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Mini-review

Treatment of addiction and anxiety using extinction approaches: Neural mechanisms and their treatment implications

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ABSTRACT

Clinical interventions which produce cue and contextual extinction learning can reduce craving and relapse in substance abuse and inhibit conditioned fear responses in anxiety disorders. In both types of disorders, classical conditioning links unconditioned drug or fear responses to associated contextual cues and result in enduring pathological responses to multiple stimuli. Extinction therapy countermeasures seek to reduce conditioned responses using a set of techniques in which patients are repeatedly exposed to conditioned appetitive or aversive stimuli using imaginal imagery, *in vivo* exposure, or written scripts. Such interventions allow patients to rehearse more adaptive responses to conditioned stimuli. The ultimate goal of these interventions, extinction of the original conditioned response, is a new learning process that results in a decrease in frequency or intensity of conditioned responses to drug or fear cues. This review explores extinction approaches in conditioned drug reward and fear responses. The behavioral, neuroanatomical and neurochemical mechanisms of conditioned reward and fear responses and their extinction are derived from our understanding of the animal literature. Extensive neuroscience research shows that even though many mechanisms differ in conditioned fear and reward, converging prefrontal cortical glutamatergic pathways underlie extinction learning. Efficacy of pharmacological and behavioral treatment approaches in addiction and anxiety disorders may be optimized by enhancing extinction and weakening the bond between the original conditioned stimuli and conditioned responses. Adjunctive pharmacotherapy approaches using agents which alter glutamate or γ-aminobutyric acid signaling or epigenetic mechanisms in prefrontal cortical pathways can enhance extinction learning. A comparative study of extinction processes and its neural mechanisms can be translated into more effective behavioral and pharmacological treatment approaches in substance abuse and anxiety.

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Learning experience involving drugs of abuse or fear responses is often associated with cue and contextual stimuli. Such stimuli in addiction include drug-related paraphernalia, money, and settings such as barrooms. Posttraumatic stress (or PTSD)-related stimuli include the people, places and things found in the accident area, war-zone, crime or abuse settings of the original trauma. Such experience associated with these conditioned stimuli is stored as emotional memories. A period of transitory memory formation followed by a period of greater memory permanence suggests that memory traces become consolidated into the structure of the brain. Extinction learning is an active process that reduces the value or salience of these conditioned cues and contexts. Longer and repeated cue/contextual re-exposure without the associated fear or drug experience reduces conditioned responding. Extinction learning can be effective for reducing cue and context induced symptoms in addiction and anxiety and can improve outcomes in these disorders. The present review addresses the mechanisms of extinction learning and its translation into exposure treatment approaches. This comparative analysis may elucidate the neural mechanisms underlying extinction learning in these clinical disorders. Efficacy of pharmacological and behavioral treatments which enhance extinction learning can improve outcomes in substance abuse and anxiety disorders.

1. Conditioned drug reward and its extinction in addiction

1.1. Definitions of conditioned drug reward and its extinction

Drugs of abuse interact with stimuli in the drug-taking environment via classical and instrumental conditioning to alter motivational responses and self-administration behaviors (Robbins et al., 2008). Pavlovian conditioning mechanisms link unconditioned drug responses to associated contextual cues, allowing the drug responses to be elicited by these non-drug stimuli. For example, drug cue exposure in heroin and cocaine abusing individuals results in real-time drug craving and consequent drug use (Epstein et al., 2009). The temporal and spatial relatedness of these contextual stimuli to motivational responses produces powerful conditioned effects (O'Brien et al., 1993). When these stimuli are encountered in an abstinent state, they can induce memories of prior drug experience, or drug craving, which can result in drug taking and relapse (Weiss, 2005). Cue-induced craving is predictive of relapse in addiction. Any improvements in our understanding of mechanisms of craving or conditioned reward will lead to a better development of treatment approaches (Sinha and Li, 2007).

