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Review

Can fear extinction be enhanced? A review of pharmacological and behavioral findings

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ABSTRACT

There is considerable interest, from both a basic and clinical standpoint, in gaining a greater understanding of how pharmaceutical or behavioral manipulations alter fear extinction in animals. Not only does fear extinction in rodents model exposure therapy in humans, where the latter is a cornerstone of behavioral intervention for anxiety disorders such as post-traumatic stress disorder and specific phobias, but also understanding more about extinction provides basic information into learning and memory processes and their underlying circuitry. In this paper, we briefly review three principal approaches that have been used to modulate extinction processes in animals and humans: a purely pharmacological approach, the more widespread approach of combining pharmacology with behavior, and a purely behavioral approach. The pharmacological studies comprise modulation by: brain derived neurotrophic factor (BDNF), D-cycloserine, serotonergic and noradrenergic drugs, neuropeptides, endocannabinoids, glucocorticoids, histone deacetylase (HDAC) inhibitors, and others. These studies strongly suggest that extinction can be modulated by drugs, behavioral interventions, or their combination, although not always in a lasting manner. We suggest that pharmacotherapeutic manipulations provide considerable promise for promoting effective and lasting fear reduction in individuals with anxiety disorders.

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Contents

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1. Introduction

In fear conditioning experiments, a so-called conditioned stimulus (CS) such as an auditory tone is presented in conjunction with an aversive unconditioned stimulus (US) such as a mild footshock, and with repeated CS–US pairings the animal or human subject learns to fear the CS (as well as the physical surroundings, or context, in which the procedure takes place). In another variant of these experiments, no CS is presented and instead the context in which the training takes place, such as the chamber in which an animal is placed, is associated with the fear-provoking stimulus (Estes and Skinner, 1941; Fanselow, 1980; LeDoux et al., 1984; Blanchard and Blanchard, 1969). Fear extinction is a behavioral procedure wherein a CS or context that was previously associated with something aversive (i.e., the US) is presented repeatedly (or for a period of time) in the absence of the aversive stimulus (Pavlov, 1927; Kalish, 1954; Bouton and Bolles, 1979; Shipley, 1974; Bouton et al., 2006b). In this manner, the animal or human subject learns that the CS or context no longer signals danger, and behavior typically changes to reflect a gradual decrease in fear. In laboratory rodents, extinction often manifests as a measurable decrease in freezing behavior (i.e., immobility due to fear or vigilance). The effectiveness of extinction is often measured in a subsequent "retrieval" test, typically where the CS is presented again in the extinction context without the US, and behavior such as freezing is monitored (Bouton et al., 2006b; Cammarota et al., 2004). In contrast, a "renewal" test typically takes place in a different context from extinction (often in the original conditioning context) and tests whether fear returns, since learning of extinction is often quite specific to the extinction context (Bouton et al., 2006b).

Understanding the neurobiological and behavioral mechanisms underlying fear extinction is of interest to both basic scientists and clinical researchers (Bouton et al., 2001; Myers and Davis, 2002; Milad and Quirk, 2012; Maren et al., 2013; Maren and Holt, 2000). Studies of extinction not only reveal fundamental properties of learning and memory, but also offer the opportunity to understand the function of neural circuits in the amygdala, hippocampus, and medial prefrontal cortex mediating memory and emotion (Phelps and LeDoux, 2005; Maren and Holt, 2000; Quirk et al., 2006). Moreover, fear extinction in laboratory animals is a model of exposure therapy in humans, where such therapy involves presenting the fear-provoking or aversive stimulus repeatedly in the absence of harm, and the individual ideally learns to fear it less (Rothbaum and Hodges, 1999; Bouton et al., 2001; Craske et al., 2008; Kaplan and Moore, 2011). Exposure therapy is commonly used to treat anxiety disorders such as post-traumatic stress disorder (PTSD) and specific phobias such as fear of heights or spiders (Parsons and Rizzo, 2008; Vansteenwegen et al., 2007). It is of high interest both to mental health care professionals and their clients to maximize the effectiveness of exposure therapy, through pharmacological or behavioral (or both) approaches.

Considerable progress has now been made in identifying neural circuits underlying the conditioning and extinction of fear. While a wide range of brain structures may play a role in fear learning, the amygdala, hippocampus, and medial prefrontal cortex (mPFC) have received much of the attention to date (Phelps and LeDoux, 2005; Maren and Quirk, 2004; Quirk et al., 2006). The amygdala plays a critical role in the acquisition of both conditioning and extinction memories (Davis et al., 2003; Rodrigues et al., 2009), whereas the hippocampus and prefrontal cortex have a principal role in regulating the retrieval of these memories (Maren, 2011). Indeed, two subregions of mPFC, prelimbic cortex and infralimbic cortex, may play a role in fear expression and suppression, respectively (Knapska and Maren, 2009; Sierra-Mercado et al., 2010).

The recent focus on cellular mechanisms of extinction learning has yielded important new information on a variety of pharmacological and behavioral tools that facilitate extinction. This has important clinical relevance for bringing basic neuroscience research to bear on clinical interventions for fear and anxiety. In what follows, we briefly review recent studies exploring the pharmacological and behavioral modulation of extinction, and suggest possible neurophysiological mechanisms of action for pharmacological interventions. This is not meant to be an exhaustive review, but rather an effort to highlight the most promising targets for pharmacological modulation of extinction. We conclude by inferring some common outcomes in these studies, and by suggesting approaches that may further optimize the effectiveness and generality of extinction learning.

2. Pharmacotherapeutic approaches

The most common approach to facilitating extinction is a pharmacotherapeutic approach wherein extinction training is conducted with a pharmacological adjunct designed to promote the function and plasticity of brain circuits involved in extinction learning and memory. Drugs are typically given systemically to model therapeutic interventions in a clinical setting, although some studies have used local intracranial infusions to isolate neural circuits upon which select drugs are acting to facilitate learning. The studies considered in this section are summarized in Table 1.

2.1. Amino acid receptor modulators

Glutamate receptor modulators. The glutamatergic neurotransmitter system is the major excitatory signaling pathway in the brain. Through its various receptor subtypes, including AMPA and NMDA receptors, glutamate may alter a broad range of learning and memory processes by interacting with both cortical and subcortical circuits. Several studies have examined systemic and intracranial administration of D-cycloserine (DCS), a partial agonist of the NMDA receptor, on extinction in both rodents and humans. In humans undergoing virtual reality exposure therapy for acrophobia (i.e., fear of heights), DCS given before therapy produced decreases in fear upon subsequent testing (Ressler et al., 2004). Likewise, a placebo-controlled study in humans found that DCS or valproic acid (an HDAC inhibitor) each facilitated extinction, but did not act synergistically when given in combination (Kuriyama et al., 2011). On the other hand, in a human study using a three-day conditioning protocol, DCS was ineffective at reducing within-session fear during extinction, or its later retention (Klumpers et al., 2012). A null result was also found in a placebo controlled study based on differential shock conditioning, where DCS was given 2–3 h before extinction training and had no effect on measures of extinction and return of fear (Guastella et al., 2007). Another study of acrophobia in which drug was given after each of two virtual reality exposure therapy sessions, produced a mixed result where DCS enhanced extinction after successful exposure sessions, but exacerbated it after unsuccessful ones (Smits et al., 2013).

