Pharmacology, Biochemistry and Behavior 99 (2011) 217–228

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

journal homepage: www.elsevier.com/locate/pharmbiochembeh

Review

The use of cognitive enhancers in animal models of fear extinction

Gary B. Kaplan [a,c,*], Katherine A. Moore [b,c,d]

[a] Mental Health and Psychiatry Services, VA Boston Healthcare System, Boston, MA, United States
[b] Research Service, VA Boston Healthcare System, Boston, MA, United States
[c] Department of Psychiatry, Boston University School of Medicine, Boston, MA, United States
[d] Tufts University School of Medicine, Boston, MA, United States

ARTICLE INFO

Available online 20 January 2011

Keywords:
Fear
Anxiety
Extinction
Gamma-aminobutyric acid
Glutamate
Brain derived neurotrophic factor
Amygdala
Prefrontal cortex
Plasticity

ABSTRACT

In anxiety disorders, such as posttraumatic stress disorders and phobias, classical conditioning pairs natural (unconditioned) fear-eliciting stimuli with contextual or discrete cues resulting in enduring fear responses to multiple stimuli. Extinction is an active learning process that results in a reduction of conditioned fear responses after conditioned stimuli are no longer paired with unconditioned stimuli. Fear extinction often produces incomplete effects and this highlights the relative permanence of bonds between conditioned stimuli and conditioned fear responses. The animal research literature is rich in its demonstration of cognitive enhancing agents that alter fear extinction. This review specifically examines the fear extinguishing effects of cognitive enhancers that act on gamma-aminobutyric acid (GABA), glutamatergic, cholinergic, adrenergic, dopaminergic, and cannabinoid signaling pathways. It also examines the effects of compounds that alter epigenetic and neurotrophic mechanisms in fear extinction. Of these cognitive enhancers, glutamatergic N-methyl D-aspartate (NMDA) receptor agonists, such as D-cycloserine, have enhanced fear extinction in a context-, dose- and time-dependent manner. Agents that function as glutamatergic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor agonists, alpha2-adrenergic receptor antagonists (such as yohimbine), neurotrophic factors (brain derived neurotrophic factor or BDNF) and histone deacetylase inhibitors (valproate and sodium butyrate) also improve fear extinction in animals. However, some have anxiogenic effects and their contextual and temporal effects need to be more reliably demonstrated. Various cognitive enhancers produce changes in cortico-amygdala synaptic plasticity through multiple mechanisms and these neural changes enhance fear extinction. We need to better define the changes in neural plasticity produced by these agents in order to develop more effective compounds. In the clinical setting, such use of effective cognitive enhancers with cue exposure therapy, using compounds derived from animal model studies, provides great hope for the future treatment of anxiety disorders.

Published by Elsevier Inc.

Contents

* Corresponding author at: VA Boston, 150 South Huntington Avenue, Boston MA 02130, United States. Tel.: +1 857 364 4016; fax: +1 508 586 0894.
E-mail address: gary.kaplan@va.gov (G.B. Kaplan).

0091-3057/$ – see front matter. Published by Elsevier Inc.
doi:10.1016/j.pbb.2011.01.009

1. Fear conditioning and its extinction in animal models

New pharmacological and psychological treatments can be targeted to the pathophysiological mechanisms underlying anxiety disorders such as posttraumatic stress disorder (PTSD) and various phobias. A novel pharmacotherapy approach for the treatment of such anxiety disorders would improve learning in exposure-based psychotherapies through cognitive enhancing agents. This review examines how various cognitive enhancers might improve extinction-based anxiety treatments by measuring their effects in animal models of conditioned fear. Using animal models of fear extinction, we review the effects of cognitive enhancing agents which alter GABAergic, glutamatergic, dopaminergic, noradrenergic, cholinergic, cannabinoid, or neurotrophic pathways or have epigenetic mechanisms. Such studies highlight the possibilities of using *combined* cognitive enhancing agents with psychotherapeutic approaches for humans with anxiety disorders.

1.1. Definitions of classical conditioning, memory consolidation and reconsolidation, and extinction

Classical conditioning develops when an organism is presented with an unconditioned stimulus (UCS) that is paired with a neutral stimulus (CS) such as a discrete cue or a specific learning context. After repeated pairings, the CS starts to produce behavioral reactions (conditioned responses or CR) that are usually similar but not identical to the unconditioned responses (UR). In fear conditioning, the UR often includes freezing behaviors and autonomic responses such as increases in respiration, heart rate, sweating, and pupillary dilation (Davis et al., 2006a). Appetitive stimuli can also produce conditioned responses. One type of reward learning uses the procedure of conditioned place preference in which the CS is associated with a rewarding stimulus, such as a drug of abuse, and elicits preference behaviors (Heinrichs et al., 2010). Consolidation of fear, appetitive and other sensory-related memories is the process by which these new memories are stored. Such memory traces are stored in neural structures as a result of the modification of synapses.

After a memory is consolidated, it may undergo two different processes, reconsolidation and extinction, both of which can be experimentally induced using repeated presentations of the CS. Reconsolidation occurs when consolidated memories are stabilized after cued retrieval and it results in maintenance of the memory trace. Thus, following the initial consolidation of a conditioned response, there is a period of transitory memory which is followed by a period of greater permanence when memory traces become reconsolidated via further changes in neural plasticity (Tronson and Taylor, 2007).

Extinction is defined as a new learning process that results in decreased frequency or intensity of learned responses to conditioned cues. Extinction develops after CS exposure in the absence of the original UCS (Tronson and Taylor, 2007; Taylor et al., 2009). In fear conditioning studies, extinction involves exposing rodents to the fear-eliciting cue(s) or context without the aversive UCS (Quirk et al., 2006; Peters et al., 2009). Extinction is thought to be an active learning process and therefore not simply a "forgetting" of conditioned behavior that reverses the original learning (Bouton, 2004). Reconsolidation processes need to be diminished in order for extinction learning to be effective. Defining the time course, context-specificity and duration of CS re-exposures involved in reconsolidation and extinction processes presents a challenge for the treatment of conditioned fear (Taylor et al., 2009; Quirk and Mueller, 2008). Reconsolidation and extinction highlight how experience dependent stimulation of neural activity produces enduring functional changes in neural excitability. Such effects produce alterations in structural plasticity and are responsible for long-term effects on fear memories and associated behaviors (Amano et al., 2010; Tronson and Taylor, 2007).

1.2. Animal models of fear conditioning and its extinction

Widely utilized animal models used to study the acquisition, expression, extinction, and reinstatement of fear involve classical (Pavlovian) conditioning (Shin and Liberzon, 2010). Variations of fear conditioning models are presented in this section so that effects of cognitive enhancers on fear extinction can be better understood. In classical conditioning of fear, a neutral stimulus (cue or context) is contingently paired with an aversive UCS which activates innate fear behaviors such as freezing or autonomic responses (UR). After conditioning, the CS elicits various learned fear responses or CR (Kim and Jung, 2006; Maren, 2008). Fear conditioning produces rapid, robust, and long-lasting fear associated learning. A single, intense footshock can produce conditioned fear learning in rodents that is retained for months (Maren, 2008). Such classical fear conditioning has primarily been employed using rodents (Kim and Jung, 2006; Maren, 2008) and in humans (Cheng et al., 2003; Alvarez et al., 2008). In rodents, behavioral responses involve behavioral suppression, motor freezing, analgesia, ultrasonic distress vocalizations and autonomic responses such as elevated heart rate, respiratory rate and blood pressure (Kim and Jung, 2006; Maren, 2008). In humans, changes in galvanic skin responding, heart rate, blood pressure, eyeblink conditioning and anxiety are often used as measures of conditioned fear (Shin and Liberzon, 2010; Cheng et al., 2008). Often, the strength of fear conditioning varies with the temporal interval between the CS and UCS.

Extinction learning can be studied in fear conditioned animals by repeatedly exposing them to fear-eliciting CS in the absence of the aversive UCS. This extinction training results in a decrease in the extent and frequency of the fearful CR (Myers and Davis, 2002, 2007). This extinction procedure produces consistent results in both appetitive and aversive paradigms and across numerous species (Myers and Davis, 2002). The determining factor for the extinction of fear conditioning appears to be the violation of the expected contingency between the CS and the UCS (Myers and Davis, 2007).

Another form of Pavlovian fear conditioning is the fear-potentiated startle model in which a neutral context or cue (CS) is first paired with an aversive footshock (UCS). After such conditioning, when the CS is paired with a novel aversive stimulus such as a sudden noise, the elicited startle response is enhanced compared to the startle response elicited by the noise alone (Davis et al., 2006a). This potentiated-startle response is long lasting (Campeau et al., 1990). The fear-potentiated startle model uses startle measurement as the dependent variable and this model has been well demonstrated in rodents (Chhatwal et al., 2005a; Walker et al., 2002) and in humans (Norrholm et al., 2006). In fear-potentiated startle, the repeated presentation of the CS without aversive consequences results in a reduction in the frequency and amplitude of the startle response (Walker and Davis, 2002).

Pavlovian fear conditioning allows for the study of the reinstatement, renewal, and spontaneous recovery of learned fear (for review see: Myers and Davis, 2002, 2007). The reinstatement of fear responses refers to the reappearance of extinguished fear responses to a CS after UCS-only presentations in the same context as the recovery test (CS-only presentations) (Bouton and King, 1983). Renewal of conditioned fear refers to the reappearance of fear responses to the CS after extinction in a novel context followed by a return to the original context (ABA design) (Bouton and Bolles, 1979; Bouton and King, 1983). Renewal can also occur when conditioning, extinction, and re-exposure testing occur in three separate contexts (ABC design) or when conditioning and extinction occur in one context, while re-exposure occurs in a novel context (AAB design) (Bouton and Ricker, 1994; Thomas et al., 2003). Spontaneous recovery refers to the reappearance of extinguished fear responses after the passage of time in the absence of any further explicit training. These behaviors highlight the context dependence of fear and extinction learning (Quirk, 2002).

Fear conditioning can also be acquired through operant conditioning paradigms in which the presentation of the aversive US is contingent upon the animal's behavior (Kim and Jung, 2006). Inhibitory avoidance occurs when an aversive stimulus such as a footshock follows an animal's behavior, such as moving to the dark compartment of a test chamber when placed in a lighted compartment or stepping down from a platform onto grid flooring. Accordingly, inhibitory avoidance is often incorporated into classical conditioning which involves UCS-CS pairings (e.g. dark compartment and footshock). Following this conditioning, the animal learns to avoid performing the response that was followed by the aversive stimulus (Kim and Jung, 2006). Inhibitory avoidance procedures produce robust fear learning (Rossato et al., 2006). Typical extinction procedures involve repeated presentations of the CS in the absence of an aversive UCS which leads to the progressive extinction of the CR (Cammarota et al., 2003).

