Long-Term Potentiation As a Substrate for Memory: Evidence From Studies of Amygdaloid Plasticity and Pavlovian Fear Conditioning

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ABSTRACT: Recent reports have raised concerns about the ability of long-term potentiation (LTP) to account for associative learning and memory. In this paper, we review the many mechanistic similarities between one form of associative learning, Pavlovian fear conditioning, and amygdaloid LTP. We then address many of the criticisms levied against LTP within the framework of fear conditioning. We believe that many of the apparent discrepancies between LTP and behavior can be generally accounted for by a failure to appreciate that learned behavior is supported by multiple synapses in an extensive network of brain structures. We conclude that LTP remains a viable substrate for memory. *Hippocampus 2002;12:592–599.* © 2002 Wiley-Liss, Inc.

KEY WORDS: amygdala freezing; associative learning

INTRODUCTION

One of the most pervasive problems in neuroscience is determining how the brain represents and stores information about the environment. It is generally believed that memories are established by changing the connectivity of neurons, but the processes that produce alterations in neuronal connectivity are highly debated. One of the leading candidate mechanisms to emerge in recent decades is long-term potentiation (LTP). LTP is defined as a persistent increase in synaptic transmission after brief high-frequency stimulation of an afferent pathway. Aside from being more enduring than other forms of synaptic enhancement, such as heterosynaptic facilitation or sensitization (Kandel and Tauc, 1965), LTP exhibits several qualitative characteristics that make it an appealing model for cellular memory (Bliss and Collingridge, 1993; Maren and Baudry, 1995).

LTP was discovered in the rabbit hippocampus (Bliss and Gardner-Medwin, 1973; Bliss and Lømo, 1973), but it has since been characterized in a variety of structures in a number of species. For example, LTP has been studied in cat auditory thalamus (Gerren and Weinberger, 1983), rat cerebral cortex (Lee, 1982; Wilhite et al., 1986; Stripling et al., 1988; Laroche et al., 1990), goldfish optic tectum (Lewis and Teyler, 1986), rat olfactory bulb and cortex (Patneau and Stripling, 1992), rat amygdala (Racine et al., 1983; Clugnet and LeDoux, 1990; Maren and Fanselow, 1995), and human hippocampus (Beck et al., 2000). Insofar as LTP may subserve memory, its anatomical pervasiveness meshes well with the notion that a stimulus may have multiple representations throughout the brain (Mowrer, 1947; Squire, 1992).

Of the properties linking LTP to memory, cooperativity and associativity stand out as being particularly important. The property of cooperativity refers to the fact that a neuron must reach a threshold of depolarization before LTP can be induced (McNaughton et al., 1978). This property ensures that not every stimulus in the environment will result in a memory trace and that LTP cannot be induced by baseline neuronal activity. The property of associativity refers to the observation that pairing stimulation of a weak pathway with stimulation of a strong pathway results in facilitated synaptic transmission in both pathways (Kelso et al., 1986). This property is of particular interest because it is also a property of many simple forms of learning, such as Pavlovian conditioning, in which stimuli are associated with each other.

In addition to the qualitative characteristics shared between memory and LTP, there is a massive body of literature to suggest that hippocampus-dependent memories rely on many of the same cellular mechanisms as hippocampal LTP. Yet in spite of the many qualitative and mechanistic similarities between LTP and memory, numerous reviews have drawn attention to the difficulties of linking LTP to memory formation (Lynch et al., 1988; Diamond and Rose, 1994; Shors and Matzel, 1997; Lechner and Byrne, 1998; Sanes and Lichtman, 1999; Sweatt, 1999; Matzel and Shors, 2001). As the similarities between hippocampus-dependent memory and LTP are reviewed in depth elsewhere in this issue, they not reviewed in the present report. Instead, we introduce another memory system in which LTP and associative memories share numerous cellular mechanisms: amygdala-dependent Pavlovian fear conditioning. We review the characteristics common to both amygdaloid LTP and fear memories. We also address many of the criticisms levied against LTP as a cellular model of Pavlovian conditioning. Combined with the abundance of evidence supporting LTP as a form of synaptic plasticity underlying hippocampal memories, we hope to convince the reader that LTP is a viable cellular mechanism of memory formation within the mammalian brain.