In rats, DCS has been reported to facilitate generalization of extinction, in that drug-treated animals were less fearful of a non-extinguished conditioned stimulus than control rats (Ledgerwood et al., 2005). Animals injected with DCS following extinction to odor cues showed enhanced retention only in cases where there had been some amount of prior within-session extinction, suggesting that to have a lasting effect the drug is not acting solely on consolidation of extinction in all animals (Weber et al., 2007). DCS enhanced extinction learning when given just after the extinction session, but this effect was blocked when animals were also given the drug prior to conditioning, consistent with functional antagonism between the behavioral effects of conditioning and extinction while on drug (Parnas et al., 2005). In another study, whereas

Table 1
Summary of pharmacological agents that enhance extinction. Only agents that enhanced extinction, either within session or during subsequent retrieval or renewal tests, are included. If route of administration indicates a brain structure, this means the drug was infused into that structure. Abbreviations: intraperitoneal (i.p.), subcutaneous (s.c.), basolateral amygdala (BLA), lateral amygdala (LA).

Category of agent	Agent	Mechanism of action	Species	Route of administration	Timing of administration relative to extinction	Reference
Amino acid receptor modulators	D-Cycloserine	NMDA receptor partial agonist	Human	Acute capsule	Before	Ressler et al. (2004)
	D-Cycloserine		Human	Acute oral powder	Before	Kuriyama et al. (2011)
	D-Cycloserine		Human	Acute capsule	After	Smits et al. (2013)
	D-Cycloserine		Rat	Acute s.c.	After	Ledgerwood et al. (2005)
	D-Cycloserine		Rat	Acute s.c.	After	Weber et al. (2007)
	D-Cycloserine		Rat	Acute s.c.	After	Parnas et al. (2005)
	D-Cycloserine		Rat	Acute i.p.	After	Toth et al. (2012)
	D-Cycloserine		Rat	Acute s.c.	Before	Bouton et al. (2008)
	D-Cycloserine		Rat	Acute s.c.	Before	Woods and Bouton (2006)
	D-Cycloserine		Rat	Acute: i.p., bilateral basolateral amygdala (BLA)	Before	Walker et al. (2002)
	D-Cycloserine		Rat	Acute bilateral BLA or LA	Before	Mao (2006)
	D-Cycloserine		Rat	Acute i.p.	Before	Yang and Lu (2005)
	D-Cycloserine		Rat	Subchronic bilateral dorsal hippocampus	Before	Ren et al. (2013)
	D-Cycloserine, picrotoxin	Picrotoxin: $GABA_A$ receptor antagonist	Rat	Acute bilateral infralimbic cortex	Before	Chang and Maren (2011)
	D-Serine	NMDA receptor agonist	Mouse	Acute i.p.	Before	Matsuda et al. (2010)
	PEPA	AMPA receptor potentiator	Mouse	Acute: i.p., bilateral mpfc, bilateral amygdala (subregion unspecified)	Before	Zushida et al. (2007)
	Bicuculline	$GABA_A$ receptor antagonist	Rat	Acute bilateral or right BLA	After	Berlau and McGaugh (2006)
	Muscimol	$GABA_A$ receptor agonist	Rat	Acute: bilateral infralimbic, bilateral BLA	Before for infralimbic, after for BLA	Akirav et al. (2006)
Monoamine modulators	Fluoxetine	Serotonin reuptake inhibitor	Rat	Chronic i.p.	Before	Deschaux et al. (2011)
	Fluoxetine		Rat	Chronic i.p.	After	Deschaux et al. (2012)
	Fluoxetine		Rat	Chronic i.p.	Before	Spennato et al. (2008)
	Fluoxetine		Mouse	Chronic (in drinking water)	Before	Karpova et al. (2011)
	Yohimbine	α_2 adrenergic antagonist	Human	Acute capsule	Before	Powers et al. (2009)
	Yohimbine		Mouse	Acute s.c.	Before	Cain (2004)
	Yohimbine		Rat	Acute i.p.	Before	Janak and Corbit (2010)
	Yohimbine		Rat	Acute i.p.	Before	Mueller et al. (2009)
	Yohimbine		Rat	Acute i.p.	Before	Morris and Bouton (2007)
	Norepinephrine	Adrenergic agonist	Rat	Acute bilateral or right BLA	After	Berlau and McGaugh (2006)
	Isoproterenol	Nonselective β adrenergic agonist	Rat	Subchronic i.p.	After	Do-Monte et al. (2010)

	Propranolol	Nonselective β adrenergic antagonist	Rat	Acute i.p.	Before	Rodriguez-Romaguera et al. (2009)
	Methylphenidate	Dopamine/norepinephrine reuptake inhibitor	Mouse	Acute i.p.	Before or after	Abraham et al. (2012)
	L-Dopa	Dopamine precursor	Mouse	Acute i.p.	After	Haaker et al. (2013)
	Tandospirone	Serotonin ($5HT_{1A}$) receptor agonist	Rat	Acute i.p.	Before and after	Saito et al. (2012)
Cholinergic, cannabinoid, and peptide modulators	Sulpiride	Dopamine (D_2) receptor antagonist	Mouse	Acute i.p.	Before	Ponnusamy et al. (2005)
	Scopolamine	Cholinergic muscarinic antagonist	Rat	Acute i.p.	Before	Zelikowsky et al. (2013)
	Cannabidiol	Non-psychotomimetic cannabinoid	Human	Acute, inhaled	After	Das et al. (2013)
	Synthetic THC	Cannabinoid (CB_1) receptor agonist	Human	Acute, capsule	Before	Rabinak et al. (2013)
	AM404	Endocannabinoid breakdown (via enzyme fatty acid amide hydrolase (FAAH)) and reuptake inhibitor	Rat	Acute i.p.	Before	Chhatwal et al. (2005)
	AM404 or cannabidiol		Rat	Acute i.c.v.	Before	Bitencourt et al. (2008)
	AM404 or WIN55212-2	WIN55212-2: CB_1 agonist	Rat	Acute i.p.	Before	Pamplona et al. (2008)
	WIN55212-2		Rat	Acute i.p.	Before	Pamplona et al. (2006)
	WIN55212-2		Rat	Acute unilateral (left or right) infralimbic	Before	Lin et al. (2009)
	AM3506	FAAH inhibitor	Mouse	Acute bilateral BLA or acute i.p.	Before	Gunduz-Cinar et al. (2012)
	Neuropeptide Y	Agonist at its own receptors (Y_1–Y_5)	Rat	Acute unilateral (left or right) lateral ventricle	Before	Lach and de Lima (2013)
	Neuropeptide Y		Rat	Acute left lateral ventricle	Before	Gutman et al. (2008)
	Neuropeptide S	Agonist at its own receptor (NPSR)	Mouse	Acute bilateral LA/BLA	Before	Jüngling et al. (2008)
Steroid hormone modulators	Cortisol	Agonist of steroid receptors	Human	Acute tablet	Before	de Quervain et al. (2011)
	Corticosterone	Agonist of steroid receptors	Mouse	Acute i.p.	Before	Brinks et al. (2009)
	Dexamethasone (by itself or with D-cycloserine)	Agonist of steroid receptors	Rat	Acute i.p.	Before	Yang et al. (2007)
	Dexamethasone		Rat	Acute i.p.	Before	Yang et al. (2006)
	RU28362	Glucocorticoid receptor agonist	Rat	Acute bilateral BLA	Before	Yang et al. (2006)
	Estrogen and/or progesterone	Agonists of their endogenous receptors	Rat (females in metestrus)	Acute s.c.	Before	Milad et al. (2009)
	Diarylpropionitrile	Estrogen receptor B (ERB) agonist	Rat (ovariectomized)	Two i.p. injections	Before	Chang et al. (2009)