With these animal models of fear conditioning and fear extinction it is possible to examine pharmacological facilitation of extinction learning. The strategy is to understand the neurotransmitter, receptor, epigenetic and neurotrophic mechanisms that are involved in fear extinction and then test signaling agents that facilitate extinction. Using cognitive enhancing agents, multiple pharmacotherapies can be developed as adjuncts to extinction learning involved in exposure therapy (Davis et al., 2006a) and these agents as tested in animals are reviewed.

1.3. Neural mechanisms in fear conditioning and extinction

In order to effectively use cognitive enhancing drugs in fear extinction, it is critical to understand the key brain regions that are functionally involved. Most studies highlight the importance of three regions in fear conditioning and its extinction: the amygdala, prefrontal cortex, and hippocampus. The amygdala is critical for the storage of both conditioned fear and extinction while the hippocampus processes contextual information and medial PFC is critical for the retrieval of extinction learning (Shin and Liberzon, 2010; Maren, 2008). Using techniques that employ lesioning, electrical stimulation, and site-specific pharmacology, a large number of studies point to the amygdala as one of the principal structures necessary for fear learning. This structure receives information about both unconditioned and conditioned stimuli and is responsible for activating a cascade of fear responses (Kim and Jung, 2006). Sensory pathways typically project to the amygdala after processing from one or more associative cortical areas and sometimes directly from the thalamus or subcortical routes (McDonald, 1998). Sensory information enters the basolateral nuclei of the amygdala (BLA) where synaptic plasticity develops and produces CS-UCS associations. Inter-amygdaloid connections to the central nucleus (CNA), the primary fear output structure, allows the learned fear association to influence various autonomic and motor centers involved in fear responses (Kim and Jung, 2006; Davis et al., 2006a; Pape and Pare, 2010).

Animal studies have also implicated the hippocampus as a vital influence in contextual fear conditioning. Projections from the hippocampal subregions to the amygdala are direct (CA1, subicular, and entorhinal) and indirect through the medial PFC (Pape and Pare, 2010). Hippocampal lesion studies have shown that this region is required for the renewal of conditioned fear responses after extinction. In rodents, hippocampal lesions impair conditioning to a contextual cue but not a discrete tone cue (Kim and Jung, 2006; Maren, 2008). Genetic studies have demonstrated the importance of the hippocampus in contextual fear learning using mutant mice with specific deficits in hippocampal long-term potentiation (LTP), a cellular model for plasticity and learning (Kim and Jung, 2006). Based on lesion studies, contextual fear conditioning is maintained relatively early after hippocampal lesioning (up to 28 days) but not after long delays (100 days) (Maren et al., 1997). This suggests that the site of contextual fear learning shifts over time.

The PFC is an essential brain region involved in the acquisition and consolidation of fear extinction (Kim and Jung, 2006; Shin and Liberzon, 2010; Kaplan et al., 2011). The PFC is known to project to the amygdala, inhibit its neuronal firing and consequently reduce fear responding. The PFC inhibits the function of BLA by suppressing the conditioned fear responses after extinction training (Kim and Jung, 2006). The complexity of the connections between the medial PFC and BLA has lead to some controversy regarding the nature of PFC influences (excitatory vs. inhibitory) over the BLA (for review see Pape and Pare, 2010). The infralimbic cortex in the medial PFC is specifically involved in the consolidation of extinction learning and plasticity develops in this region for subsequent extinction retrieval (Mueller and Cahill, 2010). It has recently been proposed that the neural circuitry underlying extinction of conditioned fear and drug seeking behaviors overlap in the PFC (Peters et al., 2009; Mueller and Cahill, 2010; Kaplan et al., 2011). For example, activation of the infralimbic PFC enhances extinction learning in both aversive (Mueller et al., 2008) and drug-seeking paradigms (Lalumiere et al., 2010).

2. Use of cognitive enhancers in fear extinction: pharmacological enhancement of fear extinction

This section examines the effects of GABAergic, glutamatergic, dopaminergic, noradrenergic, cholinergic, cannabinoid and neurotrophic agents, and compounds that have epigenetic mechanisms, as cognitive enhancers in animal models of fear extinction. Table 1 summarizes on the effects of these various cognitive enhancers on fear extinction from the animal research literature.

2.1. The role of gamma-aminobutyric acid (GABA) agents as cognitive enhancers in fear extinction

Many of the pharmacological interventions that facilitate conditioned fear and its extinction in animal models appear to do so by interacting with the major inhibitory neurotransmitter in the mammalian brain, GABA (Davis et al., 2006a). In short, conditioned fear inhibits GABAergic function in the amygdala, whereas the acquisition of fear extinction produces an adaptive upregulation of post-synaptic markers (Pape and Pare, 2010). GABA agonists disrupt the acquisition of fear conditioning while GABA antagonists facilitate such acquisition (Davis et al., 2006a; Makkar et al., 2010). The evidence suggests that GABA agonists inhibit consolidation of extinction memory (Makkar et al., 2010). Benzodiazepines such as diazepam or midazolam treatments, agents which enhance the effects of GABA binding at $GABA_A$ receptors, given shortly before (30 min and 10 min, respectively) extinction training impair extinction retention in a dose-dependent manner (Pereira et al., 1989; Hart et al., 2009). Muscimol, another GABAergic agonist, infused directly into the dorsal or ventral hippocampus, before extinction training disrupted its retention (Corcoran et al., 2005; Corcoran and Maren, 2001; Hobin et al., 2006). In contrast, Akirav et al. (2006) found that infusions of muscimol into the BLA after extinction enhanced its retention; however, the enhancement might be due to reconsolidation effects following a brief fear reactivation instead of extinction effects (Makkar et al., 2010).

However, some research suggests that the effects of benzodiazepines on extinction are state dependent and did not alter the CS–CR bond (Patel et al., 1979; Bouton et al., 1990; Nakagawa et al., 1993). That is, the presence of benzodiazepines immediately before extinction training produces an internal state that can be distinguished from the internal state of the animal during drug-free retention testing. Benzodiazepine-induced impairments in extinction retention may also be mediated by a shift in internal state between

Table 1
Effects of cognitive enhancers in animal models of fear extinction.

Agent class	Drug	Fear extinction effect	Sources
$GABA_A$ receptor antagonist and inverse agonist	Picrotoxin, bicuculline; FG 7142	Mixed results	McGaugh et al. (1990), Berlau and McGaugh (2006), and Harris and Westbrook (1998)
Glutamatergic NMDA agonist	DCS	Enhances	Ledgerwood et al. (2003, 2005), Woods and Bouton (2006), Weber et al. (2007), Parnas et al. (2005), Walker et al. (2002), and Lee et al. (2006)
Glutamatergic NMDA antagonist	AP5, MK-801, CPP	Impairs	Falls et al. (1992), Szapiro et al. (2003), Lee and Kim (1998), Lee et al. (2006), Baker and Azorlosa (1996), and Santini et al. (2001)
Glutamatergic AMPA agonist	PEPA	Enhances	Zushida et al. (2007) and Yamada et al. (2009)
Cholinergic nicotinic agonist	Nicotine	Mixed results	Smith et al. (2006), Tian et al. (2008), and Elias et al. (2010)
Cholinergic muscarinic agonist and antagonist	Oxotremorine (agonist) Scopolamine (antagonist)	Mixed results	Boccia et al. (2009) and Roldan et al. (2001)
Adrenoceptor alpha-2 antagonist	Yohimbine	Enhances	Cain et al. (2004), Hefner et al. (2008), Morris and Bouton (2007), and Mueller et al. (2009)
Cannabinoid CB1 agonist	WIN 55,212-2, AM404, cannabidiol	Mixed results	Chhatwal et al. (2005a), Chhatwal and Ressler, 2007, Pamplona et al. (2006, 2008), Lin et al. (2008, 2009a,b), and Bitencourt et al. (2008)
Cannabinoid CB1 antagonist	SR141716A, AM251	Impairs	Chhatwal et al. (2005a,b), Marsicano et al. (2002), Niyuhire et al. (2007), Varvel et al. (2005), Reich et al. (2008), and Alvarez et al. (2008)
Dopaminergic D1 agonist	SKF38393	Mixed results	Willick and Kokkinidis (1995), Borowski and Kokkinidis (1998), and Dubrovina and Zinov'eva (2010)
Dopaminergic D2 agonist	Quinpirole	Impairs	Nader and LeDoux (1999) and Ponnusamy et al. (2005)
Epigenetic agents—histone deacetylase inhibitors	Valproate, sodium butyrate	Enhances	Bredy and Barad (2008), Lattal et al. (2007), and Bredy et al. (2007)
Neurotrophic agents	BDNF and corticotrophins	Enhances	Peters et al. (2010), Choi et al. (2010), Soliman et al. (2010), Heldt et al. (2007), Chhatwal et al. (2006), and Soravia et al. (2006)

the drug and drug-free contexts, and not because the drug has disrupted extinction learning (Davis et al., 2006a; Makkar et al., 2010). In contrast, immediate post-training intraperitoneal injections of the GABA antagonists, picrotoxin or bicuculline, or of the GABA agonist muscimol improve and impair, respectively, retention of inhibitory avoidance conditioning when tested 24 h after training (Castellano and McGaugh, 1989, 1990). This suggests that GABA agents produce state-independent effects.

GABA antagonists have been shown to enhance cognition by blocking GABAergic transmission and are expected to facilitate extinction (Makkar et al., 2010). Post-extinction administration of the GABA antagonists, such as picrotoxin or bicuculline, enhanced fear recall during retention testing (Berlau and McGaugh, 2006; McGaugh et al., 1990). Animals that received bicuculline 3 h after extinction training instead of immediately afterward showed the same level of freezing during retention testing as animals that received saline, suggesting that the extinction enhancing effects of bicuculline were due to memory consolidation and not other processes (Berlau and McGaugh, 2006). However, in a series of experiments, Harris and Westbrook (1998) showed that $GABA_A$ receptor inverse agonist (an agent with opposite effects of the agonist), FG7142, slowed the rate of acquisition of fear extinction and impaired extinction during retention testing when FG7142 was given before extinction training, retention testing, or both. Also, the extinction impairment by FG7142 is context-specific. That is, injection of FG7142 prior to retention testing reinstated freezing behavior if the testing and extinction contexts were the same, but if the testing chamber was different the renewal of fear was not altered by the drug (Harris and Westbrook, 1998). However, it cannot be ruled out that the effects of FG7142 are state-dependent. In summary, GABA agonists, antagonists, and inverse agonists have been shown to have complex effects on GABAergic transmission and extinction learning.

GABAergic neurons in the amygdala play a key role in both the expression and extinction of fear conditioning. PTSD can be conceptualized as a cue- and context-associated fear conditioning process that results from amygdalar hyperresponsivity. Fear related sensory information is transmitted through the BLA which connects to the central nucleus of the amygdala (CNA) and activates fear responses through outputs to the hypothalamus and brainstem. The infralimbic cortex appears to be the primary pathway to suppress fear responses via extinction learning (Quirk and Mueller, 2008). The infralimbic cortex sends glutamatergic projections to GABAergic neurons between the BLA and CNA called the intercalated cell masses (ITC) (Likhtik et al., 2008). Activation of these ITC GABA neurons inhibits output from the CNA and reduces fear responses. Amano et al. (2010) showed that in fear extinction, increased GABA levels were found in CNA neurons along with enhancement of inputs to ITC cells during extinction training (Amano et al., 2010).