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PROPERTIES OF CS-US ASSOCIATION IN THE AMYGDALA

Pavlovian conditioning paradigms are frequently used as model systems to study learning and memory because they are simpler than other types of associative learning paradigms. Moreover, the experimenter has vigorous experimental control over the stimulus contingencies. In a typical conditioning experiment, an animal is presented with an innocuous conditional stimulus (CS) that is immediately followed by a behaviorally significant unconditional stimulus (US). With successive presentations, the CS begins to elicit a number of conditional responses (CRs). Upon later presentation of the CS alone, these responses can be quantified and used as an index of long-term memory.

One conditioning paradigm that has become increasingly popular is Pavlovian fear conditioning in rats. Fear conditioning is elicited by pairing a neutral CS with an aversive US, such as mild footshock. Discrete cues such as lights or tones may serve as CSs, and the collective set of environmental cues (the "context") can also serve as an effective CS. After a single conditioning trial, the CS alone will elicit a constellation of fear CRs, including increases in heart rate and respiration, potentiated acoustic startle, and freezing (the cessation of all movement except that necessary for breathing). The fact that fear conditioning is rapidly acquired, retained for long periods of time, and easily quantified has made it an ideal task for studying learning and memory. Furthermore, the neural circuitry underlying Pavlovian fear conditioning has been well characterized (Fendt and Fanselow, 1999; Davis, 1997; LeDoux, 2000; Maren, 2001), facilitating the study of the cellular and molecular mechanisms underlying conditional fear memories.

In this regard, a large body of literature implicates the amygdala as having a critical role in both the acquisition and expression of the CS-US association formed during fear conditioning (Fendt and Fanselow, 1999; Davis, 1997; LeDoux, 2000; Maren, 2001). The amygdala is composed of several anatomically distinct nuclei, including, but not limited to, the lateral nucleus (LA), basolateral nucleus (BL), basomedial nucleus (BM), and central nucleus (CEA). The LA, BL, and BM collectively form a group of structures termed the basolateral complex (BLA).

It is generally acknowledged that the BLA is the critical locus of plasticity underlying the formation and storage of the CS-US association (Fanselow and LeDoux, 1999; Maren, 1999a, 2000a, 2001; but see Vazdarjanova and McGaugh, 1998; Vazdarjanova, 2000). For example, the BLA is a site of convergence of information concerning auditory CSs (LeDoux et al., 1991; Romanski and LeDoux, 1993; Romanski et al., 1993) and contextual CSs (Canteras and Swanson, 1992; Maren and Fanselow, 1995; Maren et al., 1997) and aversive USs (Shi and Davis, 1999). Also, lesions of the BLA either before or after fear conditioning produce severe decrements in the performance of CRs (LeDoux et al., 1990; Sananes and Davis, 1992; Campeau and Davis, 1995; Cousens and Otto, 1998; Goosens and Maren, 2001). These lesions are equally deleterious when made up to one month after conditioning (Lee et al., 1996; Maren et al., 1996a) or when made after extensive overtraining (Maren, 1998, 1999b), demonstrating the lasting role of the BLA in fear memory. In contrast, the CEA is positioned to translate associations formed in the BLA into appropriate conditional responses. To this end, the BLA projects heavily to the CEA (Smith and Paré, 1994) and the CEA projects to the brainstem structures that control fear CRs (LeDoux et al., 1988), including the periaqueductal gray (PAG), the brain structure that mediates freezing behavior (De Oca et al., 1998). Similar to lesions of BLA, lesions of the CEA also produce severe deficits in the acquisition and performance of fear CRs (Kapp et al., 1979; Hitchcock and Davis, 1986; Falls and Davis, 1995). However, it has been argued that these deficits reflect performance deficits rather than deficits in encoding the CS-US association (Fanselow and Kim, 1994; Goosens et al., 2000).