Table 1 (*Continued*)

Category of agent	Agent	Mechanism of action	Species	Route of administration	Timing of administration relative to extinction	Reference
	Diarylpropionitrile or estradiol		Rat (ovariectomized)	Acute bilateral dorsal hippocampus	Before	Chang et al. (2009)
Other modulators	Valproic acid or sodium butyrate	Histone deacetylase (HDAC) inhibitors	Mouse	Acute i.p.	Before	Bredy et al. (2007)
	Sodium butyrate		Mouse	Acute s.c.	Before	Lattal et al. (2007)
	Trichostatin A	HDAC inhibitor	Mouse	Acute bilateral dorsal hippocampus	Before	Lattal et al. (2007)
	Valproic acid		Mouse	Acute i.p.	Before	Bredy and Barad (2008)
	Valproic acid		Mouse	Repeated i.p. injections	After	Heinrichs et al. (2013)
	Vorinostat	HDAC inhibitor	Rat	Acute i.p.	After	Matsumoto et al. (2013)
	RGFP966	HDAC3 inhibitor	Mouse	Acute s.c.	After	Malvaez et al. (2013)
	SPV106	Activator of p300/CBP-associated factor (PCAF)	Mouse	Acute i.p.	Before or after	Wei et al. (2012)
	Fibroblast growth factor-2	Agonist of fibroblast growth factor receptor 1	Rat	Acute s.c.	Before or after	Graham and Richardson (2009)
	Fibroblast growth factor-2		Rat	Acute s.c.	After	Graham and Richardson (2010)
	Fibroblast growth factor-2		Rat	Acute bilateral BLA	After	Graham and Richardson (2011)
	Magnesium-L-threonate	Multifunctional biological activity	Rat	Chronic, drinking water	Before	Abumaria et al. (2011)
	XE-991	M-type K+ channel blocker	Rat	Acute, principally unilateral infralimbic cortex	Before	Santini and Porter (2010)
	7,8 dihydroxyflavone	TrkB agonist	Mouse	Acute i.p.	Before	Andero et al. (2011)

DCS did not facilitate within-session extinction or its retention after full extinction, it facilitated retention in a subsequent test session when given after an incomplete extinction training session (Toth et al., 2012). Two studies by Bouton and colleagues found that whereas DCS facilitated within-session extinction, fear renewed when animals were subsequently tested in the original conditioning context, suggesting that the effects of DCS were context-specific (Bouton et al., 2008; Woods and Bouton, 2006). D-Serine, an agonist of the glycine site of the NMDA receptor where DCS also acts, enhanced extinction learning in mice, possibly by acting through the ERK signaling pathway (Matsuda et al., 2010).

DCS may also affect extinction measures when administered to particular brain circuits. In a fear study in which footshocks were paired with a visual stimulus, systemic DCS given before extinction facilitated this learning, as did DCS infused into the amygdala (Walker et al., 2002). Bilateral infusion of DCS into the amygdala before extinction training augmented training-induced reduction in startle and reversed the conditioning-induced increase in AMPA GluR1 receptors in this brain structure (Mao, 2006). The facilitating effect of DCS on fear extinction was blocked by bilateral amygdala infusion of inhibitors of the MAP kinase and PI3K molecular pathways (Yang and Lu, 2005). Repeated infusion of DCS into the hippocampus facilitated acquisition and retrieval of extinction memory, while also enhancing hippocampal expression of the NMDA receptor subunit NR2B (Ren et al., 2013). Infusion of DCS into infralimbic cortex before "immediate" extinction, a protocol which uses a small time interval between conditioning and extinction that can impair extinction (Maren and Chang, 2006), did not facilitate within-session extinction, but did prime subsequent re-extinction during a drug-free state (Chang and Maren, 2011). The above studies on DCS in many cases suggest facilitation of extinction, whether it is administered systemically or within local amygdalar or hippocampal circuits. These studies, along with the data on D-serine, suggest that activation of the NMDA receptor can facilitate extinction learning under some conditions, although not always in a lasting manner. Thus, data on the interaction between DCS and extinction learning further implicate the NMDA receptor in learning and memory processes.

DCS is not the only modulator of the glutamatergic system that may affect extinction learning. Systemic administration of PEPA, an AMPA receptor (AMPAR) potentiator, before extinction significantly facilitated learning both during extinction and in subsequent tests in a dose-dependent fashion. These effects were blocked by administration of NBQX, an AMPAR antagonist. PEPA had a more significant electrophysiological effect on neurons in the mPFC compared to neurons in the BLA or hippocampus, which is likely due to PEPA's greater affinity for the specific AMPAR subtypes that are expressed in larger numbers in mPFC. This was supported by further studies indicating that infusion of PEPA into mPFC facilitated extinction much more significantly than infusion into the amygdala (Graham et al., 2011; Zushida et al., 2007). These findings on PEPA implicate the AMPA receptor in extinction learning, and when combined with the above data on NMDA receptor activation suggest that a range of glutamatergic receptors affect such learning. Perhaps other glutamatergic receptor types, including metabotropic receptors, modulate extinction learning in a manner that could be influenced by pharmacological agents, and this could be tested in future studies.

GABA receptor antagonists. The inhibitory neurotransmitter, GABA, may also play a role in extinction learning. Because GABA is the major inhibitory neurotransmitter in the brain, it is uniquely positioned to suppress excitatory circuits believed to affect fear responses. Consistent with this, bilateral infusion of bicuculline, an antagonist of the $GABA_A$ receptor, into BLA of rats following extinction of a contextual fear memory resulted in enhanced extinction (Berlau and McGaugh, 2006). Moreover, infusion of the $GABA_A$ antagonist picrotoxin into the infralimbic cortex buffers against the immediate extinction deficit (Chang and Maren, 2011). Perhaps surprisingly, a separate group found that infusion of the $GABA_A$ *agonist* muscimol into BLA after a short session of extinction to a cued fear memory also resulted in long-term extinction enhancement. Interestingly, muscimol infused into infralimbic cortex also resulted in extinction enhancement, but only when the infusion occurred before the extinction training (Akirav et al., 2006). These studies suggest that modulating GABAergic signaling in BLA or infralimbic cortex can enhance extinction learning. Perhaps the paradoxical findings of agonists and antagonists having similar effects are due to experimental differences in the precise timing of the drug infusions relative to extinction training. In any case, these data indicate that amino acid neurotransmitter systems in the brain are important for extinction learning, and are promising targets for modulating the long-term suppression of fear.

2.2. Monoamine modulators

Three major monoamine neurotransmitter systems—serotonin, norepinephrine, and dopamine—have been strongly implicated in neuropsychiatric disorders such as major depression, bipolar disorder, schizophrenia, and anxiety disorders, in the last several decades. They are widely distributed in the forebrain and innervate all of the major brain areas implicated in extinction learning including the medial prefrontal cortex, amygdala, and hippocampus. Not surprisingly, recent data suggest that these neuromodulators play a role in extinction learning.