Extinction develops when pathways conveying sensory inputs about fear-eliciting cues in the amygdala develop experience-dependent forms of synaptic plasticity (such as LTP) (Davis et al., 2006a). Expression of gephyrin, a $GABA_A$ receptor clustering protein, is downregulated in the amygdala after fear acquisition and upregulated after extinction training (Ressler et al., 2002; Chhatwal et al., 2005b). Fear conditioning produced decreases in amygdalar GABAergic plasticity which was measured by decreased mRNA expression of $GABA_A$ receptor $\alpha1$ and $\alpha5$ subunits and GABA synthesizing protein GAD67, as well as decreased benzodiazepine binding (Heldt and Ressler, 2007). In contrast, fear extinction produced increases in mRNA expression of $GABA_A$ receptor subunits $\alpha2$ and $\beta2$, and gephyrin and reduced GABA transporter-1 (Heldt and Ressler, 2007). Lin et al. (2009a) measured the effects of fear conditioning of miniature inhibitory postsynaptic currents (mIPSC) in the BLA and protein levels of $GABA_A$ receptor subunits. Fear conditioning decreased the frequency and amplitude of mIPSC and protein levels of gephyrin and $\beta2$ while fear extinction reversed these effects. The effect of bilateral amygdalar infusions of an inhibitory peptide of $GABA_A$ receptors was measured in this last study. Blocking the insertion of $GABA_A$ receptors with this inhibitory peptide blocked fear extinction (Lin et al., 2009a). In summary, fear conditioning produces GABAergic synaptic plasticity in the amygdala as defined by downregulation of markers of GABAergic function while fear extinction produced an upregulation of these markers. Selective modulation of plasticity of GABAergic amygdalar neurons may ultimately prove useful in treatment of anxiety (Davis et al., 2006a). Although the GABA agonists may produce state-dependent changes in fear conditioning and its extinction, more fundamental changes in GABAergic signaling and plasticity have been demonstrated.

2.2. The role of glutamatergic agents in fear extinction

The brain's major excitatory neurotransmitter, glutamate, has three major classes of receptors: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), N-methyl D-aspartate (NMDA), and metabotropic glutamate receptors (Davis et al., 2006a). NMDA receptors are important in learning and memory and in experience-dependent forms of plasticity such as LTP. Administration of NMDA receptor antagonists before training blocks the extinction of the fear-potentiated startle response, contextual fear conditioning, inhibitory avoidance, and eye blink conditioning (Szapiro et al., 2003; Lee and Kim, 1998; Lee et al., 2006; Baker and Azorlosa, 1996; Falls et al., 1992). The use of NMDA antagonists immediately after extinction trials also blocks extinction learning, suggesting that NMDA receptor activation is involved in consolidation of extinction (Santini et al., 2001; Ledgerwood et al., 2003). NMDA antagonists may block fear acquisition by disrupting glutamatergic transmission of sensory information to the amygdala (Davis et al., 2006a). Fear extinction may involve experience-dependent plasticity between sensory pathways and GABAergic interneurons within the amygdala, suggesting a mechanism for NMDA receptor antagonist effects on fear extinction (Davis et al., 2006a).

Since NMDA receptor antagonists block fear extinction, many studies have examined the effects of cognitively enhancing NMDA receptor agonists, such as D-cycloserine (DCS), on fear extinction (Davis et al., 2006a). DCS binds to NMDA receptors as a partial agonist at the glycine site and enhances receptor efficacy by stimulating high-affinity glycine binding (Norberg et al., 2008). The promise of clinical translation using DCS is heightened by the fact that the drug has already been approved for human use by the FDA (Davis et al., 2006a). In a meta-analysis of animal and human studies using DCS, Norberg et al. (2008) summarized that DCS enhanced fear extinction in animals and also improved exposure therapy effects in humans with specific phobias, panic disorder, or obsessive compulsive disorder. At post-treatment, both animal and human studies were associated with moderate to large effect sizes (Norberg et al., 2008). Given the effects on fear extinction in both animal and human studies, DCS is a promising agent for improving exposure-based therapy outcomes in anxiety.

One study by Walker et al. (2002) showed that rats given a relatively high dose of DCS (15 and 30 mg/kg), compared to vehicle or low dose DCS (3.25 mg/kg), demonstrated more robust extinction of fear-potentiated startle when tested 24 h later. DCS was given 30 min before a single extinction training session in this last study. Administration of a glycine site antagonist (HA-966) also blocked the DCS-induced enhancement of extinction. Extending these findings, Ledgerwood et al. (2003) found that DCS (2.5, 5, and 10 mg/kg doses) given immediately after training dose-dependently enhanced extinction of conditioned freezing in rats tested 24 h after extinction training. This finding suggests that DCS mediates extinction by acting on memory consolidation after such training. Lee et al. (2006) compared the effects of systemic and intra-BLA administrations of NMDA agonist DCS and noncompetitive NMDA receptor antagonist (+)-5-methyl-10,11-dihydro-SH-dibenzo[a,d]cyclohepten-5,10-imine maleate (MK-801) on fear extinction. When long extinction training sessions were used, MK-801 blocked extinction of conditioned freezing, and DCS potentiated extinction. However effects were reversed when shorter extinction training sessions were used, possibly reflecting drug-induced changes in memory reconsolidation instead of extinction after a brief fearful reactivation (Lee et al., 2006).

DCS does not interfere with reacquisition of fear learning (Ledgerwood et al., 2005), but DCS given immediately after extinction training prevents reinstatement of conditioned freezing in rats (Ledgerwood et al., 2004). Ledgerwood et al. (2005) showed that DCS may lead to a generalization of extinction to other CSs previously paired with the same US but not extinguished. Studies have also shown that although DCS enhances fear extinction learning it does not eliminate the renewal effect (Woods and Bouton, 2006; Bouton et al., 2008). Rats were conditioned in one context and then extinguished in a second context preceded by administration of saline or DCS (15 or 30 mg/kg). When subsequently re-exposed to the CS in the extinction training context, extinction was enhanced in rats that had received the 30 mg/kg dose compared to rats that had received saline. However, when re-exposed in the original conditioning context, the DCS group showed a substantial renewal of fear that was similar in strength to the one observed in the saline controls. That is, although DCS may facilitate fear extinction and prevent reinstatement, it does not alter the context-specificity of the learning, and therefore may not protect against relapse (the return of fear or anxiety symptoms) in translational uses (Woods and Bouton, 2006; Bouton et al., 2008). More research is needed to determine the long-term effects of DCS on fear extinction and to understand the optimal timing, number, and size of doses.

Evidence suggests that the effects of DCS decrease over repeated sessions (i.e. with chronic use) and that a single acute dose of DCS produces the greatest inhibitory effects (Parnas et al., 2005; Norberg et al., 2008; Grillon, 2009; Davis et al., 2006a,b). Since DCS plasma levels peak within hours after oral administration, maximal concentrations would develop during the period of post-session memory consolidation if given around a fear extinction or exposure therapy session (Davis et al., 2006a,b). Post-training administration of DCS might allow clinicians to give the drug after sessions in which within-session extinction occurred (Norberg et al., 2008). This would correspond to evidence in the animal literature which suggests that long-term DCS facilitation is only seen in animals showing within-session extinction (Weber et al., 2007; Norberg et al., 2008; Grillon, 2009). DCS was more effective when given a limited number of times and when administered close to the extinction training session (Walker et al., 2002; Ledgerwood et al., 2005; Norberg et al., 2008). More research is needed to clarify whether DCS can be effective for individuals who did not respond previously to exposure therapy alone. Also it is unclear whether DCS is effective as a cognitive enhancer in a broader range of anxiety-related disorders (Norberg et al., 2008). DCS did improve patient outcomes for symptom severity, cognition, and functional impairment in social phobia when compared with placebo (Guastella et al., 2008). Importantly, evidence indicates that the effects obtained with experimental manipulation of NMDA receptor activity, for example with DCS, are not due to state-dependent changes in neuronal activity, but instead reflect specific receptor-mediated changes in learning and consolidation of extinction. Systemic application of an NMDA receptor antagonist during extinction of conditioned freezing and suppression of bar pressing interfered with extinction recall when tested 24 h but not 1.5 or 48 h later (Santini et al., 2001).

Studies also show that NR2B subunits of NMDA receptors in the BLA are required for acquisition, not consolidation of fear extinction. These NR2B subunits in the mPFC appear to be involved in the consolidation but not the acquisition of extinction (Sotres-Bayon et al., 2007, 2009). Interestingly, reacquisition of fear extinction seems to involve NMDA receptors in both the BLA and mPFC, and consolidation again involves NMDA receptors in the mPFC (Laurent et al., 2008; Laurent and Westbrook, 2008; Burgos-Robles et al., 2007). Overall the NR2B subunit is critical for these phase-dependent roles of NMDA receptors in extinction (Pape and Pare, 2010). Calcium-mediated burst firing in infralimbic and ventromedial PFC neurons predicted subsequent recall of fear extinction and this burst activity was necessary for consolidation of extinction and was dependent on NMDA receptor activation (Burgos-Robles et al., 2007). Therefore, NMDA receptor mediated bursting in infralimbic neurons seems to initiate Ca^{2+}-dependent intracellular cascades that stabilize fear extinction memory.

Although DCS is the most studied cognitive enhancer its mechanisms of action are incompletely understood (Davis et al., 2006b). DCS appears to alter NMDA receptor mediated intracellular events such as calcium flux. Systemic DCS improved fear extinction when it was coadministered with intra-amygdala injections of either protein synthesis inhibitor, mitogen-activated protein kinase inhibitor, a transcription inhibitor or a translation inhibitor and these findings suggest that these intracellular signaling pathways are critical (Yang and Lu, 2005). Fear conditioning is associated with AMPA receptor (GluR1) increases in the amygdala, while DCS reversed fear conditioning and produced an internalization of GluR1 (Mao et al., 2008). These DCS effects were blocked by proteasome inhibitors. This suggests that DCS may induce the erasure of fear memory through GluR1 receptor internalization (Mao et al., 2008).