Other evidence furthering the claim that the BLA is the locus of CS-US association during fear conditioning and a site of long-term storage comes from studies employing reversible inactivation techniques. The infusion of muscimol, a $GABA_A$ receptor agonist, into specific brain structures has proved to be a powerful new tool in determining precisely when a structure is engaged in processing a memory; muscimol produces a time-limited functional "lesion" of a target structure. In several studies, muscimol was infused into the amygdala before either fear conditioning or extinction testing. These studies have confirmed an important role for the BLA in both the acquisition and expression of conditional fear (Helmstetter and Bellgowan, 1994; Muller et al., 1997; Wilensky et al., 1999). Similar results have been obtained with intra-BLA infusion of NMDA receptor antagonists. That is, infusion of D,L-2-amino-5-phosphonovaleric acid (APV) produces robust deficits in both the acquisition (Miserendino et al., 1990; Campeau et al., 1992; Fanselow and Kim, 1994; Maren et al., 1996b; Gewirtz and Davis, 1997) and, in many cases, the expression of conditioned fear (Maren et al., 1996a; Lee and Kim, 1998; Fendt, 2001; Lee et al., 2001). Antagonists of both metabotropic glutamate receptors (Fendt and Schmid, 2002; Rodrigues et al., 2002) and L-type voltage-gated calcium channels (Bauer et al., 2002) have also been shown to prevent the acquisition of conditioned fear. These studies indicate that amygdaloid LTP is critical for the acquisition of fear memories.

Electrophysiological studies also suggest that the amygdala is involved in the acquisition and expression of CS-US associations. Numerous studies have revealed that auditory fear conditioning induces long-term conditional CS-evoked plasticity in both the amygdala (Maren et al., 1991; Quirk et al., 1995, 1997; Collins and Paré, 2000; Maren, 2000b) and its auditory afferents, including the medial division of the medial geniculate nucleus (MG) (Supple and Kapp, 1989; Edeline and Weinberger, 1992; McEchron et al., 1996) and the auditory cortex (Weinberger et al., 1984; Quirk et al., 1997). Interestingly, the development of conditional plasticity in the MG requires a functional amygdala at the time of fear conditioning (Poremba and Gabriel, 2001; Maren et al., 2001). It has also been shown that some components of conditional plasticity in the auditory cortex are amygdala-dependent (Armony et al., 1998). Thus, it seems that the amygdala is required to establish associative neuronal activity in extra-amygdaloid structures during fear conditioning. This associative neuronal activity

appears to reflect facilitated signal transmission in the thalamo-amygdaloid pathway. Conditional unit activity peaks at short latencies (<20 ms) after CS onset, and thus is consistent with a thalamic rather than a cortical origin (Quirk et al., 1995; Maren, 2000b). Also, conditional plasticity appears in LA in fewer training trials than the plasticity observed in auditory association cortex (Quirk et al., 1997). Lastly, it was recently shown that a subset of neurons in the dorsal portion of LA maintain conditional increases in unit activity throughout both training and extinction (Repa et al., 2001).

Using a variety of techniques, recent studies have begun to identify intracellular signaling molecules that are recruited during fear conditioning. These molecules presumably initiate the synaptic changes underlying CS-US association. Intra-cranial infusion of protein synthesis inhibitors prevents the formation of long-term fear memories after both auditory (Schafe et al., 1999) and contextual (Bourtchouladze et al., 1998) fear conditioning. In situ hybridization has revealed mitogen-activated protein kinase (MAPK) is activated in the BLA during consolidation of conditional fear memories (Schafe et al., 2000). Inhibition of protein kinase A (PKA) in the BLA has also been shown to interfere with the formation of long-term fear memories (Schafe et al., 1999; Goosens et al., 2000). The cyclic adenosine monophosphate (cAMP) response element-binding protein (CREB) appears to be an important transcription factor within the amygdala; increasing CREB levels within the BLA by viral-mediated gene transfer enhanced the acquisition of fear conditioning (Josselyn et al., 2001). CREB levels in the amygdala also have been shown to increase after fear conditioning in a mouse strain transgenic for a CRE-lac Z reporter (Impey et al., 1998). Almost nothing is known about the function of these molecules within BLA neurons, but future research will undoubtedly be aimed at determining the order in which these molecules are recruited, as well as the contribution of each to synaptic plasticity.