Serotonergic antidepressants. Several studies suggest that selective serotonin reuptake inhibitor (SSRI) antidepressants, such as fluoxetine and citalopram, can alter extinction learning. Chronic administration of citalopram to rats, given between fear conditioning and extinction, impaired acquisition of extinction, and downregulated the NR2B subunit of the NMDA receptor in the lateral and basal nuclei of the amygdala (Burghardt et al., 2013). In contrast, fluoxetine given chronically in the period between conditioning and extinction, prevented return of fear produced by a low intensity version of an extinguished auditory cue (Deschaux et al., 2011). In an extension of the previous study, chronic fluoxetine, given between extinction and a subconditioning procedure, protected against stress-induced return of fear (Deschaux et al., 2012). Likewise, in rats that were fear conditioned with eyelid shocks, chronic treatment with fluoxetine blocked re-emergence of fear upon exposure to a less intense stressor consisting of fewer shocks (Spennato et al., 2008). In mice, combining chronic fluoxetine treatment with extinction training produced an enduring loss of conditioned fear memory, whereas drug or extinction given alone were ineffective (Karpova et al., 2011). This latter study illustrates the potential power of combining pharmacological treatments with behavioral therapy, where use of only one of these two approaches may not be therapeutic, and further that the two approaches interact in ways that are not yet well understood. In summary, many of these studies suggest facilitation of extinction by SSRIs, including through suppressing the effects of psychological stress.

Noradrenergic drugs. The neurotransmitter norepinephrine is associated with memory for emotionally arousing stimuli, and its release during extinction may enhance memory formation through activation of beta adrenoceptors (Mueller and Cahill, 2010; Roozendaal and McGaugh, 2011). Whereas adrenergic signaling is critical for the retrieval of intermediate-term contextual and spatial memories, it is not necessary for the retrieval or consolidation of emotional memories in general (Murchison et al., 2004). The norepinephrine release-enhancing drug, yohimbine, has been associated with facilitation of extinction, but there are conflicting data on this topic (Holmes and Quirk, 2010). A placebo controlled

study of claustrophobic persons found that yohimbine given prior to exposure therapy reduced fear during a behavioral test one week later (Powers et al., 2009). However, in a differential fear conditioning paradigm in persons, yohimbine given prior to fear conditioning impaired extinction learning and also increased fear during a subsequent test (Soeter and Kindt, 2011a,b).

In a comparison of massed versus spaced extinction trials presented to mice, yohimbine facilitated extinction for both trial types, whereas the beta adrenoceptor blocker propranolol incubated cue-based fear during spaced trials (Cain, 2004). In rats trained to lever-press for food, yohimbine given prior to extinction facilitated this learning during a subsequent test, whereas propranolol impaired it (Janak and Corbit, 2010). Another study found that yohimbine given prior to extinction training dose-dependently reduced within-session freezing, but had no lasting effect on this behavior during a retrieval test (Mueller et al., 2009). Whereas yohimbine given prior to extinction produced a lasting decrease in freezing when paired with extinction training, it did not erase the fear memory since freezing renewed during testing outside the extinction context (Morris and Bouton, 2007). These data show that yohimbine can facilitate extinction in humans and animal models, although not always in a lasting manner (Holmes and Quirk, 2010).

The non-selective beta adrenoceptor antagonist drug, propranolol, may also modulate extinction learning. In a differential fear conditioning paradigm in humans, propranolol did not affect physiological measures of extinction such as startle reflex and skin conductance, but did cognitively impair extinction learning (Bos et al., 2012). However, in a study of persons with PTSD that also included persons exposed to trauma who had not developed PTSD, propranolol given after extinction of a conditioned response did not affect retention of this response (Orr et al., 2006).

In rodents, propranolol infused into infralimbic cortex prior to extinction training impaired retrieval of extinction the next day (Mueller et al., 2008). Propranolol infused into the right basolateral amygdala blocked enhancement of extinction produced by local administration of the GABAergic antagonist bicuculline, whereas infusion of norepinephrine into this brain structure enhanced extinction (Berlau and McGaugh, 2006). Repeated systemic injections of propranolol given 30 min before or just after extinction, impaired acquisition or consolidation of this process, whereas the beta adrenoceptor agonist isoproterenol facilitated consolidation (Do-Monte et al., 2010). In contrast, another study found that systemic propranolol given acutely before extinction reduced within-session freezing, but had no lasting effect on retention of extinction (Rodriguez-Romaguera et al., 2009). Systemic propranolol also reversed impairment of reconsolidation of cue-conditioned fear that was induced by the glucocorticoid antagonist, mifepristone (Pitman et al., 2011). Since extinction is sensitive to noradrenergic drugs such as propranolol and may require memory retrieval, it has been suggested that this retrieval occurs during and several hours after extinction learning to consolidate memory of extinction (Ouyang and Thomas, 2005). In summary, many of the above studies suggest that systemic or local (infralimbic cortex, amygdala) propranolol administration impairs extinction learning, but this may depend on trial spacing, among other factors (Cain, 2004).

Dopaminergic agents. Dopamine has been implicated in many learning and memory processes, often as a mediator of memory consolidation through its role as a promoter of long-term potentiation in regions of the brain such as the mPFC (where synaptic potentiation has been found to occur and correlate with extinction learning (Saito et al., 2012)). Output neurons in the mPFC receive a large number of dopaminergic inputs from the ventral tegmental area and are thought to be involved in communicating fear inhibition learned through extinction via their excitatory projections to GABAergic interneurons in the amygdala, thereby reducing its activity and the subsequent expression of fear-related behavior.

A number of behavioral studies have explored dopamine's role in extinction memory consolidation. For example, the administration of methylphenidate, a dopamine and norepinephrine reuptake inhibitor commonly known as Ritalin, was found to enhance contextual extinction learning and retention when given both before and after extinction training (Abraham et al., 2012). Haaker et al. (2013) found that systemic administration of L-dopa, dopamine's biosynthetic precursor, following extinction led to an enhancement of extinction such that typically context-dependent extinction learning became context-independent (i.e., a reduction in renewal). They also found that L-dopa administration following extinction training reduced spontaneous recovery and reinstatement (Haaker et al., 2013).

A separate study found that systemic injections of tandospirone, a serotonin 1A receptor (5HT1AR) agonist, given both before and after extinction, ameliorated extinction deficits related to early life footshock stress in mice. It was found that the extinction enhancements related to an increase in mPFC dopamine release, which in turn increased mPFC activity during extinction retrieval. Importantly, there was no increase in serotonin release in the mPFC (Saito et al., 2012). Finally, and perhaps paradoxically, systemic administration of sulpiride, a dopamine D2 receptor antagonist, before extinction training resulted in enhanced extinction memory retention during subsequent tests, whereas quinpirole, a D2 agonist, resulted in diminished extinction learning. Significantly, sulpiride also resulted in enhanced extinction learning and retention when administered before extinction that used spaced CS presentations, a form of training that does not normally result in robust extinction memory retention (Ponnusamy et al., 2005). These data on dopamine suggest a role for modulation of extinction processes that may depend on receptor subtype.

Collectively, the above studies suggest that pharmacological agents which act on serotonin, norepinephrine, and dopamine signaling pathways alter extinction learning. One possibility is that boosting synaptic levels of any of these three molecules facilitates extinction, although at the receptor subtype level there may be functional opposition within each transmitter system. Of the three systems, norepinephrine may be the one most implicated in memory processes to date, and serotonin the least, although the widespread and overlapping brain distribution of all three transmitter systems may suggest that they interact in fear learning. If so, this may be exploited pharmacologically with novel multi-drug treatments to enhance extinction learning, a subject for future studies.

2.3. Cholinergic, cannabinoid, and peptide modulators

Like the signaling pathways described above, the cholinergic, cannabinoid, and peptide modulatory transmitter systems are very broadly distributed in the brain. Their circuits modulate diverse cognitive processes. The cholinergic system, for example, is strongly implicated in learning and memory, as well as attention. Endocannabinoids and peptide transmitters may also affect learning and memory by modulating the release of other transmitters, including norepinephrine.