Modulation of glutamate AMPA receptors has been implicated as a mechanism in other fear extinction studies. AMPA receptor positive modulators have been shown to improve performance on several cognitive tasks (Woolley et al., 2009). AMPA receptor positive modulator, 5-(1-piperidinylcarbonyl)-2,1,3-benzoxadiazole (CX691) reduced conditioned fear suggesting that such compounds may be beneficial in the treatment of anxiety disorders (Woolley et al., 2009). Intra-medial PFC and intra-amygdala infusions of an AMPA receptor agonist given 15 min prior to extinction training, 4-[2-(phenylsulfonylamino)ethylthio]-2,6-difluorophenoxyacetamide (PEPA) facilitated fear extinction (Zushida et al., 2007). In this study, intra-mPFC administration of PEPA facilitates extinction much more potently than an intra-amygdala administration. Infusions of PEPA in both regions had no effect on fear acquisition or consolidation, and the effects of PEPA on fear extinction were attenuated by an AMPA receptor antagonist drug pre-administration. Taken together, these results suggest that AMPA receptor agonist enhances fear extinction primarily through effects in the medial PFC (Zushida et al., 2007). Yamada et al. (2009) compared PEPA to DCS with administrations either 15 or 30 min before re-exposure to clarify the role of NMDA receptors. They found that PEPA enhanced the extinction of contextual fear learning but not its reconsolidation, while DCS enhanced both processes, and both PEPA and DCS suppressed reinstatement of fear. Facilitation of reconsolidation is a problematic potential side effect of cognitive enhancing agents when used with exposure therapies. Thus, extinction-specific agents such as PEPA are promising therapeutics.

2.3. The role of cholinergic agents in fear extinction

Nicotinic acetylcholine neurotransmission has been identified in enhancement of cognition and is a target for fear learning and fear extinction (for earlier reviews see: Tinsley et al., 2004; Levin and Simon, 1998). Nicotine, the prototypical nicotinic acetylcholine agonist, has been shown to dose-dependently enhance contextual fear conditioning when given before conditioning (Gould and Wehner, 1999; Gould and Higgins, 2003), and the enhancement is maintained at a one week retest with and without prior nicotine administration (Gould and Higgins, 2003). The effects of pre-training nicotine are specific for hippocampus-dependent forms of conditioning, such as contextual and trace cued fear conditioning, with no effect on hippocampus-independent cued delay fear conditioning (Gould and Wehner, 1999; Gould and Higgins, 2003; Gould et al., 2004).

Few studies have examined the effects of nicotine on fear extinction learning, but those that do suggest increased nicotinic signaling may have differing effects on extinction depending on timing of nicotine dose. Chronic nicotine pre-treatment did not alter subsequent acquisition of contextual fear conditioning or fear extinction, but enhanced the retention of fear conditioning during extinction training (Tian et al., 2008). Rats pre-treated with continuous low-dose nicotine during adolescence show enhanced fear acquisition compared to saline controls, and they failed to extinguish the learned fear, while continuous pre-treatment during adulthood did not affect fear acquisition or extinction (Smith et al., 2006). Acute administration of nicotine during extinction training enhances extinction whereas administration during conditioning and extinction may strengthen contextual fear memories and interfere with extinction. In an AAA context design (Elias et al., 2010), nicotine administration before conditioning did not alter extinction. Nicotine administered prior to extinction sessions enhanced such learning, and nicotine administered before both conditioning and extinction sessions decreased extinction. In an ABA design in this study, nicotine administered before extinction sessions and re-exposure enhanced extinction and blocked context renewal of conditioned fear, while nicotine administered before conditioning, extinction, and re-exposure sessions did not alter extinction but enhanced the context renewal of conditioned fear. Thus, nicotine administration given in proximity to fear conditioning may strengthen contextual fear acquisition and interfere with extinction, while nicotine administered during extinction only and continued through re-exposure enhances extinction independent of the context and also attenuates the context renewal of conditioned fear.

Nicotine given immediately after contextual fear conditioning did not enhance acquisition, indicating that the cognitive enhancing effects of nicotine may be state-dependent (Gould and Higgins, 2003). However, recent work by Kenney et al. (2010) suggests that nicotine may alter synaptic plasticity underlying the consolidation of contextual fear memories. Transcriptional upregulation of hippocampal jun-N terminal kinase 1 (JNK1) mRNA was found in fear conditioned mice in the presence of nicotine, whereas neither learning alone nor nicotine administration alone altered JNK1 mRNA expression. Furthermore, the upregulation of JNK1 was absent in beta-2 nicotinic receptor subunit knockout mice, which are mice that do not show enhanced learning by nicotine. Finally, hippocampal JNK activation was increased in mice that were administered nicotine before conditioning, and the inhibition of JNK during consolidation prevented the nicotine-induced enhancement of contextual fear conditioning. Although the fear acquisition enhancing effects of nicotine appear to be state-dependent, nicotine administration before conditioning has been shown to alter hippocampal plasticity resulting in enhanced contextual memories. It is possible that similar effects may occur with fear extinction such that nicotine administration before extinction alters nicotinic cholinergic signaling resulting in enhanced consolidation.

Agonists at acetylcholine muscarinic receptors generally enhance memory and learning in animal models while muscarinic antagonists disrupt acquisition of new learning (Power et al., 2003; Tinsley et al., 2004; Rogers and Kesner, 2004; Gale et al., 2001; Soares et al., 2006). Muscarinic acetylcholine neurotransmission has also been implicated in fear learning (for review see: Tinsley et al., 2004; Power et al., 2003). Cholinergic mechanisms within the BLA may alter consolidation of extinction learning. Boccia et al. (2009) showed that intra-BLA infusions of muscarinic antagonist oxotremorine enhanced fear extinction when administered immediately after extinction training sessions. The effects of oxotremorine were not due to non-specific effects and the agent did not alter reinstatement of extinguished fear. Muscarinic antagonist agents have also been implicated in the recovery of conditioned fear after its extinction. Roldan et al. (2001) used a single-trial inhibitory avoidance protocol followed by extinction training. Muscarinic receptor antagonist scopolamine, given prior to retention testing, produced dose-dependent and time-dependent recovery of the previously extinguished avoidance response.

2.4. The role of adrenergic agents in fear extinction

Norepinephrine (NE) plays a critical role in attention, cognition and its extinction in PFC systems. Psychostimulants, such as adrenergic agent yohimbine, can enhance memory and learning. Although new memory consolidation is improved by noradrenergic

signaling, some uncertainty remains as to whether NE enhances extinction memories (for review see: Mueller and Cahill, 2010; Davis et al., 2006a). Studies show that noradrenergic signaling modulates extinction in aversive, appetitive and drug-related learning paradigms (Mueller and Cahill, 2010). Systemic administration of noradrenergic drugs around fear extinction trainings yielded mixed results (Mueller and Cahill, 2010). Yohimbine, an alpha2-receptor antagonist that promotes NE release, is one of the most well studied cognitive enhancers of fear extinction (Holmes and Quirk, 2010). Systemic administration of yohimbine facilitates fear extinction when training occurs in a context different from conditioning (Cain et al., 2004; Hefner et al., 2008; Morris and Bouton, 2007), but not when the context is the same (Mueller et al., 2009). Yohimbine-induced enhancement of extinction was dose-dependent and occurred only with the administration of an optimal drug dose (Morris and Bouton, 2007). Like DCS, the enhancement of fear extinction by yohimbine appears to be context-specific. Administration of yohimbine prior to extinction training did not impair renewal of freezing behavior in either an ABA or ABC design (Morris and Bouton, 2007). Thus, as with DCS, yohimbine may not be completely effective in preventing relapse in translational applications because of their contextual specificities.

NE is critical to fear responses and administration of epinephrine resulted in the reinstatement of extinguished fear without re-exposure to the fear context (Morris et al., 2005). Interestingly, post-extinction training using intra-amygdala infusions of NE facilitated the extinction of inhibitory avoidance (Berlau and McGaugh, 2006) showing the role of amygdalar NE in extinction learning. Fear-induced NE release in the amygdala may prepare this structure for subsequent consolidation of extinction. Administration of propranolol, a beta-receptor antagonist, has been shown to impair subsequent retrieval of extinction of contextual (Ouyang and Thomas, 2005), but not cued fear (Cain et al., 2004; Ouyang and Thomas, 2005; Rodriguez-Romaguera et al., 2009). In the cued fear paradigms, propranolol administration 20 min before extinction training reduced fear expression without affecting later extinction recall (Cain et al., 2004; Rodriguez-Romaguera et al., 2009). Pre-extinction session infusions of propanolol into the infralimbic PFC impaired the retrieval of extinction the next day (Mueller et al., 2008). To summarize, NE signaling has demonstrated a critical role in the acquisition, expression, extinction and retrieval of conditioned fear.

Since both NE and serotonin reuptake inhibition by antidepressants reduces anxiety- and depression-related behaviors, serotonin reuptake might be a mechanism for fear extinction. There are few such studies but one examined the knockout of serotonin reuptake genes in mice and tested such mice in fear conditioning and extinction paradigms (Wellman et al., 2007). Interestingly, fear conditioning and extinction were normal in knockout mice but these mice demonstrated a deficit in extinction recall. In knockout mice, dendritic branches of infralimbic pyramidal neurons were increased in length and BLA neurons had greater spine density compared to wild-type mice, suggesting the importance of this plasticity in extinction recall.

Translational studies have examined the effects of adrenergic drugs for the treatment of clinical disorders in humans. Yohimbine has historically been used as a challenge procedure to induce anxiety among individuals with anxiety disorders (Mueller and Cahill, 2010). However, animal studies have unexpectedly found that yohimbine enhances extinction. Few clinical trials have examined yohimbine as a treatment in anxiety except for Powers et al. (2009) who used it in claustrophobic anxiety. Claustrophobia subjects took either yohimbine or placebo 1 h prior to two separate exposures to a small, dark, and enclosed space. Both treatment and control groups showed significant reductions in claustrophobic anxiety during the first exposure compared to a pre-treatment baseline with no difference between the groups. However, the yohimbine treated group did show a significant reduction in peak fear during a one week follow-up exposure compared to the control group. One interpretation is that yohimbine enhanced extinction consolidation after the first exposure session resulting in the significant reduction seen at the follow up visit. As a classic anxiogenic, yohimbine has induced flashbacks in patients with PTSD (Southwick et al., 1993) and panic attacks in those with panic disorder (Charney et al., 1987). Thus, yohimbine as a treatment for such patients would generally be contraindicated (Davis et al., 2006a).

2.5. The role of cannabinoid agents in fear extinction

The endogenous cannabinoid (CB) system has become a major focus in the search for pharmacological interventions for fear extinction (for review see: Davis et al., 2006a; Chhatwal and Ressler, 2007; Varvel et al., 2009). CB1 receptor agonists and antagonists produce complex cognitive effects and alter extinction learning. CB1 receptors are involved in the processing of sensory information and in learning and are found at highest concentrations in the medial PFC, hippocampus, and BLA. Cannabinoid synaptic transmission is a source for plasticity in the form of LTP in these regions. CB1 antagonist rimonabant (SR141716A) does not appear to affect the acquisition of cued fear conditioning but does impair extinction learning in several protocols including fear-potentiated startle (Chhatwal et al., 2005a), auditory fear conditioning (Marsicano et al., 2002; Niyuhire et al., 2007), contextual fear conditioning (Suzuki et al., 2004), escape behavior in a water maze (Varvel et al., 2005), and passive avoidance of a foot shock (Niyuhire et al., 2007).