PROPERTIES OF LTP IN THE AMYGDALA

LTP has been characterized in the rat amygdala in vivo using tetanic stimulation of a number of afferents, including the pyriform cortex (Racine et al., 1983), the MG (Clugnet and LeDoux, 1990), and the hippocampus (Maren and Fanselow, 1995). Establishing the presence of LTP in the latter two pathways is particularly critical in advancing the claim that amygdaloid LTP may underlie fear memories: these are thought to be the primary pathways by which contextual and auditory information reach the amygdala. Amygdaloid LTP has also been demonstrated in vitro after stimulation of these same afferents (Chapman et al., 1990; Bauer et al., 2001). The induction of these forms of LTP can be blocked by administration of NMDA receptor antagonists (Gean et al., 1993; Maren and Fanselow, 1995; Huang and Kandel, 1998), or metabotropic glutamate receptor antagonists (Fendt and Schmid, 2002; Rodrigues et al., 2002), much as the acquisition of fear conditioning is prevented by antagonism of these receptors. While NMDA receptor independent LTP has also been induced in the thalamo-amygdala pathway (Chapman and Bellavance, 1992; Li et al., 1995; Weisskopf and LeDoux., 1999; Bauer et al., 2002), its behavioral relevance to fear conditioning is unclear. Our laboratory has demonstrated that there is no behavioral savings of conditional fear after training under amygdaloid NMDA receptor antagonism (Goosens et al., 1999), suggesting that NMDA receptor-independent amygdaloid synaptic plasticity does not contribute to the behavioral expression of conditional fear. However, NMDA receptor-independent synaptic plasticity may be critical for forms of amygdala-dependent learning other than fear conditioning.

In addition to the importance of the NMDA receptor to both fear conditioning and amygdaloid LTP, many of the intracellular molecules that play a critical role in the acquisition of conditional fear also seem to play a role in amygdaloid LTP. For example, using slice preparations, bath application of a MAPK inhibitor impairs the maintenance of amygdaloid LTP, much as intra-amygdala MAPK inhibition impairs the consolidation of conditional fear (Huang et al., 2000; Schafe et al., 2000). Bath application of PKA or protein synthesis inhibitors also interferes with amygdaloid LTP (Huang et al., 2000). Lastly, tetanization of amygdala neurons increases activation of CREB (Huang et al., 2000).

Some of the most compelling evidence that LTP is an important mechanism for fear learning comes from studies that directly compare the synaptic changes that accompany fear conditioning with the synaptic changes that accompany amygdaloid LTP in awake, behaving animals. LeDoux and colleagues have assessed both the effects of LTP induction on CS-evoked activity in the LA, and the effects of fear conditioning on CS-evoked field potentials in LA. These investigators found that the induction of LTP in the thalamo-amygdala pathway increased the magnitude of CS-evoked potentials in the LA (Rogan and LeDoux, 1995), much as fear conditioning increases the magnitude of CS-evoked unit activity (Quirk et al., 1995, 1997). In a separate study, stimulation of the thalamo-amygdala pathway produced a larger response in the amygdala neurons after fear conditioning relative to the response before conditioning (Rogan et al., 1997a), paralleling the changes observed after amygdaloid LTP induction (Rogan and LeDoux, 1995). In similar fashion, McKernan and Shinnick-Gallagher (1997) reported that fear conditioning increased synaptic currents in single LA neurons. It has also been shown that amygdaloid LTP depends on both contiguity and contingency of the incoming stimuli, in the same way as behavioral learning (Bauer et al., 2001). Associative LTP was induced in the amygdala by pairing weak presynaptic stimulation of a CS pathway with depolarization of the postsynaptic amygdala neuron. The addition of unpaired depolarizations of the postsynaptic amygdala neuron to paired presentations of stimulation was shown to reduce LTP, much as unpaired US presentations added to paired CS-US presentations decrease behavioral learning (Rescorla, 1968). Most recently, it was observed that fear conditioning produced an LTP-like enhancement of neurotransmitter release in the cortico-amygdala pathway, while reducing LTP-induced enhancement of synaptic plasticity (Tsvetkov et al., 2002). Collectively, these studies show that fear conditioning and amygdaloid LTP produce parallel changes in synaptic efficacy in amygdala neurons.