Cholinergic modulators. Lesion and inactivation studies have shown that the context-specificity of extinction depends on the hippocampus, and that infusion of intrahippocampal (or systemic) scopolamine, a cholinergic muscarinic antagonist, blocks contextual fear conditioning (Zelikowsky et al., 2013). Systemic low dose scopolamine also attenuated the renewal of fear, in both a novel and the original conditioning context, further suggesting that it interferes with the contextualization of extinction learning (Zelikowsky et al., 2013). This result suggests that the modulatory

neurotransmitter, acetylcholine, affects generalization of fear learning, possibly through hippocampal mechanisms.

Endocannabinoids. The endocannabinoid neurotransmitter system in general, and its CB1 receptor in particular, may play an important role in the modulation of fear extinction (Lafenêtre et al., 2007). In humans, cannabidiol, a non-psychotomimetic cannabinoid, produced no acute effect on extinction, but when given after this procedure it enhanced consolidation of extinction (Das et al., 2013). In a placebo controlled study in healthy persons, synthetic D9-tetrahydrocannabinol (THC) given prior to fear extinction, improved extinction retrieval upon testing the next day (Rabinak et al., 2013).

In rats, the CB1 antagonist rimonabant dose-dependently decreased extinction learning, whereas AM404, an inhibitor of endocannabinoid breakdown and reuptake, dose-dependently enhanced extinction (Chhatwal et al., 2005). Intracerebroventricular administration of AM404 or cannabidiol, given prior to extinction, facilitated extinction of contextual fear memory in a persistent manner (Bitencourt et al., 2008). The CB1 agonist WIN55212-2 or AM404, given prior to extinction, facilitated within-session contextual extinction learning, while also producing a lasting effect upon testing a week later (Pamplona et al., 2008). Likewise, administration of rimonabant before extinction training disrupted extinction of a 24 h contextual fear memory, whereas WIN55212-2 facilitated it (Pamplona et al., 2006). Infusion of CB1 antagonist AM251 into infralimbic cortex attenuated cue-alone induced reduction of fear-potentiated startle, whereas WIN55212-2 facilitated extinction, possibly by activating the ERK signaling pathway (Lin et al., 2009).

In a mouse model of impaired extinction, the drug AM3506, which reduces degradation of the endocannabinoid anandamide, enhanced retrieval of extinction when given systemically or infused into the amygdala prior to extinction (Gunduz-Cinar et al., 2012). CB1 receptor deficient mice exhibited strongly and selectively impaired short-term and long-term extinction in auditory fear conditioning tests, and this effect was mimicked in wild type mice by administration of rimonabant (Marsicano et al., 2002). In CB1 receptor conditional knockout mice, reconstitution of CB1 function exclusively in dorsal telencephalic glutamatergic neurons impaired fear extinction in auditory fear conditioning (Ruehle et al., 2013). In summary, many of the above studies suggest that enhancement of endocannabinoid signaling through the CB1 receptor facilitates extinction learning, whereas diminishing CB1 receptor signaling with drugs such as rimonabant impairs such learning.

Neuropeptides. Neuropeptide Y, an abundant peptide in the central nervous system, appears to counteract the effects of stress and enhance fear extinction in preclinical models (Bowers et al., 2012). Intracerebroventricular administration of neuropeptide Y prior to extinction inhibited contextual fear, an effect that was blocked by the Y1 receptor antagonist, BIBO3304 (Lach and de Lima, 2013). Also, intracerebroventricular administration of neuropeptide Y before extinction training enhanced retention of both the contextual and cued components of conditioned fear, whereas intra-basolateral amygdala administration of BIBO3304 prior to extinction produced a large deficit in extinction retention (Gutman et al., 2008). In constitutive knockout mice, deletion of neuropeptide Y impaired fear extinction, as did simultaneous deletion of its Y1 and Y2 receptors, suggesting that endogenous signaling of the peptide promotes extinction (Verma et al., 2012).

Neuropeptide S, a neurotransmitter of ascending brainstem cells, can facilitate fear extinction, and may play a general role in promoting long-term memory independent of memory content or task (Okamura et al., 2010). In mice, neuropeptide S facilitated extinction when administered into the amygdala (Jüngling et al., 2008). Physiologically, neuropeptide S may promote extinction by boosting mPFC dopamine, since central administration of this peptide dose-dependently enhanced extracellular dopamine in this brain region (Si et al., 2010). In summary, endogenous neuropeptide Y and neuropeptide S signaling may enhance extinction.

In summary, the above studies on cholinergic, cannabinoid, and neuropeptide signaling suggest a role in extinction learning. In this regard, more evidence appears to have been amassed for endocannabinoids rather than the cholinergic system. Given the importance of the latter system in learning and memory in general, the role of agents that act on this system in fear learning appears to be a topic that would benefit greatly from further investigation in animal models and humans. This clinically relevant topic includes investigating the effects of cholinesterase inhibitor drugs, which are readily available for human use.

2.4. Steroid hormone modulators

Consistent with the studies reviewed above on other molecules that have widespread effects on brain functioning, steroid hormone modulators such as cortisol and estrogen also appear to affect extinction learning, possibly through interaction with the amygdala and hippocampus.

Glucocorticoids. Glucocorticoids are a class of steroid hormones that regulate immune, inflammatory, and stress responses, while also potentially affecting learning and memory processes. In a placebo-controlled study in persons with acrophobia, the glucocorticoid cortisol given prior to exposure therapy produced facilitation of extinction as measured 3–5 days or one month after the sessions (de Quervain et al., 2011). Corticosterone, the rodent analog of cortisol, given just after fear acquisition facilitated extinction in BALB/c mice, whereas corticosterone given just before acquisition impaired extinction in C57BL/6J mice (Brinks et al., 2009). In rats, the synthetic glucocorticoid agonist dexamethasone facilitated extinction in a fear-potentiated startle paradigm, an effect that was blocked by the corticosteroid synthesis inhibitor metyrapone (Yang et al., 2007). In the same study, co-administration of dexamethasone and DCS in subthreshold doses, synergistically enhanced extinction (Yang et al., 2007). In a related study, systemic administration of dexamethasone also facilitated extinction, as did intra-amygdalar infusion of the glucocorticoid receptor agonist RU28362 (Yang et al., 2006). In summary, many of these studies suggest that glucocorticoids can enhance extinction learning.

Gonadal steroids. Levels of gonadal hormones, including estrogen and progesterone, modulate a variety of fear learning-associated processes, including extinction learning and retention. In cycling female rats, whose hormone levels fluctuate throughout their estrous cycles, better extinction consolidation was observed during the high estrogen/progesterone (proestrus) phase. When estrogen and/or progesterone were injected before extinction training in female rats during their low estrogen/progesterone phase (metestrus), consolidation of the extinction memory was enhanced, an effect that was blocked with estrogen and progesterone receptor antagonists (Milad et al., 2009). Chang et al. (2009) also found that female rats in proestrus exhibited enhanced extinction learning compared to normal male rats. Administration of diarylpropionitrile, an estrogen receptor B (ERB) agonist, enhanced contextual extinction learning in ovariectomized (OVX) rats. Interestingly, propyl-pyrazole-triol, an estrogen receptor alpha agonist, did not enhance extinction learning, indicating that estrogen's role in extinction learning is likely mediated by ERB activity. Infusion of diarylpropionitrile or estradiol into the hippocampus of OVX rats before extinction training also resulted in reduced freezing during extinction training and in later retention tests. This suggests that estrogen is likely enhancing extinction via its action on ERB receptors in the hippocampus (Chang et al., 2009).