Another CB1 receptor antagonist AM251 has been shown to have a mixture of effects on anxiety and conditioning. AM-251, given 30 min before testing, reduced conditioned freezing in a mouse model (Mikics et al., 2006). Arenos et al. (2006) reported that AM-251 administered to Long-Evans rats prior to conditioning or testing reduced contextual fear expression, while AM-251 given prior to conditioning increased fear expression when tested in a novel context. In contrast, Reich et al. (2008) reported that AM251 administered before conditioning and/or testing enhanced acquisition of both trace and delay fear conditioning. AM251 also increased generalized fear (baseline freezing) and cued freezing during recall testing while impairing extinction for both baseline fear and cued fear conditioning. AM251 appears to produce anxiogenic effects and affects fear behavior in a state-dependent manner without altering short or long term memory consolidation (Reich et al., 2008). However, bilateral infusions of AM251 into the CA1 region of the hippocampus after re-exposure to the conditioning context facilitated the reconsolidation of the fear memory, while the same local infusion blocked extinction learning (de Oliveira Alvares et al., 2008). Infralimbic infusions of AM251, given 30 min prior to extinction training, also impaired the extinction of fear potentiated startle in a rat model (Lin et al., 2009b). Supporting these results were findings that extinction of fear conditioning was impaired in CB1 receptor knockout mice (Marsicano et al., 2002; Varvel et al., 2005; Kamprath et al., 2006). In summary, the effects of CB1 antagonism on fear acquisition and expression are inconsistent, and CB1 antagonism generally impairs fear extinction.

Given these CB1 antagonist effects, it would be hypothesized that CB1 agonists should facilitate such extinction learning. There are mixed results with the administration of the CB1 agonist WIN 55,212-2. This CB1 agonist given 30 min before testing has been shown to increase the expression of conditioned fear (Mikics et al., 2006) and does not appear to affect fear extinction (Chhatwal et al., 2005a; Pamplona et al., 2006). However, systemic administration of a low dose of this CB1 agonist before extinction did facilitate extinction in other studies (Pamplona et al., 2006, 2008). The timing and location of drug administration are critical as infralimbic infusions of WIN 55,212-22 prior to extinction training facilitated the extinction of fear-potentiated startle (Lin et al., 2008, 2009b). Chronic administration of this drug prior to fear conditioning impaired extinction and attenuated the extinction

facilitating effect of acute pre-extinction training infralimbic infusions (Lin et al., 2008).

Improvements in fear extinction learning have been demonstrated with administration of AM404, an inhibitor of cannabinoid breakdown and reuptake. AM404 has been shown to have anxiolytic effects, decreasing anxiety in defensive startle, elevated plus-maze, and ultrasonic vocalization tests (Bortolato et al., 2006), without effecting baseline startle (Bortolato et al., 2006; Chhatwal et al., 2005a). Infralimbic infusions of AM404 after training reduced the fear-potentiated startle (Lin et al., 2009b). Using a fear-potentiated startle model, AM404 produced dose-dependent enhancement of cued fear conditioning (Chhatwal et al., 2005a; Lin et al., 2009b) and decreased shock-induced reinstatement (Chhatwal et al., 2005a). Systemic administration of AM404 or cannabidiol, a phytocannabinoid, given before extinction training extinguished fear responses (Bitencourt et al., 2008). AM404 and cannabidiol both have anxiolytic-like effects in naive and conditioned rats (Bitencourt et al., 2008). Chhatwal and Ressler (2007) showed that AM404 and similar compounds are anxiolytic and contrast with the majority of agents that enhance extinction which are often anxiogenic. Their anxiolytic effects make these agents especially attractive because they facilitate inhibition of fear through extinction-like processes and avoid the amnestic effects of many anxiolytics (Chhatwal and Ressler, 2007).

2.6. The role of dopaminergic agents in fear extinction

In general, activation of dopamine D1 and D2 dopamine receptors in the prefrontal cortex reverses cognitive deficits and enhances cognition in healthy subjects. However, these cognitive effects are task-dependent and dopaminergic drugs produce complex and non-uniform effects. Both dopamine D1 receptor agonist SKF38393 and enhancers of dopaminergic efflux, amphetamine and cocaine, attenuated the extinction of a fear-potentiated startle response in rats (Willick and Kokkinidis, 1995; Borowski and Kokkinidis, 1998). The injection of cocaine or SKF38393 after extinction produced the renewal of fear-potentiated startle responses (Borowski and Kokkinidis, 1998). In a promising cognitive enhancement study, Dubrovina and Zinov'eva (2010) examined extinction of passive avoidance in intact mice and mice with depression-like behaviors. This depression-like behavior resulted from sessions of forced swimming in a water bath for three days that resulted in learned immobility. In intact mice, activation and blockade of D1 receptors with SKF38393 and SCH23390, respectively, had no effect on extinction in the passive avoidance task. Activation of D2 receptors with quinpirole, but not blockade with sulpiride, led to a deficit in the extinction of the same task. In this model, activation of D1 receptors with SKF38393 normalized extinction while the D2 agonist quinpirole had no effect. The normalization of extinction was also produced with the blockade of both types of dopamine receptor by SCH23390 and sulpiride.

Modulation of dopaminergic systems in the medial PFC would be expected to modulate the rate of extinction (Quirk et al., 2006). In a review of extinction circuits involved in fear learning in the PFC, Peters et al. (2009) explained that the prelimbic and infralimbic cortices may provide a switch for expression of conditioned fear and its extinction, respectively (Peters et al., 2009). Microinfusions of the D1 receptor antagonist SCH23390 into the infralimbic PFC before extinction training impaired such learning while microinfusions of SCH23390 into the BLA caused impairments in fear acquisition (Hikind and Maroun, 2008). D1-receptor knockout mice also showed deficits in extinction (El-Ghundi et al., 2001). In contrast, systemic administration of D2 antagonist sulpiride to mice facilitated extinction of conditioned fear (Ponnusamy et al., 2005). Notably, sulpiride-treated animals demonstrated extinction to spaced presentations of the CS, a protocol that produced no extinction in vehicle-treated controls (Ponnusamy et al., 2005). In summary, cognitive enhancing dopamine D1 and D2 agonists appear to have mixed effects related to fear extinction.

2.7. Cognitive enhancers affecting epigenetic and neurotrophic mechanisms

Epigenetic mechanisms and neurotrophic factors represent novel targets for enhancing cognition and altering gene expression and associated plasticity. Certain drugs modify transcriptional pathways via histones which are highly basic proteins that organize DNA within the nucleus. Histone deacetylases are agents which modify histone tails and alter neuronal gene transcription. Histone deacetylase (HDAC) inhibitor treatment enhanced extinction training as it increased dendritic sprouting, synaptic connections, and neurotrophic factor expression (Bredy and Barad, 2008). Fear extinction was associated with histone acetylation around the BDNF gene promoter and also increased BDNF mRNA expression in PFC (Bredy et al., 2007). In this last study, HDAC inhibitor valproate enhanced fear extinction and synergized the behavioral effects of extinction training. Valproate enhanced the effects of extinction training on histone H4 acetylation around BDNF gene promoters and on BDNF mRNA expression. HDAC inhibitors, sodium butyrate and trichostatin A, produced greater effects in context-evoked fear extinction compared to vehicle control treatment (Lattal et al., 2007). There appears to be a relationship between histone modification, epigenetic regulation of neurotrophic factors, neural plasticity and fear extinction. HDAC inhibitors may be useful agents for enhancing fear extinction through specific plasticity mechanisms in the PFC.

Agents directly enhancing BDNF levels also produce increases in fear extinction via synaptic plasticity in the PFC. BDNF infused into the infralimbic PFC reduced conditioned fear in the absence of extinction training (Peters et al., 2010). These behavioral effects involved NMDA receptors and did not eliminate the original fear memory. Rats with impairments in fear extinction demonstrated reductions in BDNF levels in hippocampal inputs to the infralimbic PFC. By restoring BDNF levels in subjects with low hippocampal levels, extinction was improved. Mice expressing a human variant of BDNF demonstrated impaired fear extinction like the human phenotype (Soliman et al., 2010). This human phenotype showed impairments in frontal-amygdalar activity and this suggest the importance of BDNF targets in fear extinction. Mice with BDNF deletions also showed reduced fear extinction as demonstrated by fear-potentiated startle and freezing behaviors (Heldt et al., 2007). BDNF mediates its effects via tropomyosin receptor kinase B (TrkB) signaling. A lentivirus encoding a dominant-negative TrkB was used to antagonize BDNF signaling during fear extinction (Chhatwal et al., 2006). Lentivirus-infected rats showed impairments in their retention of extinction, suggesting that amygdala TrkB signaling is necessary for the formation of stable extinction memories. In summary, these studies show that direct BDNF treatment or its regulation by HDAC inhibitor treatment enhances infralimbic neural circuitry and increases fear extinction.

Corticotrophins are agents that potentially regulate fear extinction via epigenetic, neurotrophin and other mechanisms. Elevated glucocorticoid levels impair the retrieval of fear stimuli and may also inhibit retrieval of fear memory associated with phobias. Agents that mimic the effects of cortisol and that antagonize the effects of corticotrophin releasing factor (CRF) have been utilized in fear extinction. In a fear-potentiated startle procedure, rats given light-shock pairings (fear conditioning) followed by light-alone extinction training were then given unsignaled shocks to reinstate fear to the light (Waddell et al., 2008). Intracerebroventricular administration of a CRF antagonist prior to reinstatement training dose-dependently prevented such effects and suggests that such an agent could prevent this form of fear relapse. In subjects with social phobia study (Soravia et al., 2006), cortisone administered before a stressor significantly reduced self-reported fear during the anticipation, exposure, and recovery phases.

In a study of spider phobics from the same report, repeated oral administration of cortisone, but not placebo, before exposure to a spider photograph reduced the CS-induced fear. This effect was maintained when subjects were exposed to the stimulus two days after the last cortisone administration, suggesting that this agent enhanced fear extinction.

3. Conclusions

A greater understanding of the use of cognitive enhancers in fear extinction through animal models will translate into more effective interventions for extinguishing fear memories in the clinical setting. In animal models of fear extinction, electrophysiological changes (e.g. amygdalar LTP) occur and produce consequent changes in structural plasticity. Alterations in genetic and protein expression produce synaptic plasticity and these adaptive changes result in reorganization of neural circuitry. Even after extinction of fear conditioning, fear cues and contexts can evoke fear responses and the associated synaptic and signaling mechanisms underlying these persistent fear responses are important to understand. We have reviewed that in fear extinction, there are widespread and important changes in GABA and glutamatergic signaling in key cortical, hippocampal and amygdala pathways that result in the inhibition of fear outputs. We have reviewed how other neurotransmitter and neurotrophic systems contribute to the development and expression of fear extinction.