CRITICISMS OF LTP AS A MECHANISM FOR CONDITIONING

Although there are obvious mechanistic similarities between the formation of amygdaloid LTP and conditional fear memories, recent reviews claim that there are several characteristics of associative learning paradigms that are not compatible with various properties of LTP (Shors and Matzel, 1997; Matzel and Shors, 2001). These discrepancies between LTP and learning, however, are easily reconciled within extant fear conditioning literature, and might also be similarly accommodated within other associative learning paradigms.

For example, it has been observed that the optimal inter-stimulus interval (ISI) during associative LTP (0–100 ms) is much shorter than the ISI between CS-US pairings in most conditioning paradigms (Shors and Matzel, 1997; Matzel and Shors, 2001). That is, when weak stimulation of one pathway is paired with strong stimulation of a second pathway, LTP is induced only when the stimuli are delivered within 100 ms of one another (Kelso et al., 1986; Gustafsson et al., 1987). In contrast, conditioning paradigms vary greatly in the ISI between the CS and US. Particularly problematic for those who are skeptical of a role for LTP in conditioning are those paradigms in which conditioning is obtained with ISI of hours, as is the case in conditional taste aversions (Yamamoto et al., 1994). However, two mechanisms capable of generating prolonged neuronal representations of stimuli have been reported within the circuitry underlying aversive conditioning. First, researchers are now beginning to characterize neurons that delay firing for up to several seconds after depolarization. These neurons have been observed in several cortical areas (Nisenbaum et al., 1994; Kawaguchi, 1995), and are particularly evident in perirhinal cortex (Faulkner and Brown, 1996, 1999), a region known to play an important role in the expression of conditional fear responses (Rosen et al., 1992; Corodimas and LeDoux, 1995). This newly described class of neurons may play a role in maintaining a CS representation in paradigms where several seconds lapse between CS and US presentation, such as eyeblink conditioning or fear conditioning. For paradigms in which the critical associative structures lack delay neurons, or in which the ISI span minutes to hours, it is thought that small populations of neurons may maintain a representation of a stimulus for extended periods of time. Network models based on this type of connectivity have been described for both the amygdala (Faulkner et al., 1997; Tieu et al., 1999) and the hippocampus (Kesner and Rolls, 2001).

Another feature of LTP that may seem incongruous with some forms of conditioning is that the expression of LTP requires tens of seconds to minutes before it reaches its asymptotic level. In contrast, as an animal receives fear-conditioning trials, conditional responding can be observed within the conditioning session after only one trial. Thus, it has been said that LTP does not easily accommodate immediate retention of conditional responding (Matzel and Shors, 2001). Although there is almost nothing known about the cellular processes that support the expression of freezing behavior immediately after a fear conditioning trial, mechanisms of enhanced synaptic transmission other than LTP, such as post-tetanic potentiation, may play a role (for review, see Zucker, 1989). Alternatively, short-term expression of CRs (when the animal is given a CS alone presentation within minutes of a conditioning trial) may rely on rapid mechanisms of facilitated synaptic transmission related to LTP, such as the insertion of AMPA receptors in the post-synaptic membrane (for review, see Malinow and Malenka, 2002). Although speculative, there is some tentative support of this hypothesis. For example, AMPA receptors can be rapidly mobilized after tetanizing stimuli are delivered (Man et al., 2000; Lu et al., 2001), and AMPA receptors play a role in conditional fear (Maren, 1996; Rogan et al., 1997b). In short, the fact that immediate and short-term expression of CRs may not rely on LTP does not preclude LTP from being the mechanism that supports long-term expression of those CRs.