In summary, since glucocorticoids have been shown to enhance extinction learning in preclinical models, future studies of these

stress-related hormones could more extensively investigate their interaction with psychological stress in altering fear learning. Regarding gonadal steroids and the estrous cycle: it largely remains to be determined if extinction training, including modulation by any of the treatments described in this paper, is more effective in certain phases in human females.

2.5. Other modulators

Histone acetylation modulators. Changes in gene expression in varying neuronal populations underlie the synaptic and cellular changes that facilitate new memory formation and learning. There are a variety of epigenetic processes that regulate gene expression. For example, the lysine residues present on the histone proteins of chromatin can be acetylated or deacetylated, resulting in chromatin restructuring and subsequent increases or decreases in gene expression. Acetylation of chromatin histone proteins typically results in a relaxing of the chromatin structure, via the disassembly of nucleosomes, such that specific, previously 'unusable,' DNA promoter regions become available for the binding of transcription factors. The acetylation process is regulated by a family of enzymes including histone deacetylase (HDAC) and histone acetyltransferase (HAT). HDACs typically function to reduce histone acetylation within the nucleus, and thus, compounds that inhibit HDAC activity, including valproic acid (VPA) and sodium butyrate (NaB), can increase acetylation and gene expression.

Bredy et al. (2007) have shown that extinction training results in increased histone 4 (H4) acetylation around the P4 BDNF promoter region in PFC of extinguished mice compared to unextinguished mice and naïve mice. BDNF exon I and II mRNA expression also correspondingly increased in the PFC of extinguished mice. VPA, which has clinically been used as a mood stabilizer and anticonvulsant, increases BDNF mRNA and protein levels in PFC and in cell culture. When administered prior to partial extinction training (that is, extinction training that alone does not yield extinction retention), VPA enhanced long-term extinction memory retention in a dose-dependent manner. NaB administration prior to partial extinction training yielded similar results. VPA, in conjunction with partial extinction, led to increases in H4 histone acetylation around BDNF promoters P1 and P4, and an increase in BDNF exon IV mRNA expression in PFC that matched levels seen in animals that underwent full extinction regimens but received no drug treatment (Bredy et al., 2007).

HDAC inhibitors have also been shown to enhance the retention of contextual extinction memories. Intraperitoneal administration of NaB and intrahippocampal infusion of trichostatin A, an HDAC inhibitor that has been previously shown to alter histone acetylation in the hippocampus, before partial extinction reduced freezing in subsequent (1 day later) testing for contextual extinction memory (Lattal et al., 2007). Interestingly, HDAC inhibitors have also been shown to enhance extinction memory retrieval such that they become context-independent when paired with certain extinction training paradigms (spaced CS presentations during extinction) (Bredy and Barad, 2008).

A recent study that used VPA or NaB found that repeated treatments of VPA facilitated acquisition and retention of fear extinction in mice when used with longer duration conditioned stimuli that weakened extinction training, suggesting sensitivity to precise parameters of the extinction protocol (Heinrichs et al., 2013). In rats exposed to the single prolonged stress model of PTSD, another HDAC inhibitor, vorinostat, facilitated extinction learning when given after a second extinction training session (Matsumoto et al., 2013).

In separate studies aimed at identifying the specific classes of HDAC enzymes involved in extinction learning in mice, viral overexpression of HDAC1 enhanced extinction (Bahari-Javan et al., 2012), selective knockout of HDAC2 facilitated extinction learning (Morris et al., 2013), and systemic treatment with the HDAC3 inhibitor RGFP966 facilitated extinction in a manner that was resistant to reinstatement (Malvaez et al., 2013). These three studies suggest that different classes of HDAC molecules have distinct and possibly functionally opposed roles in extinction learning, with HDAC1 possibly being different from HDAC2 and HDAC3.

Histone acetyltransferase (HAT) enzymes, including p300 and CBP (CREB-binding protein) have also been implicated as important regulators of extinction learning processes in the infralimbic cortex. In the PFC, p300 and CBP were shown to be involved with creation of the extinction memory via mediation of long-term potentiation (LTP). Wei et al. (2012) showed that systemic administration of the PCAF (p300/CBP-associated factor; transcriptional co-activator of p300 and CBP) activating drug SPV106, before extinction training resulted in enhancement of extinction memory formation and reduction in renewal. These effects were related to PCAF's enhancing effect on LTP in the infralimbic cortex, and its possible disruption of the reconsolidation of the original fear memory (Wei et al., 2012).

Fibroblast growth factor-2. Fibroblast growth factor-2 (FGF2), a mitogenic neurotrophic factor that is expressed in a large number of brain areas, has been linked to neural plasticity and memory (Zechel et al., 2010). It has been studied most extensively in the hippocampus, where it affects neurogenesis, neurorepair, and neuroplasticity. In cultured hippocampal neurons, FGF2 application significantly increased the number of functional, excitatory synapses compared to untreated neurons (Li et al., 2002). Systemic administration of FGF2 both before and after extinction training significantly enhanced retention of the extinction memory, compared to vehicle treated animals that received more extensive training (Graham and Richardson, 2009). Subsequent studies have shown that FGF2 administered systemically after extinction training also reduced renewal of fear in the original training context, as well as when animals received a single, stress-inducing reminder shock before testing (Graham and Richardson, 2009, 2010).

Recent studies involving FGF2 have shown that intra-BLA infusion results in the same extinction enhancement seen with systemic administration, including general extinction enhancement, prevention of stress related relapse, and prevention of renewal in the original conditioning context (Graham and Richardson, 2011). Based on the time course of administration that yields the most significant enhancement of extinction, it is hypothesized that FGF2 is facilitating conversion of the extinction memory from short-term to long-term storage, and/or erasing, in part, the original fear memory trace (Graham and Richardson, 2009, 2011). Thus, FGF2 may facilitate extinction learning in a lasting manner.

Magnesium. The systemic administration of magnesium-L-threonate (MgT) elevates magnesium levels in the brains of rats. This increases synaptic plasticity in the hippocampus and PFC, as well as NMDA receptor signaling, BDNF levels, and presynaptic puncta in the PFC. MgT, administered both before and after fear acquisition (conditioning) significantly enhanced retention of subsequent extinction training. Interestingly, while significant changes occurred in the PFC as a result of MgT treatment (increased NMDAR currents, increased BDNF expression, enhanced synaptic plasticity), similar changes were not observed in the basolateral nucleus of the amygdala, indicating that the extinction enhancements driven by MgT may result from PFC-specific changes (Abumaria et al., 2011).

M-type potassium channel modulators. M-type K+ (potassium) channels regulate the intrinsic excitability of neurons in a variety of brain structures, which directly relates to burst firing of action potentials. In infralimbic cortex, M-type K+ channels have been shown to regulate excitability and bursting, such that increased excitability yields increased bursting frequencies. Behavioral studies have shown that the degree of bursting in infralimbic cortex is

directly related to fear expression and correlated with retrieval of extinction. Santini and Porter (2010) showed that infusion of XE-991, an M-type K+ channel blocker, into infralimbic cortex before extinction training enhanced extinction and increased recall of the extinction memory during later tests. The facilitated extinction and extinction recall was likely due to increased burst firing in infralimbic cortex. This suggests that increased activity in infralimbic cortex during extinction training affects the encoding and retention of extinction memories (Santini and Porter, 2010).