Animal models have been created to examine drug cue or contextual responses seen in human addiction. Several animal models demonstrate the powerful effects of drug cues or contexts on motivational responses. For example in the conditioned place preference model, an environmental context or cue is paired with experience of the drug (Sanchis-Segura and Spanagel, 2006). This conditioning results in the animal developing learning preferences for the drug associated contextual cue. Similarly, auditory or visual cues can be paired with drug self-administration and can be provided in relationship to operant responding (Sanchis-Segura and Spanagel, 2006; Nic Dhonnchadha et al., 2010). These cues act as conditioned reinforcers which increase behavioral responding for the drug.

Extinction is defined as a learning process that produces a reduction in the frequency or intensity of learned responses to conditioned drug cues. Extinction occurs after the removal of the unconditioned stimulus (UCS) that reinforced the learning in the conditioning environment (Franken et al., 1999). In place conditioning studies, extinction involves exposing rodents to the previously drug-paired context in a drug-free state (Epstein et al., 2006; Shaham et al., 2003; Heinrichs et al., 2010). Extinction is an active process that results in the devaluation of conditioned stimuli. Repeated cue or contextual re-exposures without the UCS inhibits conditioned responding. However, following extinction of drug self-administration or place preferences, the presentation of drug associated stimuli can trigger renewed drug-seeking behaviors and also serve as a measure of relapse and craving (Sanchis-Segura and Spanagel, 2006). Extinction is not simply a "forgetting" of conditioned behavior but instead is a new learning process which acts to mask or inhibit original learning (Bouton, 2004).

Consolidation is a memory storage process occurring after a novel learning experience. Once a memory is stored, repeated presentation of the original conditioned stimulus (CS) initiates two processes, reconsolidation and extinction. The preservation of the original memory trace following initial retrieval is termed reconsolidation. Reconsolidation processes are most prominent when they are coincident with CS presentation and need to be masked in order for extinction learning to be efficacious. Thus, dual reconsolidation and extinction processes provide a framework for understanding and altering new memories. Defining the time course and duration of CS re-exposures in each of these reconsolidation and extinction processes presents a challenge for the treatment of both addiction and conditioned fear (Taylor et al., 2009; Quirk and Mueller, 2008; Tronson and Taylor, 2007).

1.2. Neuroanatomical and neurochemical systems underlying conditioned reward and its extinction

The major components of the neural circuitry for cue and context induced reward and relapse include the prefrontal cortex, which includes prelimbic (PL) and infralimbic (IL) subregions, the basolateral amygdala (BLA), hippocampus, nucleus accumbens (NAc), ventral pallidum, and ventral tegmental area (VTA) as highlighted in Fig. 1. Drugs of abuse produce direct motivational effects by activating dopaminergic neurons originating in the VTA which project to the amygdala, NAc, anterior cingulate cortex and PFC (Hammer, 2002). Exposures to conditioned drug cue and context exposures also activate the mesolimbic dopaminergic system. In support of dopamine's role, cocaine dependent humans viewing drug cues demonstrate craving with correlated increases striatal dopamine levels (Volkow et al., 2006). In conditioned drug reward, classically conditioned cue and contextual responses are established via activation of neurons in the medial PFC (Taylor et al., 2009). Glutamatergic neurons from the prelimbic cortex (PL) of the PFC and from the basolateral amygdala (BLA) project to the NAc core region and to the VTA (Kauer and Malenka, 2007) and are hypothesized to activate drug-seeking behavior (McFarland et al, 2003; Di Ciano and Everitt, 2004). Inactivation of these PL cortical neurons reduces relapse in rat models (LaLumiere and Kalivas, 2008). In contrast, glutamatergic projections from the infralimbic cortex (IL) to the NAc shell subregion are hypothesized to extinguish drug-seeking behavior (Peters et al., 2008; LaLumiere et al., 2010).