Extinction in animal models is proposed to have parallels in psychotherapeutic clinical approaches via exposure therapy. Following the experience of trauma, many people can have persistent symptoms of arousal, avoidance and re-experiencing of the traumatic event. Such individuals experience distress and avoidance when confronted with thoughts, feelings, and situations related to the trauma. Exposure therapy produces extinction of trauma-related thoughts, feelings, and behaviors. Patients learn to understand that their fears and reactions to these stimuli are unrealistic (Foa, 2006). Thus, fear extinction therapies have been found to be efficacious in the treatment of PTSD (Foa, 2006; Schnurr et al., 2007). Several factors limit efficacy of extinction learning and often extinction reminders and prolonged treatment are needed. The relative permanence of the CS and CR bonds in fear, and its resistance to extinction could account for the partial efficacy of such treatment.

Because of the incomplete effects of fear extinction learning, cognitive enhancing agents which improve such extinction can be helpful. However, only a few of these agents produce reliable and dose-, context- and time-dependent effects in these models. Of all these cognitive enhancers, NMDA agonists appear to be most reliable for the enhancement of fear extinction across models. Other cognitive enhancers such HDAC inhibitors, BDNF/TrkB agents, glutamatergic AMPA agonists, and alpha-2 antagonist also enhance fear extinction, but more study of these effects and their temporal- and context-dependence are necessary. A few other cognitive enhancers have produced mixed effects on fear extinction and more studies are needed to clarify the effects of GABAergic antagonists, cholinergic nicotinic agonists, cannabinoid CB1 agonists, and dopamine D1 and D2 agonists. The adrenergic alpha-2 antagonist yohimbine has been shown to consistently facilitate fear extinction in animals (Cain et al., 2004; Hefner et al., 2008; Morris and Bouton, 2007; Mueller et al., 2009) and has been applied in translation research with humans (Powers et al., 2009). However, as an anxiogenic agent, the successful and safe use of yohimbine as a treatment for fear extinction is questionable (Davis et al., 2006a, Mueller and Cahill, 2010). The success of DCS as a fear extinction agent raises interesting questions about its neural mechanisms so that other similar agents can be pursued in testing.

NMDA agonists produce increases in synaptic efficiency in corticolimbic pathways that appear critical in mediating fear extinction. Intra-amygdala infusion of NMDA receptor antagonists blocks the development of conditioned fear and of amygdalar LTP. The consolidation of *fear extinction* involves glutamatergic NMDA receptor-mediated burst firing in infralimbic portions of the PFC. Interference with infralimbic PFC glutamatergic pathways using NMDA receptor antagonists inhibits fear extinction and conversely NMDA agonist treatments (such as with DCS) enhance it. Additional glutamatergic changes in plasticity in cortico-amygdalar pathways are mediated by AMPA receptor trafficking that appears critical to various aspects of conditioned fear. Mechanisms of fear conditioning and its extinction are most carefully studied at the plasticity in cortico-amygdalar pathways where glutamate AMPA receptor subunits are involved.

Extinction enhancing agents which alter the acquisition and expression of fear extinction when given outside of the learning context produce state independent effects and appear to alter the CS–CR bond related to fear conditioning. Such agents will have enduring effects inhibiting renewal and recovery of fear conditioning. Some of the learning mechanisms which regulate extinction learning involve NMDA and GABA receptors, transcriptional regulation, epigenetic mechanisms and neurotrophic factor-induced increases in plasticity in cortico-amygdalar pathways. Extinction learning may reverse the synaptic changes induced by fear conditioning and result in the reversal of amygdalar LTP. NMDA agonists appear to trigger a signaling cascade resulting in AMPA receptor subunit internalization in the amygdala (Yang and Lu, 2005; Mao et al., 2008). The distinctive intra-cellular mechanisms of DCS offer one explanation for its unique success and point to new avenues of research in the search for cognitive enhancing agents. These cognitive enhancers induce receptor mediated AMPA receptor internalization and enduring alterations in synaptic transmission that result in changes in the number and morphology of dendritic spines at cortical inputs to amygdalar neurons.

Various cognitive enhancers produce changes in cortico-amygdala synaptic plasticity through multiple mechanisms and these neural changes enhance fear extinction. Greater precision in our understanding of the effects of cognitive enhancers on functional and structural plasticity will result in the development of new and effective pharmacological approaches in fear extinction and exposure therapies. Research related to the use of cognitive enhancers in fear extinction, which define the mechanisms of functional and structural plasticity underlying by extinction learning, provides great hope for the treatment of anxiety disorders.

Acknowledgements

The authors acknowledge grants from the Department of Veterans Affairs (Merit Reviews) and the Department of Defense (CDMRP Concept Award). Both authors contributed to and have approved the final draft of the manuscript.

References

Akirav I, Haizel H, Maroun M. Enhancement of conditioned fear extinction by infusion of the GABAA agonist muscimol into the rat prefrontal cortex and amygdala. Eur J Neurosci 2006;23:758–64.
Alvarez RP, Biggs A, Chen G, Pine DS, Grillon C. Contextual fear conditioning in humans: cortical–hippocampal and amygdala contributions. J Neurosci 2008;28:6211–9.
Amano T, Unal CT, Paré D. Synaptic correlates of fear extinction in the amygdala. Nat Neurosci 2010;13:489–94.
Arenos JD, Musty RE, Bucci DJ. Blockade of cannabinoid receptors alters contextual learning and memory. Eur J Pharmacol 2006;539:177–83.
Baker JD, Azorlosa JL. The NMDA antagonist MK-801 blocks the extinction of Pavlovian fear conditioning. Behav Neurosci 1996;110:618–20.
Berlau DJ, McGaugh JL. Enhancement of extinction memory consolidation: the role of the noradrenergic and GABAergic systems within the basolateral amygdala. Neurobiol Learn Mem 2006;86:123–32.
Bitencourt RM, Pamplona FA, Takahashi RN. Facilitation of contextual fear memory extinction and anti-anxiogenic effects of AM404 and cannabidiol in conditioned rats. Eur Neuropsychopharmacol 2008;18(12):849–59.