Methylene blue. Methylene blue (MB) is a neuroprotective redox compound that globally enhances brain metabolic activity by increasing cytochrome oxidase activity. Cytochrome oxidase is an enzyme involved in the formation of water and ATP during oxidative phosphorylation, and is therefore a critical agent in the storage of cellular energy. MB has been used to treat various brain-related disorders, including dementia and depression. Systemic administration of MB after extinction training resulted in enhanced retention of the extinction memory, as indicated by reduced freezing in post-extinction tests. The degree of enhanced extinction was directly related to increases in cytochrome oxidase-mediated metabolic activity in cortical areas including infralimbic cortex (Gonzalez-Lima and Bruchey, 2004).

Caloric restriction. Caloric restriction (CR) causes changes in the brain that mimic those seen after long-term SSRI treatment, including increased plasticity, likely via increased BDNF expression. In mice, CR enhances extinction acquisition and retention, changes that are also observed in SSRI-treated animals. Importantly, the extinction enhancing effects of CR are not seen in serotonin transporter (SERT) knockout mice, indicating that CR's effects in the brain are likely mediated by a SERT-related mechanism. It was also found that in SSRI-treated animals, CR did not act synergistically with this drug treatment to additionally enhance extinction. Serotonin, which often acts as a modulator of signaling initiated by other neurotransmitters, has been shown to decrease excitatory glutamatergic activity in the lateral amygdala (LA) via the activation of GABAergic interneurons. By reducing activity in the LA, increased serotonin acts as an anxiolytic agent (Riddle et al., 2013).

3. Behavioral approaches

A number of studies have examined the effects on extinction of modulating behavioral parameters of this procedure, without use of pharmaceuticals. Here we focus on studies that varied trial spacing, used multiple contexts, or added concurrent excitor stimuli.

3.1. Massed extinction

The time elapsed between fear conditioning and extinction plays an important role in the effectiveness of extinction, since extinction training that takes place only minutes after conditioning ("immediate" extinction), versus 24 h later ("delayed" extinction), is less effective at reducing long-term fear (Maren and Chang, 2006). However, another study in rats found *less* spontaneous recovery of fear following immediate than delayed extinction, but only with a relatively long extinction-test interval (7 days); a short interval (48 h) produced the opposite effect (Johnson et al., 2010).

The timing between stimulus presentations *within* an extinction session may also affect the robustness of extinction, such as so-called massed extinction where multiple CS trials are given with little temporal spacing. In fear-conditioned rats, where the CS was a light stimulus paired with footshock, massed extinction (given as a single, long CS) produced less effective extinction than distributed stimuli (Baum et al., 1990). Another rat study concluded that massed extinction trials produce better short-term but worse long-term loss of context-conditioned fear responses than spaced trials (Li and Westbrook, 2008). A more recent study found that massed extinction treatment in rats attenuated the strong renewal of fear induced by a delayed interval between extinction and test (Laborda and Miller, 2013). In mice, both short-term and long-term fear extinction was greater with temporally massed presentations of the CS than spaced ones, where this finding may be the opposite of that for fear acquisition (Cain et al., 2003).

In a series of rat fear conditioning experiments, extinction trials widely spaced in time produced greater reduction in fear at test than more closely spaced trials, and also this spacing attenuated later renewal of fear in the conditioning context (Urcelay et al., 2009b). In contrast, in animals conditioned with a mixture of intertrial intervals (ITIs) that received extinction training with a variety of ITIs, this produced variation in within-session extinction, but had little effect on spontaneous recovery or reinstatement (Moody et al., 2006). In a human contingency learning task, progressively increasing spacing between extinction trials resulted in faster within-session extinction, but this did not have a lasting effect on a subsequent test in the extinction context, or on a renewal test in the training context (Orinstein et al., 2010). In summary, variations in trial spacing may alter within-session extinction, but not always in lasting manner upon subsequent testing, and the effectiveness of massed extinction versus temporally spaced CS trials has varied across experiments and the particular parameters used.

3.2. Multiple contexts

The context in which an individual is located, including temporally, plays a critical role in Pavlovian fear conditioning, extinction, and retrieval of extinction (Maren et al., 2013). One possibility is that when extinction takes place in multiple contexts, the individual generalizes such that extinction in a novel context is enhanced. In a human predictive learning paradigm, extinction in multiple contexts, relative to that in a single context, reduced response recovery upon testing in a novel context (Glautier et al., 2013). In a human study of spider phobia, extinction in multiple contexts was able to reduce renewal of fear more than extinction in a single context (Shiban et al., 2013). Similarly, repeated exposure of individuals to videotapes of spiders in multiple contexts, versus in a single context, produced generalization of extinction when a videotape of the spider was presented in a new location (Vansteenwegen et al., 2007). In a human fear conditioning paradigm, extinction in three different contexts as opposed to one resulted in attenuated renewal of fear in a novel context (Balooch et al., 2012). However, in a study of persons who drank alcohol heavily, extinction to alcohol-based cues was not enhanced by exposure to multiple contexts (MacKillop and Lisman, 2008). Likewise, in a shock-based fear conditioning procedure in humans, conducting extinction in three or five different contexts did not attenuate renewal of fear (Neumann et al., 2007).

In a conditioned suppression paradigm in rats, where animals were extinguished in either one or three contexts and then tested in a novel context, those that had been exposed to the three contexts exhibited less responding to the CS (Gunther et al., 1998). Extinction in multiple contexts and a massed extinction treatment each attenuated the strong return of fear produced by testing long after extinction, and the two treatments interacted to further minimize return of fear (Laborda and Miller, 2013). However, another rat study found that extinction in multiple contexts did not reduce the size of the final renewal effect, upon testing in a new context (Bouton et al., 2006a). Holmes and Westbrook (2013) recently showed that extinction of reinstated or ABC renewed fear responses in rats rendered them resistant to subsequent ABA renewal, illustrating suppression of fear renewal

across contexts. These studies suggest that extinction in multiple contexts can produce generalization of learning under some circumstances.

3.3. Concurrent excitors

Use of a concurrent excitor stimulus, which is initially paired with the US like a standard CS, can result in diminished renewal of fear when presented during extinction (Urcelay et al., 2009a). An early study on this topic used a Pavlovian magazine approach or instrumental discriminative training in rats to demonstrate enhancement of extinction by a concurrent excitor (Rescorla, 2000). A more recent study found that addition of multiple conditioned excitors to a target excitor enhanced the effectiveness of extinction, by reducing fear during renewal testing (McConnell et al., 2012). In a human fear conditioning experiment, there was *impaired* extinction to a target CS when it was presented with another excitor during the extinction procedure; removal of the concurrent excitor elicited pre-extinction levels of conditioned responding (Vervliet et al., 2007). Also, in a human autonomic fear conditioning paradigm, extinction was disrupted either when the excitor stimulus was a predictor of shock or when it was a predictor of no shock (Lovibond et al., 2000). These studies suggest that excitor stimuli provide a novel approach for altering extinction learning.