LTP has also been criticized as a mechanism for fear memory because the degree of potentiation usually increases with successive applications of high frequency stimulation, but it is possible to establish robust, and even asymptotic, long-term fear memories by administering only a single conditioning trial (Shors and Matzel, 1997; Matzel and Shors, 2001). This type of criticism relies on an oversimplified view of conditioning circuitry. Although much research is aimed at finding the critical locus of activity during associative learning, many other brain areas exhibit plasticity during learning. Thus, in eyeblink conditioning, the hippocampus shows synaptic facilitation (Weisz et al., 1984) although it is not the site of the engram (Krupa et al., 1993). Similarly, in fear conditioning, the MG and cortical areas show conditional activity (Supple and Kapp, 1989; Quirk et al., 1997; Armony et al., 1998), yet the amygdala appears to be the critical site of plasticity (Fanselow and LeDoux, 1999; Maren et al., 2001). While a single conditioning trial may produce subasymptotic levels of plasticity in the critical locus of association, it is possible that the combination of subasymptotic levels of plasticity throughout multiple brain structures is sufficient to drive conditional behavior. In support of this, it has been shown that subasymptotic increases in conditional unit activity after eyeblink conditioning still support robust conditional behavior (Freeman et al., 1997). Insofar as LTP may subserve memory, subasymptotic LTP in one brain area need not translate into a weak behavioral response.

LTP has also been criticized as an untenable mechanism for conditioning because degradation of LTP does not parallel behavioral changes during the "forgetting" of a learned task (Shors and Matzel, 1997; Matzel and Shors, 2001). That is, the decay of LTP often does not follow the rate of forgetting. Also, LTP is not more easily induced after it has decayed (de Jonge and Racine, 1985): unlike behavioral learning, there is no facilitation of reacquisition. Again, this type of criticism relies on an oversimplified view of the circuitry involved in conditioning. Just as conditioning produces conditional increases in unit activity in multiple brain areas, learning presumably induces LTP-like processes in multiple brain areas as well. The decay of LTP in a given structure may not correlate with behavioral forgetting precisely because synaptic plasticity in other areas may compensate to maintain a conditional response. Similarly, synaptic plasticity in other brain areas may facilitate behavioral reacquisition of a task without facilitating the reacqui-

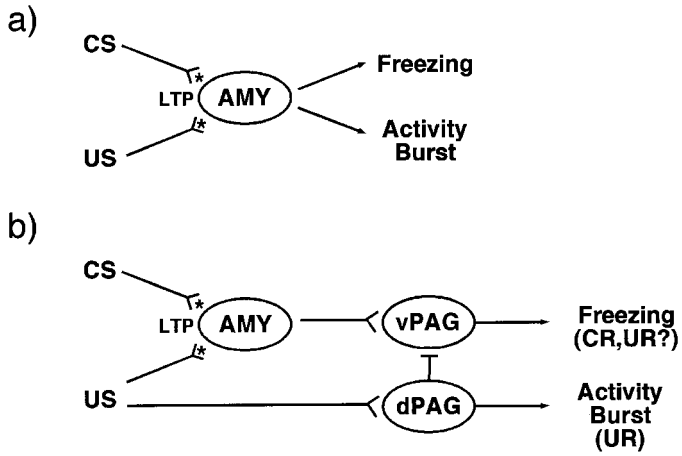

FIGURE 1. a: In this simple model of fear conditioning, the CS and US converge on the amygdala (AMY). The AMY projects to the periaqueductal gray (PAG). By this model, CS-US presentations induce associative LTP in the postsynaptic AMY neuron, and produce facilitated synaptic transmission in both the CS-AMY and US-AMY pathways. Thus, later stimulation of the US pathway alone should produce an increased UR, a pattern of results that is not borne out by experimental data. Also, this model cannot easily explain why activity bursts are not observed as CRs. b: In this model of fear conditioning, the CS and US converge upon the amygdala, which then projects to the ventral PAG to initiate conditional freezing behavior. However, the US pathway also projects to the dorsal PAG, a structure known to receive direct projections from pain pathways (Behbehani, 1995). When CS-US pairings are presented, associative LTP is induced in the neurons of AMY, which then activates neurons in the vPAG. The activation of the US pathway also activates neurons in the dPAG, resulting in the expression of an activity burst UR. By this model, associative LTP in the AMY neurons leave the activity burst UR unaffected, and the activity burst UR does not become a CR after conditioning.