Boccia MM, Blake MG, Baratti CM, McGaugh JL. Involvement of the basolateral amygdala in muscarinic cholinergic modulation of extinction memory consolidation. Neurobiol Learn Mem 2009;91:93–7.
Borowski TB, Kokkinidis L. The effects of cocaine, amphetamine, and the dopamine D1 receptor agonist SKF 38393 on fear extinction as measured with potentiated startle: implications for psychomotor stimulant psychosis. Behav Neurosci 1998;112(4):952–65.
Bortolato M, Campolongo P, Mangieri RA, et al. Anxiolytic-like properties of the anandamide transport inhibitor AM404. Neuropsychopharmacology 2006;31: 2652–9.
Bouton ME. Context and behavioral processes in extinction. Learn Mem 2004;11: 485–94.
Bouton ME, Bolles RC. Role of conditioned contextual stimuli in reinstatement of extinguished fear. J Exp Psychol Anim B 1979;5:368–78.
Bouton ME, King DA. Contextual control of the extinction of conditioned fear: tests for the associative value of the context. J Exp Psychol Anim B 1983;9:248–65.
Bouton ME, Ricker ST. Renewal of extinguished responding in a second context. Anim Learn Behav 1994;22:317–24.
Bouton ME, Kenney FA, Rosengard C. State-dependent fear extinction with two benzodiazepine tranquilizers. Behav Neurosci 1990;140:44–55.
Bouton ME, Vurbic D, Woods MA. D-cycloserine facilitates context-specific fear extinction learning. Neurobiol Learn Mem 2008;90(3):504–10.
Bredy TW, Barad M. The histone deacetylase inhibitor valproic acid enhances acquisition, extinction, and reconsolidation of conditioned fear. Learn Mem 2008;15:39–45.
Bredy TW, Wu H, Crego C, Zellhoefer J, Sun YE, Barad M. Histone modifications around individual BDNF gene promoters in prefrontal cortex are associated with extinction of conditioned fear. Learn Mem 2007;14:268–76.
Burgos-Robles A, Vidal-Gonzalez I, Santini E, Quirk GJ. Consolidation of fear extinction requires NMDA receptor-dependent bursting in the ventromedial prefrontal cortex. Neuron 2007;53:871–80.
Cain CK, Blouin AM, Barad M. Adrenergic transmission facilitates extinction of conditional fear in mice. Learn Mem 2004;11:179–87.
Cammarota M, Bevilaqua LR, Kerr D, Medina JH, Izquierdo I. Inhibition of mRNA and protein synthesis in the CA1 region of the dorsal hippocampus blocks reinstallment of an extinguished conditioned fear response. J Neurosci 2003;23:737–41.
Campeau S, Liang KC, Davis M. Long-term retention of fear-potentiated startle following a short training session. Anim Learn Behav 1990;18:462–8.
Castellano C, McGaugh JL. Retention enhancement with posttraining picrotoxin: lack of state dependency. Behav Neural Biol 1989;51:165–70.
Castellano C, McGaugh JL. Effects of post-training bicuculline and muscimol on retention: lack of state dependency. Behav Neural Biol 1990;54:156–64.
Charney DS, Woods SW, Goodman WK, Heninger GR. Neurobiological mechanisms of panic anxiety: biochemical and behavioral correlates of yohimbine-induced panic attacks. Am J Psychiatry 1987;144:1030–6.
Cheng DT, Knight DC, Smith CN, Stein EA, Helmstetter FJ. Functional MRI of human amygdala activity during Pavlovian fear conditioning: stimulus processing versus response expression. Behav Neurosci 2003;117:3-10.
Cheng DT, Disterhoft JF, Power JM, Ellis DA, Desmond JE. Neural substrates underlying human delay and trace eyeblink conditioning. Proc Natl Acad Sci USA 2008;105: 8108–13.
Chhatwal JP, Ressler KJ. Modulation of fear and anxiety by the endogenous cannabinoid system. CNS Spectr 2007;12(3):211–20.
Chhatwal JP, Davis M, Maguschak KA, Ressler KJ. Role of endogenous cannabinoids in cognition and emotionality. Enhancing cannabinoid neurotransmission augments the extinction of conditioned fear. Neuropsychopharmacology 2005a;30(3): 516–24.
Chhatwal JP, Myers KM, Ressler KJ, Davis M. Regulation of gephyrin and GABAa receptor binding within the amygdala after fear acquisition and extinction. J Neurosci 2005b;25:502–6.
Chhatwal JP, Stanek-Rattiner L, Davis M, Ressler KJ. Amygdala BDNF signaling is required for consolidation but not encoding of extinction. Nat Neurosci 2006;9: 870–2.
Choi DC, Maguschak KA, Ye K, Jang SW, Myers KM, Ressler KJ. Prelimbic cortical BDNF is required for memory of learned fear but not extinction or innate fear. Proc Natl Acad Sci USA 2010;107:2675–80.
Corcoran KA, Maren S. Hippocampal inactivation disrupts contextual retrieval of fear memory after extinction. J Neurosci 2001;21:1720–6.
Corcoran KA, Desmond TJ, Frey KA, Maren S. Hippocampal inactivation disrupts the acquisition and contextual encoding of fear extinction. J Neurosci 2005;25: 8978–87.
Davis M, Myers KM, Chhatwal J, Ressler KJ. Pharmacological treatments that facilitate extinction of fear: Relevance to psychotherapy. NeuroRx: The Journal of the American Society for Experimental NeuroTherapeutics 2006a;3:82–96.
Davis M, Ressler K, Rothbaum BO, Richardson R. Effects of D-cycloserine on extinction: translation from preclinical to clinical work. Biol Psychiatry 2006b;60:369–75.
De Oliveira Alvares L, Pasqualini Genro B, Diehi F, Molina VA, Quillfeldt. Opposite action of hippocampal CB1 receptors in memory reconsolidation and extinction. Neurosci 2008;154(4):1648–55.
Dubrovina NI, Zinov'eva DV. Effects of activation and blockade of dopamine receptors on the extinction of a passive avoidance reaction in mice with a depressive-like state. Neurosci Behav Physiol 2010;40(1):55–9.
El-Ghundi M, O'Dowd BF, George SR. Prolonged fear responses in mice lacking dopamine D1 receptor. Brain Res 2001;892:86–93.
Elias GA, Gulick D, Wilkinson DS, Gould TJ. Nicotine and extinction of fear conditioning. Neuroscience 2010;165:1063–73.
Falls WA, Miserendino MJD, Davis M. Extinction of fear-potentiated startle: blockade by infusion of an NMDA antagonist into the amygdala. J Neurosci 1992;12:854–63.
Foa EB. Psychosocial therapy for posttraumatic stress disorder. J Clin Psychiatry 2006;67(Suppl 2):40–5.
Gale GD, Anagnostaras SG, Fanselow MS. Cholinergic modulation of Pavlovian fear conditioning: effects of intrahippocampal scopolamine infusion. Hippocampus 2001;11:371–6.
Gould TJ, Higgins JS. Nicotine enhances contextual fear conditioning in C57BL/6J mice at 1 and 7 days post-training. Neurobiol Learn Mem 2003;80:147–57.
Gould TJ, Wehner JM. The enhancement of contextual fear conditioning. Behav Brain Res 1999;102:31–9.
Gould TJ, Feiro O, Moore D. Nicotine enhances trace cued fear conditioning but not delay cued fear conditioning in C57BL/6 mice. Behav Brain Res 2004;155: 167–73.
Grillon C. D-cycloserine facilitation of fear extinction and exposure-based therapy might rely on lower-level, automatic mechanisms. Biol Psychiatry 2009;66(7): 636–41.
Guastella AJ, Richardson R, Lovibond PF, Rapee RM, Gaston JE, Mitchell P, et al. A randomised controlled trial of D-cycloserine enhancement of exposure therapy for social phobia. Biol Psychiatry 2008;63:544–9.
Harris JA, Westbrook FR. Evidence that GABA transmission mediates context-specific extinction of learned fear. Psychopharmacology 1998;140:105–15.
Hart G, Harris JA, Westbrook FR. Systemic or intra-amygdala injection of a benzodiazepine (midazolam) impairs extinction but spares re-extinction of conditioned fear responses. Learn Mem 2009;16:53–61.
Hefner K, Whittle N, Juhasz J, Norcross M, Karlsson RM, Saksida LM, et al. Impaired fear extinction learning and cortico-amygdala circuit abnormalities in a common genetic mouse strain. J Neurosci 2008;28:8074–85.
Heinrichs SC, Leite-Morris KA, Carey RJ, Kaplan GB. Baclofen enhances extinction of opiate conditioned place preference. Behav Brain Res 2010;207(2):353–9 Mar 5.
Heldt SA, Ressler KJ. Training-induced changes in the expression of $GABA_A$-associated genes in the amygdala after the acquisition and extinction of Pavlovian fear. Eur J Neurosci 2007;26:3631–44.
Heldt SA, Stanek L, Chhatwal JP, Ressler KJ. Hippocampus-specific deletion of BDNF in adult mice impairs spatial memory and extinction of aversive memories. Mol Psychiatry 2007;12:656–70.
Hikind N, Maroun M. Microinfusion of the D1 receptor antagonist, SCH23390 into the IL but not the BLA impairs consolidation of extinction of auditory fear conditioning. Neurobiol Learn Mem 2008;90:217–22.
Hobin JA, Ji J, Maren S. Ventral hippocampal muscimol disrupts context-specific fear memory retrieval after extinction in rats. Hippocampus 2006;16:174–82.
Holmes A, Quirk GJ. Pharmacological facilitation of fear extinction and the search for adjunct treatments for anxiety disorders—the case of yohimbine. Trends Pharmacol Sci 2010;31:2–7.
Kamprath K, Marsicano G, Tang J, Monory K, Bisogno T, Di Marzo V, et al. Cannabinoid CB1 receptor mediates fear extinction via habituation-like processes. J Neurosci 2006;26(25):6677–86.
Kaplan GB, Heinrichs SC, Carey RJ. Treatment of addiction and anxiety using extinction approaches: neural mechanisms and their treatment implications. Pharmacol Biochem Behav 2011;97:619–25.
Kenney JW, Florian C, Portugal GS, Abel T, Gouls TJ. Involvement of hippocampal Jun-N terminal kinase pathway in the enhancement of learning and memory by nicotine. Neuropsychopharmacology 2010;35:483–92.
Kim JJ, Jung MW. Neural circuits and mechanisms involved in Pavlovian fear conditioning: a critical review. Neurosci Biobehav Rev 2006;30:188–202.
Lalumiere RT, Niehoff KE, Kalivas PW. The infralimbic cortex regulates the consolidation of extinction after cocaine self-administration. Learn Mem 2010;17 168-7.
Lattal KM, Barrett RM, Wood MA. Systemic or intrahippocampal delivery of histone deacetylase inhibitors facilitates fear extinction. Behav Neurosci 2007;121:1125–31.
Laurent V, Westbrook RF. Distinct contributions of the basolateral amygdala and the medial prefrontal cortex to learning and relearning extinction of context conditioned fear. Learn Mem 2008;15:657–66.
Laurent V, Marchand AR, Westbrook RF. The basolateral amygdala is necessary for learning but not relearning extinction of context conditioned fear. Learn Mem 2008;15:304–14.
Ledgerwood L, Richardson R, Cranney J. Effects of D-cycloserine on extinction of conditioned freezing. Behav Neurosci 2003;117:341–9.
Ledgerwood L, Richardson R, Cranney J. D-cycloserine and the facilitation of extinction of conditioned fear: consequences for reinstatement. Behav Neurosci 2004;118(3): 505–13.
Ledgerwood L, Richardson R, Cranney J. D-cycloserine facilitates extinction of learned fear: Effects on reacquisition and generalized extinction. Biol Psychiatry 2005;57: 841–7.
Lee H, Kim JJ. Amygdalar NMDA receptors are critical for new fear learning in previously fear-conditioned rats. J Neurosci 1998;18:8444–54.
Lee JL, Milton AL, Everitt BJ. Reconsolidation and extinction of conditioned fear: inhibition and potentiation. J Neurosci 2006;26:10051–6.
Levin ED, Simon BB. Nicotinic acetylcholine involvement in cognitive function in animals. Psychopharmacology 1998;138:217–30.
Likhtik E, Popa D, Apergis-Schoute J, Fidacaro GA, Paré D. Amygdala intercalated neurons are required for expression of fear extinction. Nature 2008;454:642–5.
Lin HC, Mao SC, Chen PS, Gean PW. Chronic cannabinoid administration in vivo compromises extinction of fear memory. Learn Mem 2008;15(12):876–84.