In addiction, the functional significance of each brain region is seen in Fig. 1. The PFC is responsible for executive function, decision-making, and the implementation of goal-directed actions. Subregions of the PFC that is important in these functions are the PL, IL and anterior cingulate cortex. The anterior cingulate cortex attaches motivational value to internal and external stimuli. The PL guides response initiation while the IL oversees response inhibition; both regions guide actions and outcomes. Several studies show that activation of the PL induces drug and fear responding while IL inhibits behavioral responding. These findings suggest that that PL-IL serve as on–off mechanisms in both conditioned drug reward and conditioned fear responding (LaLumiere and Kalivas, 2008; Peters et al, 2008; Quirk and Mueller, 2008; LaLumiere et al., 2010; (Weiss, 2005). The BLA processes appetitive and aversive stimuli and mediates approach or avoidance behavior. The hippocampus has a substantial role in cue and contextual associative learning and in memory consolidation and retrieval. The mesocorticolimbic dopamine projections that originate

from the VTA are involved in the initiation of motivational responses. The NAc integrates reward information from dopaminergic neurons and translates it to behavioral output regions through the ventral pallidum.

1.3. Translation of extinction learning into treatment for addiction

Drug dependent individuals demonstrate enduring cue and contextual reactivity even a year after intensive treatment, showing that cue reactivity is slow to extinguish. Increasing the rate and effectiveness of extinction learning is highly desirable in addictive disorders. One goal in the psychotherapy and rehabilitation of patients with substance use disorders is to impede reconsolidation of drug cues and/or facilitate extinction learning. Some support for the clinical efficacy of an extinction-related treatment approach has been demonstrated in abstinent cocaine addicts who were repeatedly exposed to drug associated paraphernalia and outcomes were improved (O'Brien et al., 1993). Such an extinction based treatment is cue exposure treatment (CET). CET is a manualized presentation of drug-related cues and it has been shown to reduce cue activated emotional responses. This extinction treatment approach reduces craving and relapse but has been only partially effective in clinical trials. An early trial of CET in alcohol dependent patients utilized repeated exposure to the sight and smell of preferred drinks in a laboratory setting (Drummond and Glautier, 1994). During a six-month follow-up, this CET treatment increased latency of relapse to heavy drinking and reduced alcohol consumption. In opiate addicted subjects, exposure of subjects to opiate related stimuli produced cue-induced negative emotions that also diminished after a cue exposure treatment protocol (Franken et al., 1999). This dampening of cue reactivity was maintained for at least 6 weeks after the last cue exposure therapy session.

However, subsequent trials of CET did not show similar efficacy. In a more recent trial, patients with alcohol dependence were assigned to either cue exposure or a standard cognitive behavioral treatment (Loeber et al., 2006). Both treatments reduced self-reported craving and increased self-reported measures of confidence to avoid relapse. However, relapse rates and other important drinking variables were not different at the 6-month follow-up in this last study. In a nicotine dependence treatment study (Niaura et al, 1999), cigarette smokers were assigned different conditions: (1) brief cognitive behavioral therapy (CBT); (2) CBT and nicotine gum; (3) CBT and cue exposure; and (4) CBT and cue exposure with nicotine gum. Abstinence rates were measured at 1, 3, 6 and 12-month post-treatment and the time to first slip. In this treatment study, there also were no differential treatment effects on abstinence rates or relapse times, suggesting no specific treatment efficacy. Other clinical trials (Marissen et al., 2007; Conklin and Tiffany, 2002) show that CET did not reduce relapse in substance use disorders and overall there is mixed efficacy of CET for relapse prevention (Havermans and Jansen, 2003). These studies suggest that additional psychosocial interventions such as cognitive reframing and motivational enhancement might be necessary with extinction learning. Additionally, the specific elements of extinction such as timing and intensity of cue exposure, duration of treatment, and type of substance use disorder may affect outcomes.