sition of LTP in a structure in which it has decayed. Collectively, these points emphasize that LTP in a single brain area is an impoverished way to view memory, particularly in the context of multiple memory systems (Squire, 1992; Stanton, 2000).

Lastly, it has been argued that if LTP is the mechanism subserving conditioning, it necessarily follows that URs must become CRs, and the response to stimulation of the US pathway should be facilitated as conditioning progresses (Matzel and Shors, 2001) (Fig. 1a). In contrast, for many forms of conditioning, including fear conditioning, the CR and UR are not the same. Furthermore, there are several reports of decreasing UR amplitudes as conditioning proceeds (Young et al., 1976; Schreurs et al., 1995, 2000). Together, these data might be taken to support the claims that LTP cannot support conditioning. While the simple consideration of the circuitry underlying fear conditioning illustrated in Figure 1a does make the stated predictions, a finer grained analysis of the circuitry demonstrates that these predictions are not necessary (Fig. 1b). During Pavlovian fear conditioning, the CS and US converge on the amygdala, which projects to the ventral PAG (vPAG), the structure implicated in generating freezing behavior (De Oca et al., 1998). However, a second US pathway likely projects to the dorsal PAG (dPAG), a structure known to receive direct projections from pain pathways (Behbehani, 1995). The dPAG is thought to be responsible for generating the activity burst UR, and it is also thought to contain an inhibitory projection to the vPAG (Fanselow, 1991; Chandler et al., 1993). Thus, CS-US presentations activate not only the AMY-vPAG pathway, but also the dPAG, allowing for the expression of the activity burst UR while inhibiting expression of freezing behavior. According to this model, changes in amygdala neurons produced by the convergence of the CS and US do not (and would not be expected to) affect the UR because a pathway that bypasses the amygdala controls the UR.

Furthermore, it is clear that the activity burst UR does not become a CR after conditioning. In support of this model, amygdala lesions have been shown to leave the performance of multiple URs intact, including the activity burst (Antoniadis and McDonald, 2001). This finding suggests that URs are generally under the control of amygdala-independent US pathways. This redundancy in US pathways is likely to occur in multiple conditioning paradigms, and again emphasizes that one should always consider the possibility that information about a stimulus may be carried in multiple parallel pathways. It should also be noted that the UR might be altered either during conditioning or in response to unpaired US presentations after conditioning. Mechanisms such as habituation or analgesia may reduce unconditional responding if fear conditioning trials are delivered repeatedly. Conditional analgesia elicited by contextual cues may also attenuate unconditional responding to an unpaired US presentation after conditioning. Thus, behavioral measures of UR are not necessarily accurate indices of potentiation in a US pathway.

CONCLUSIONS

There is an abundance of literature demonstrating strong parallels between the mechanisms that subserve fear conditioning and the mechanisms that underlie amygdaloid LTP. That is, manipulations that affect behavioral learning alter amygdaloid LTP in a similar fashion. Specifically, LTP can be induced by high-frequency stimulation of auditory and contextual CS pathways, the induction and expression of LTP are NMDA receptor-dependent, and intracellular signaling molecules needed for behavioral learning are also required for the formation and maintenance of amygdaloid LTP. Furthermore, criticisms levied against LTP as a mechanism subserving associative learning within conditioning paradigms can be overcome by a more careful consideration of the literature. Together with the evidence from hippocampally-based learning systems, it is concluded that LTP is an excellent candidate mechanism for long-term memory formation.

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