition and expression of Pavlovian fear conditioning (Maren, Aharonov, Stote, and Fanselow, in press). Because NMDA receptors are not typically required for the expression of LTP, these data suggest that the primary action of APV (at least at the doses used in behavioral experiments) is to attenuate synaptic transmission in the amygdala. Of course, the concurrent blockade of LTP and synaptic transmission produced by NMDA receptor antagonists are confounded in many behavioral experiments, so further study is required to determine if there are conditions under which NMDA receptor antagonists will block LTP induction while having minimal effects on normal synaptic transmission. Thus, although the available data indicate that NMDA receptors in the amygdala are required for the acquisition of conditional fear, it is not clear whether NMDA receptor-dependent LTP *per se* is required for this form of learning.

Amygdala LTP and Synaptic Potentials to Peripheral Stimuli

Another line of work that is suggestive of a role for amygdaloid LTP in learning involves the study of thalamo-amygdala synaptic transmission in vivo. Rogan and LeDoux (1995) have recorded extracellular field potentials in the lateral amygdaloid nucleus following either electrical stimulation of the medial geniculate body or peripheral auditory stimulation. Using this technique, these investigators have demonstrated that LTP induction in thalamo-amygdaloid projections is associated with a concomitant increase in the amplitude of auditory evoked potentials in the lateral nucleus (Rogan and LeDoux, 1995). Thus, artificially increasing synaptic strength in the thalamo-amygdala pathway augments the transmission of peripheral stimuli that use the potentiated pathway. Insofar as fear conditioning is associated with enhanced transmission through the thalamo-amygdala pathway, which is suggested by associative increases in auditory-evoked unit activity in the basolateral complex (Maren et al., 1991; Quirk et al., 1995), it is tempting to speculate that learning-related increases in thalamo-amygdala transmission are mediated by synaptic LTP in this circuit. It has yet to be demonstrated, however, that fear conditioning is actually associated with an increase in synaptic strength in CS pathways to the amygdala. Moreover, it has yet to be shown that blockade of synaptic plasticity in the amygdala prevents both conditioning and conditional changes in amygdaloid synaptic transmission and unit activity. Hence, these data hint at the mechanism whereby auditory transmission to the amygdala might be increased during fear conditioning, but further work is required to verify whether this mechanism is actually at work during learning.

Associative LTP as a Synaptic Mechanism for Pavlovian Fear Conditioning

Assuming that LTP in the amygdala is the synaptic mechanism for the acquisition of conditional fear, it is of interest to consider how such a mechanism might operate during learning. As was mentioned earlier, LTP induction in the hippocampus requires coincident pre- and postsynaptic activity. As a result, hippocampal LTP exhibits a property known as associativ-

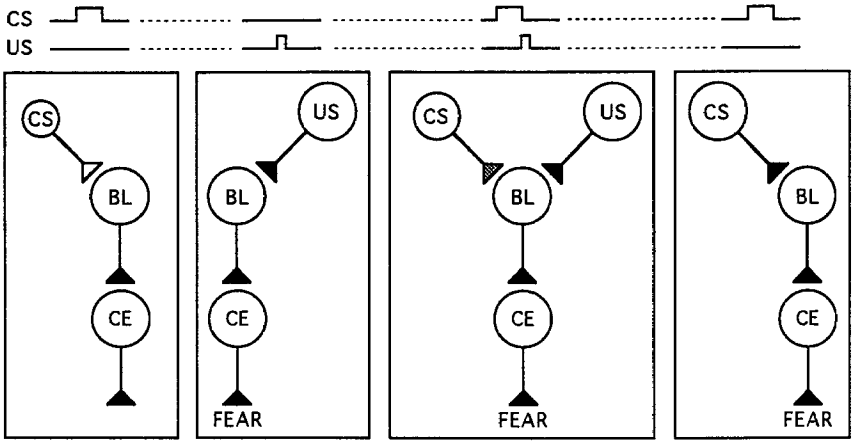

Fig. 6. Associative LTP as a model for Pavlovian fear conditioning. The figure illustrates the state of synaptic transmission in amygdaloid circuits before (left and center-left), during (center-right), and after (right) fear conditioning. The onset of CSs and USs is illustrated above each panel. Synaptic weight is indicated by both shading in the synaptic terminal (triangles; black = strong, gray = intermediate, white = weak) and cell body diameter (large = strong, small = weak). Before fear conditioning (left), synaptic transmission in the CS pathway is not sufficient to activate neurons in the basolateral complex (BL) and, in turn, the central nucleus of the amygdala (CE). Thus, the CS does not by itself elicit fear prior to training. In contrast, the US strongly activates the amygdaloid circuitry prior to CS-US pairing (center-left) and generates an unconditional fear response (UR). During CS-US pairings (center-right), the strong depolarization produced by the US pathway permits the establishment of LTP at synapses in the CS pathway. Following CS-US pairing (right), associative LTP in the CS pathway allows it to strongly activate the BL and CE to produce a conditional fear response (CRs).

ity (Barrionuevo and Brown, 1983; Kelso et al., 1986; Wigstrom and Gustafsson, 1986; Brown et al., 1990). Thus, LTP can be induced in "weak" synaptic pathways (which are normally not able to support LTP) if activity in these pathways is paired with activity in a "strong" pathway. Both the Hebbian and associative properties of LTP are a direct consequence of the physiological properties of NMDA receptors. That is, NMDA receptor activation requires both presynaptic glutamate release and strong postsynaptic depolarization, which removes the Mg^{2+} block of the channel and allows Ca^{2+} to flow into the postsynaptic cell. Thus, whereas the weak pathway can supply glutamate, it cannot produce sufficient postsynaptic depolarization to activate NMDA receptors and induce synaptic enhancement. This situation can be overcome, however, if the glutamate released in the weak pathway is paired with the postsynaptic depolarization produced by a strong pathway. The association of activity in the weak and strong pathways results in the strengthening of weak synapses, which ultimately enables the weak pathway to strongly activate the postsynaptic neuron(s).