Lin HC, Mao SC, Gean PW. Block of γ-aminobutyric acid—a receptor insertion in the amygdala impairs extinction of conditioned fear. Biol Psychiatry 2009a;66:665–73.
Lin HC, Mao SC, Su CL, Gean PW. The role of prefrontal cortex CB1 receptors in the modulation of fear memory. Cereb Cortex 2009b;19(1):165–75.
Makkar SR, Zhang SQ, Cranney J. Behavioral and neural analysis of GABA in the acquisition, consolidation, reconsolidation, and extinction of fear memory. Neuropsychopharmacology 2010;35:1625–52.
Mao SC, Lin HC, Gean PW. Augmentation of fear extinction by D-cycloserine is blocked by proteasome inhibitors. Neuropsychopharmacology 2008;33:3085–95.
Maren S. Pavlovian fear conditioning as a behavioral assay for hippocampus and amygdala function: cautions and caveats. Eur J Neurosci 2008;28:1661–6.
Maren S, Aharonov G, Fanselow MS. Neurotoxic lesions of the dorsal hippocampus and Pavlovian fear conditioning in rats. Behav Brain Res 1997;88(2):261–74.
Marsicano G, Wotjak CT, Azad SC, Bisogno T, Rammes G, Cascio MG. The endogenous cannabinoid system controls extinction of aversive memories. Nature 2002;418: 530–4.
McDonald AJ. Cortical pathways to the mammalian amygdala. Prog Neurobiol 1998;55: 257–332.
McGaugh JL, Introini-Collison IB, Nagahara AH, Cahill L, Brioni JD, et al. Involvement of the amygdaloid complex in neuromodulatory influences on memory storage. Neurosci Biobehav Rev 1990;14:425–31.
Mikics E, Dombi T, Barsvári B, Varga B, Ledent C, Freund TF, et al. The effects of cannabinoids on contextual conditioned fear in CB1 knockout and CD1 mice. Behav Pharmacol 2006;17(3):223–30.
Morris RW, Bouton ME. The effect of yohimbine on the extinction of conditioned fear: a role for context. Behav Neurosci 2007;121:501–14.
Morris RW, Westbrook RF, Killcross AS. Reinstatement of extinguished fear by beta-adrenergic arousal elicited by a conditioned context. Behav Neurosci 2005;119: 1662–71.
Mueller D, Cahill SP. Noradrenergic modulation of extinction learning and exposure therapy. Behav Brain Res 2010;208(1):1-11.
Mueller D, Porter JT, Quirk GJ. Noradrenergic signaling in infralimbic cortex increases cell excitability and strengthens memory for fear extinction. J Neurosci 2008;28: 369–75.
Mueller D, Olivera-Figueroa LA, Pine DS, Quirk GJ. The effects of yohimbine and amphetamine on fear expression and extinction in rats. Psychopharmacology 2009;204:599–606.
Myers KM, Davis M. Behavioral and neural analysis of extinction. Neuron 2002;36: 567–84.
Myers KM, Davis M. Mechanisms of fear extinction. Mol Psychiatry 2007;12:120–50.
Nader K, LeDoux JE. Inhibition of the mesoamygdala dopaminergic pathway impairs the retrieval of conditioned fear associations. Behav Neurosci 1999;113:891–901.
Nakagawa Y, Iwasaki T, Ishima T, Kimura K. Interaction between benzodiazepine and GABA-A receptors in state-dependent learning. Life Sci 1993;52:1935–45.
Niyuhire F, Varvel SA, Thorpe AJ, Stokes RJ, Wiley JL, Lichtman AH. The disruptive effects of the CB(1) receptor antagonist rimonabant on extinction learning in mice are task-specific. Psychopharmacology 2007;191:223–31.
Norberg MM, Krystal JH, Tolin DF. A meta-analysis of D-cycloserine and the facilitation of fear extinction and exposure therapy. Biol Psychiatry 2008;63:1118–26.
Norrholm SD, Jovanovic T, Vervliet B, Myers KM, Davis M, Rothbaum BO, et al. Conditioned fear extinction and reinstatement in a human fear-potentiated startle paradigm. Learn Mem 2006;13:681–5.
Ouyang M, Thomas SA. A requirement for memory retrieval during and after long-term extinction learning. Proc Natl Acad Sci U S A. 2005;2:9347–52.
Pamplona FA, Prediger RD, Pandolfo P, Takahashi RN. The cannabinoid receptor agonist WIN 55, 212-2 facilitates the extinction of contextual fear memory and spatial memory in rats. Psychopharmacology 2006;188:641–9.
Pamplona FA, Bitencourt RM, Takahashi RN. Short- and long-term effects of cannabinoids on the extinction of contextual fear memory in rats. Neurobiol Learn Mem 2008;90:290–3.
Pape HC, Pare D. Plastic synaptic networks of the amygdala for the acquisition, expression, and extinction of conditioned fear. Physiol Rev 2010;90:419–63.
Parnas AS, Weber M, Richardson R. Effects of multiple exposures to D-cycloserine on extinction of conditioned fear in rats. Neurobiol Learn Mem 2005;83:224–31.
Patel JB, Ciofalo B, Iorio LC. Benzodiazepine blockade of passive avoidance task in mice: a state-dependent phenomenon. Psychopharmacology 1979;61:25–8.
Pereira ME, Rosat R, Huang CH, Godoy MGC, Izquierdo I. Inhibition by diazepam of the effect of additional training and of extinction on the retention of shuttle avoidance behavior in rats. Behav Neurosci 1989;103(1):202–5.
Peters J, Kalivas PW, Quirk GJ. Extinction circuits for fear and addiction overlap in prefrontal cortex. Learn Mem 2009;16:279–88.
Peters J, Dieppa-Perea LM, Melendez LM, Quirk GJ. Induction of fear extinction with hippocampal-infralimbic BDNF. Science 2010;328(5983):1288–90.
Ponnusamy R, Nissim HA, Barad M. Systemic blockade of D2-like dopamine receptors facilitates extinction of conditioned fear in mice. Learn Mem 2005;12(4):399–406.
Power AE, Vazdarjanova A, McGaugh JL. Muscarinic cholinergic influences in memory consolidation. Neurobiol Learn Mem 2003;80:178–93.
Powers MB, Smits JA, Otto MW, Sanders C, Emmelkamp PM. Facilitation of fear extinction in phobic participants with a novel cognitive enhancer: a randomized placebo controlled trial of yohimbine augmentation. J Anxiety Disord 2009;23:350–6.
Quirk GJ. Memory for extinction of conditioned fear is long-lasting and persists following spontaneous recovery. Learn Mem 2002;9:402–7.
Quirk GJ, Mueller D. Neural mechanisms of extinction learning and retrieval. Neuropsychopharmacology 2008;33:56–72.
Quirk GJ, Garcia R, Gonzalez-Lima F. Prefrontal mechanisms in extinction of conditioned fear. Biol Psychiatry 2006;60:337–43.
Reich CG, Mohammadi MH, Alger BE. Endocannabinoid modulation of fear responses: learning and state-dependent performance effects. J Psychopharmacol 2008;22: 769–77.
Ressler KJ, Paschall G, Zhou X, Davis M. Regulation of synaptic plasticity genes during consolidation of fear conditioning. J Neurosci 2002;22:7892–902.
Rodriguez-Romaguera J, Sotres-Bayon F, Mueller D, Quirk GJ. Systemic propranolol acts centrally to reduce conditioned fear in rats without impairing extinction. Biol Psychiatry 2009;65:887–92.
Rogers JL, Kesner RP. Cholinergic modulation of the hippocampus during encoding and retrieval of tone/shock-induced fear conditioning. Learn Mem 2004;11:102–7.
Roldan G, Cobos-Zapiain G, Quirarte GL, Prado-Alcala RA. Dose- and time-dependent scopolamine-induced recovery of an inhibitory avoidance response after its extinction in rats. Behav Brain Res 2001;121:173–9.
Rossato JI, Bevilaqua LRM, Lima RH, Medina JH, Izquierdo I, Cammarota M. On the participation of hippocampal p38 mitogen-activated protein kinase in extinction and reacquisition of inhibitory avoidance memory. Neuroscience 2006;143: 15–23.
Santini E, Muller RU, Quirk GJ. Consolidation of extinction learning involves transfer from NMDA-independent to NMDA-dependent memory. J Neurosci 2001;21: 9009–17.
Schnurr PP, Friedman MJ, Engel CC, Foa EB, Shea MT, Chow BK, et al. Cognitive behavioral therapy for PTSD in women: a randomized controlled trial. JAMA 2007;28(8):820–30 297.
Shin LM, Liberzon I. The neurocircuitry of fear, extinction, and stress disorders. Neuropsychopharmacology 2010;35:169–91.
Smith LN, McDonald CG, Bergstrom HC, Brielmaier JM, Eppolito AK, Wheeler TL, et al. Long-term changes in fear conditioning and anxiety-like behavior following nicotine exposure in adult versus adolescent rats. Pharmacol Biochem Behav 2006;85:91–7.
Soares JCK, Fornari RV, Oliveira MGM. Role of muscarinic M1 receptors in inhibitory avoidance and contextual fear conditioning. Neurobiol Learn Mem 2006;86: 188–96.
Soliman F, Glatt CE, Bath KG, Levita L, Jones RM, Pattwell SS, et al. A genetic variant BDNF polymorphism alters extinction learning in both mouse and human. Science 2010;327(5967):863–6.
Soravia LM, Heinrichs M, Aerni A, Maroni C, Schelling G, Ehlert U, et al. Glucocorticoids reduce phobic fear in humans. Proc Natl Acad Sci USA 2006;103:5585–90.
Sotres-Bayon F, Bush DE, LeDoux JE. Acquisition of fear extinction requires activation of NR2B-containing NMDA receptors in the lateral amygdala. Neuropsychopharmacology 2007;32:1929–40.
Sotres-Bayon F, Diaz-Mataix L, Bush DE, LeDoux JE. Dissociable roles for the ventromedial prefrontal cortex and amygdala in fear extinction: NR2B contribution. Cereb Cortex 2009;19:474–82.
Southwick SM, Morgan A, Nagy LM, Bremner D, Nicolaou AL, Johnson DR, et al. Trauma related symptoms in veterans of Operations Desert Storm: a preliminary report. Am J Psychiatry 1993;150:1524–8.
Suzuki A, Josselyn SA, Frankland PW, Masushige S, Silva AJ, Kida S. Memory reconsolidation and extinction have distinct temporal and biochemical signatures. J Neurosci 2004;24(20):4787–95.
Szapiro G, Vianna MRM, McGaugh JL, Medina JH, Izquierdo I. The role of NMDA glutamate receptors, PKA, MAPK, and CAMKII in the hippocampus in extinction of conditioned fear. Hippocampus 2003;13:53–8.
Taylor JR, Olausson P, Quinn JJ, Torregrossa MM. Targeting extinction and reconsolidation mechanisms to combat the impact of drug cues on addiction. Neuropharmacology 2009;56:186–95.
Thomas BL, Larsen N, Ayres JJB. Role of context similarity in ABA, ABC, and AAB renewal paradigms: implications for theories of renewal and for treating human phobias. Learn Motiv 2003;34:410–36.
Tian S, Gao J, Han L, Fu J, Li C, Li Z. Prior chronic nicotine impairs cued fear extinction but enhances contextual fear conditioning in rats. Neuroscience 2008;153:935–43.
Tinsley MR, Quinn JJ, Fanselow MS. The role of muscarinic and nicotinic cholinergic neurotransmission in aversive conditioning: Comparing Pavlovian fear conditioning and inhibitory avoidance. Learn Mem 2004;11:35–42.
Tronson NC, Taylor JR. Molecular mechanisms of memory reconsolidation. Nat Rev Neurosci 2007;8:262–75.
Varvel SA, Anum EA, Lichtman AH. Disruption of CB(1) receptor signaling impairs extinction of spatial memory in mice. Psychopharmacology 2005;179:863–72.
Varvel SA, Wise LE, Lichtman AH. Are CB(1) receptor antagonists nootropic or cognitive impairing agents? Drug Dev Res 2009;70:555–65.
Waddell J, Bouton ME, Falls WA. Central CRF receptor antagonist a-helical CRF9-41 blocks reinstatement of extinguished fear: the role of the bed nucleus of the stria terminalis. Behav Neurosci 2008;122:1061–9.
Walker DL, Davis M. The role of amygdala glutamate receptors in fear learning, fear-potentiated startle, and extinction. Pharmacol Biochem Behav 2002;71(3): 379–92.
Walker DL, Ressler KJ, Lu K, Davis M. Facilitation of conditioned fear extinction by systemic administration or intra-amygdala infusions of D-cycloserine as assessed with fear-potentiated startle in rats. J Neurosci 2002;22:2343–51.
Weber M, Hart J, Richardson R. Effects of D-cycloserine on extinction of learned fear to an olfactory cue. Neurobiol Learn Mem 2007;87:476–82.
Wellman CL, Izquierdo A, Garrett JE, Martin KP, Carroll J, Millstein R, et al. Impaired stress-coping and fear extinction and abnormal corticolimbic morphology in serotonin transporter knock-out mice. J Neurosci 2007;27:684–91.
Willick ML, Kokkinidis L. Cocaine enhances the expression of fear-potentiated startle: evaluation of state-dependent extinction and the shock-sensitization of acoustic startle. Behav Neurosci 1995;109(5):929–38.

Woods AM, Bouton ME. D-cycloserine facilitates extinction but does not eliminate renewal of the conditioned emotional response. Behav Neurosci 2006;120:1159–62.
Woolley ML, Water KA, Gartlon JE, Lacroix LP, Jennings C, Shaughnessy F, et al. Evaluation of the pro-cognitive effects of the AMPA receptor positive modulator, 5-(1-piperidinylcarbonyl)-2, 1, 3-benzoxadiazole (CX691), in the rat. Psychopharmacology 2009;202:343–54.
Yamada D, Zushida K, Wada K, Sekiguchi M. Pharmacological discrimination of extinction and reconsolidation of contextual fear memory by a potentiator of AMPA receptors. Neuropsychopharmacology 2009;34:2574–84.
Yang YL, Lu KT. Facilitation of conditioned fear extinction by D-cycloserine is mediated by mitogen-activated protein kinase and phosphatidylinositol 3-kinase cascades and requires de novo protein synthesis in basolateral nucleus of amygdala. Neurosci 2005;134:247–60.
Zushida K, Sakurai M, Wada K, Sekiguchi M. Facilitation of extinction learning for contextual fear memory by PEPA: a potentiator of AMPA receptors. J Neurosci 2007;27:158–66.