3.4. Post-retrieval extinction

A few fairly recent studies, both in humans and in rats, have suggested that carrying out extinction during the memory reconsolidation period may weaken if not erase the original fear memory. Monfils and colleagues found that a conditioned auditory fear memory in rats can be destabilized and "reinterpreted" as safe by presenting the animal with a retrieval trial before the extinction session (Monfils et al., 2009). Likewise, this group of researchers found that activating fear memories during reconsolidation in humans and then "updating" them with non-fearful information, can selectively suppress the original fear memories for at least a year (Schiller et al., 2010). These researchers also suggested that extinction during the reconsolidation period may reduce or erase fear by diminishing prefrontal cortical signaling (Schiller et al., 2013). In contrast to these results, a study in rats found that a single retrieval trial prior to extinction *enhanced* renewal and reinstatement of extinguished responding, and this was not observed if the retrieval and extinction took place in different contexts. These authors suggested that their contrasting results may be related to occasion setting contextual associations versus direct context-conditioned stimulus associations formed by the retrieval trial, or due to discrimination versus generalization between the circumstances of conditioning and extinction (Chan et al., 2010). In a human study, a behavior-alone approach targeting extinction during reconsolidation did not erase a conditioned fear memory, although the beta blocker propranolol given during reconsolidation selectively deleted the fear-arousing aspects of the memory (Soeter and Kindt, 2011a,b). In contrast to Schiller et al. (2010) which measured skin conductance alone, Kindt and Soeter also found that extinction learning during the reconsolidation window did not prevent recovery of fear on multiple indices of conditioned responding, including skin conductance, startle response, and unconditioned stimulus-expectancy (Kindt and Soeter, 2013). In summary, there are conflicting findings, both in animals and in humans, as to whether "editing" fear during reconsolidation with extinction trials can erase or at least suppress the original, conditioned fear memory.

4. Drug-induced extinction

There has been considerable evidence to suggest that neural plasticity in mPFC participates in the extinction of conditional fear. Quirk and colleagues recently examined whether infusion of brain-derived neurotrophic factor (BDNF), a growth factor that is critically important for neural plasticity (Edelmann et al., 2013), into mPFC would promote fear suppression. Interestingly, they found that BDNF infusion into the infralimbic region of mPFC after fear conditioning, and in the absence of extinction training, reduced conditional fear (Peters et al., 2010). In other words, BDNF infusion into mPFC alone and without presentation of CS-alone trials appeared to result in fear extinction. Further experiments showed that this "BDNF-induced extinction" was not the result of disruption in the original fear memory (Peters et al., 2010). Because BDNF has been shown to exert some of its effects via N-methyl-D-aspartate (NMDA) receptors, a subsequent study was done in which the NMDAR antagonist CPP (3(2-carboxypiperazin-4-yl)-propyl-1-phosphonic acid) was administered systemically in conjunction with mPFC BDNF infusion. Extinction retention in the absence of extinction training was then measured and compared to BDNF-alone and saline-alone infusion groups. The administration of CPP blocked the extinction producing effects of BDNF-alone infusion, resulting in BDNF + CPP freezing levels that were comparable to the saline-infused rats (Peters et al., 2010).

To further elucidate the neuroanatomical basis of BDNF-mediated extinction, BDNF levels were analyzed in mPFC, amygdala, and hippocampus of rats that had undergone extinction and retention testing and been subsequently separated into "Extinction Success" and "Extinction Failure" groups based on their freezing levels during retention. It was found that BDNF levels in the hippocampus, but not the amygdala or mPFC, were elevated in the Success group compared to the Failure group. Based on these results, and previous work showing that hippocampal terminals release BDNF in the infralimbic cortex, antibodies that inactivate BDNF were infused into infralimbic cortex in one group of animals, while a control group received saline infusion. Both of these groups received BDNF infusion into the hippocampus, whereas another control group received saline injections in both infralimbic cortex and hippocampus. The animals that received hippocampal BDNF and infralimbic cortex saline infusion showed extinction learning in the absence of extinction training, similar to what was seen following infralimbic cortex BDNF infusions. Importantly, animals that received BDNF infusion in the hippocampus and BDNF-inactivating antibodies in the infralimbic cortex showed significantly reduced extinction learning. These experiments indicate that BDNF activity in the infralimbic cortex is likely derived from hippocampal input and functions primarily through the NMDAR system. Thus, BDNF in the infralimbic cortex may be driving increased infralimbic cortex activity that in turn drives extinction-related behavior in animals that receive no extinction training (Graham and Richardson, 2009, 2010; Peters et al., 2010).

However, this putative effect of BDNF may differ for the prelimbic division of mPFC. A recent mouse study that used virally mediated knockdown of the BDNF gene or pharmacological rescue with a TrkB (a receptor that BDNF activates) agonist indicated that prelimbic BDNF is critical for consolidation of learned fear memories but not fear extinction (Choi et al., 2010). Another recent mouse study that used the systemically administered TrkB agonist, 7,8-dihydroxyflavone, found that it enhanced extinction learning, including in mice exposed to immobilization stress that had an extinction deficit. The authors suggest that this drug may have been acting through amygdalar mechanisms (Andero et al., 2011).

5. Conclusions

As reviewed above, there is a large body of evidence suggesting that various neuropharmacological agents can interact with extinction training to facilitate (or in some cases impair) learning. Peters et al. (2010) even suggests that pharmacological modulation alone, in that case using BDNF administration, can alter extinction-related learning. A number of studies reviewed above indicate that behavioral manipulation of extinction training parameters, such as trial spacing and use of excitors, also impacts extinction learning. Collectively, these studies suggest that the efficacy of exposure therapy in humans may depend to a large degree on the specific pharmaceutical and behavioral parameters used in the procedure.

The above studies that used pharmacological agents to modulate extinction learning (see Table 1 for a summary) clearly indicate that a broad range of drugs, acting through a wide variety of neurophysiological mechanisms, can alter such learning, sometimes in a lasting manner. No single neurotransmitter system, receptor subtype, or second messenger system is responsible for these effects. This is perhaps not surprising, given that there are a number of neurophysiological ways to access the circuits that underlie fear learning, although further downstream in their signaling pathways there may be shared molecular pathways upon which these agents are acting. Pharmacological studies that administered drugs to local brain regions also suggest, not surprisingly, that the neural substrates of extinction learning comprise corticolimbic circuits including hippocampus, amygdala, and mPFC, as well as other regions. One issue to consider when pairing pharmacological agents with extinction learning is that the interoceptive, drug-induced state may itself form part of the "context", and may boost fear-related measures in subsequent testing while off drug due to a change in interoceptive context (Bouton et al., 1990; Maren et al., 2013).

How do these pharmacological findings relate to enhancing exposure therapy in humans? Whereas for practical and immediate purposes we must focus on systemic administration of pharmaceuticals that are approved for human use, basic studies on treatments such as BDNF or methylene blue should not be ignored as they may eventually be used, in some form, for human therapy. But for now, drugs that act on major neurotransmitter systems, such as serotonin, norepinephrine, or glutamate, may provide relatively safe and potentially effective means for enhancing extinction learning. While poly-drug administration may eventually prove more effective than use of single agents, a more immediate question for exposure therapy is the relative effectiveness of the drugs described above. At this point, it is not clear if one class of compounds is superior to the others, and the efficacy of a particular class of drugs may be influenced by a number of factors including age, gender, and any other of a variety of individual differences.

Regarding the enhancement of extinction through behavioral approaches alone, there are promising albeit mixed results for modulation of learning through variations in trial spacing, number of contexts, and use of concurrent excitors. Perhaps there is an optimal inter-trial spacing, as well as optimal temporal spacing *between* sessions (and number of sessions or contexts used) that maximizes extinction learning, which may vary for different individuals. Gaining further understanding of how such optimized behavioral parameters may interact with systemic pharmacological agents would shed further light on enhancement of extinction learning and, by extension, exposure therapy. Future studies that simultaneously vary pharmacological and behavioral parameters, including when these drug and non-drug variables individually enhance extinction learning, could lead to improved treatment for anxiety disorders such as specific phobias and PTSD.

Conflicts of interest statement

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