As stated in the Introduction, it is generally believed that Pavlovian fear conditioning results in the formation of an association between the CS and the US. Although there is debate on this matter, there is considerable evidence that suggests that the CS-US association is both formed and stored at the locus of CS-US convergence in the amygdala. How might this come about? Consider the illustration in Fig. 6. Prior to fear conditioning, an auditory CS does not evoke a fear response. To the extent that amygdala neurons are required for the production of fear responses, it is assumed that the auditory CS pathway does not possess sufficient synaptic strength to induce these responses. On the other hand, the shock US readily generates fear responses, presumably by strongly activating amygdaloid neurons. Thus, it is apparent that the CS and US pathways are respectively

"weak" and "strong" regarding their ability activate amygdaloid neurons before conditioning. During training, however, activity in the weak CS pathway is paired with strong depolarization generated in the US pathway. It is through this temporal association of the CS and US that synapses in the CS pathway are potentiated, presumably through a mechanism akin to associative LTP. This potentiation enables the formerly weak CS pathway to produce strong activation of the amygdala and consequent fear responses following conditioning. Although this mechanism appears plausible, further studies are required to determine whether synaptic circuitry in the amygdala exhibits the sort of associative LTP that has been identified in the hippocampus.

Of course, such a simple model for relating amygdaloid synaptic plasticity to fear conditioning cannot account for the richness of learning phenomena in Pavlovian paradigms. Although associative LTP at a single synapse may be able to account for first- and second-order conditioning, for example, it cannot easily account for such phenomena as blocking, negative transfer, and latent inhibition, to name a few. Indeed, Diamond and Rose (1994) and Gallistel (1995) have raised doubts about the heuristic value of using the associative property of LTP as a model for classical conditioning. Among other things, these authors argue that the temporal properties of associative LTP induction are not congruent with optimal Pavlovian conditioning parameters. For example, Diamond and Rose (1994) point out that associative LTP can be established with either simultaneous or backward pairings of the weak and strong pathways, arrangements that typically do not support Pavlovian conditioning. However, whereas simultaneous or backward CS-US pairings fail to support conditioning in several Pavlovian conditioning paradigms, fear conditioning can be quite robust under these conditions (e.g., Heth and Rescorla, 1973). Moreover, even in cases where there is divergence between LTP induction and fear conditioning parameters, one can certainly imagine mechanisms in the brain that reunite temporally discontiguous events under conditions that will favor associative LTP. However, it is true that associative LTP cannot underlie all forms of Pavlovian conditioning, and that the optimal induction parameters for learning and associative LTP are different. Nonetheless, it seems worthwhile to carefully evaluate learning paradigms on a task-by-task basis to determine the extent to which synaptic plasticity mechanisms can account for the conditioning phenomena. And although there is currently no data available on the associative nature of LTP in the amygdala, there seems to be good correspondence between the properties of associative LTP in other neural systems and the properties expected of a cellular mechanism for fear conditioning (Fanselow, 1993; Maren and Fanselow, 1996).

Conclusions

The evidence reviewed here reveals that our knowledge of the anatomy, physiology, and pharmacology of synaptic circuits in the amygdala has progressed considerably in the last decade. Anatomical data indicate that the amygdala consists of two subsystems, the basolateral complex and central nucleus, which have unique cell types, afferent and efferent connectivity, and neurotransmitter systems. Evidence indicates that the basolateral complex is a locus for sensory convergence, whereas the central nucleus is a locus for motor divergence. As in other neural circuits, excitatory synaptic transmission in both the basolateral complex and central nucleus is mediated by AMPA and NMDA receptors, whereas feed-forward inhibitory synaptic transmission is mediated by $GABA_A$ and $GABA_B$ receptors.

Repetitive stimulation of excitatory, glutamatergic afferents induces both short- and long-term enhancements of synaptic transmission in the amygdala. In some cases, synaptic LTP in the amygdala requires NMDA receptor activation, although this appears to depend on the particular afferent pathway under study. Once induced, LTP (at least that in the baso-

lateral complex in vivo) may be mediated by an increase in presynaptic glutamate release. Pavlovian fear conditioning, which requires both the basolateral complex and central nucleus of the amygdala, may be mediated by synaptic plasticity mechanisms, such as LTP, insofar as intra-amygdala infusions of NMDA receptor antagonists prevent the acquisition of conditional fear. Consistent with this, transmission through auditory CS pathways to the amygdala is enhanced following amygdaloid LTP induction. Hence, associative LTP in CS pathways to the amygdala may be a synaptic mechanism for Pavlovian fear conditioning.

Although the available evidence supports a role for amygdaloid LTP in Pavlovian fear conditioning, further research is required to determine if amygdaloid circuits exhibit synaptic LTP during learning, if NMDA receptor antagonists prevent these neurophysiological changes, if the effects of NMDA receptor antagonists on learning are the result of impaired LTP or attenuated synaptic transmission, and whether amygdaloid LTP exhibits properties that are expected of a synaptic mechanism for fear conditioning. Answers to these questions should propel the emerging physiology of fear conditioning circuits.

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