A better understanding of the neural substrates underlying extinction will translate into treatment outcomes in addiction. In particular, pharmacotherapy can augment motivational and cognitive psychotherapeutic approaches in extinction learning. Future pharmacotherapy approaches may use glutamatergic, γ-aminobutyric acid (GABA) receptor agents, cholinergic or other neurotransmitter receptor agents to enhance CET (Schroeder and Packard, 2004). For example, N-methyl-D-aspartate (NMDA) agonist D-cycloserine (DCS) has clear efficacy in enhancing extinction learning. In a meta-analysis of thirty animal and human DCS studies, Norberg et al. (2008) found that DCS significantly enhanced extinction in animals and exposure therapy in humans. In human addiction, DCS attenuated reactivity to smoking cues in nicotine dependent smokers (Santa Ana et al., 2009). In this double-blind, placebo-controlled pilot laboratory study, smokers were randomized to DCS or placebo, plus cue exposure therapy. DCS significantly reduced smoking cue reactivity in response to *in vivo* smoking cues as measured by physiological and urge cues.

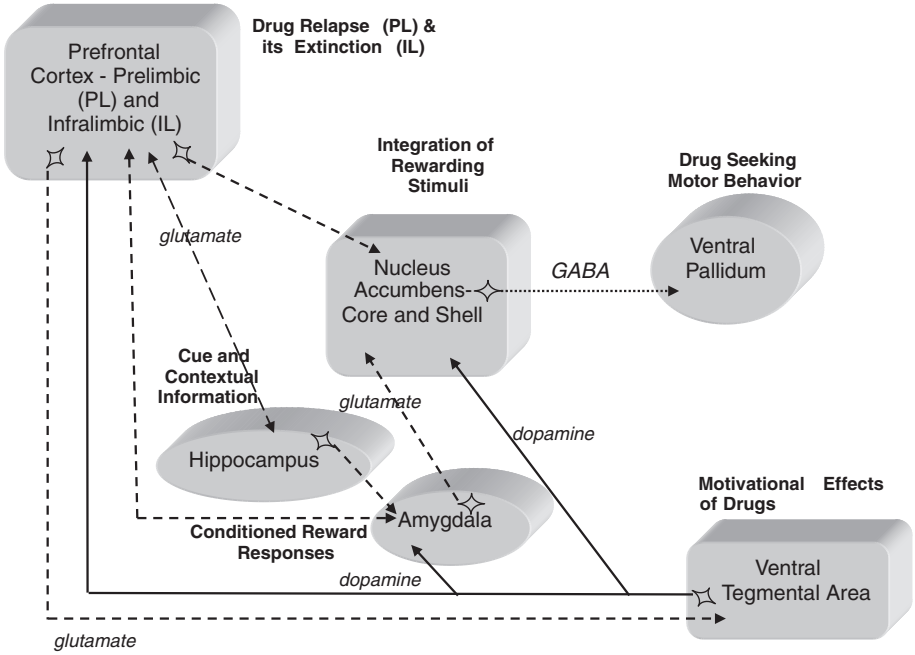

Fig. 1. Neural circuitry of conditioned drug responding and its extinction. Mesocorticolimbic dopamine originates from neurons in the VTA which innervate the NAc, amygdala, and various regions of prefrontal cortex (bold lines) and are involved in motivational responses in addiction. Glutamatergic neurons (dashed lines) from the prelimbic cortex (PL) of the PFC and from the basolateral amygdala (BLA) project to the NAc core region and to the VTA and activate drug-seeking behavior. In contrast, glutamatergic projections from the infralimbic cortex (IL) to the NAc shell are hypothesized to extinguish drug-seeking behavior. The PL and IL may serve as on–off mechanisms in cue responding addiction.

These preliminary findings provide support for DCS combined with cue exposure therapy in attenuating conditioned responses to drug cues.

Challenges exist in the use of pharmaceutical treatments as counter-conditioning treatments to block conditioned responses (CR) associated with drugs. One complication is that the pharmaceuticals introduce stimuli that can mask the CS so that it no longer evokes the CR. In treatment, the original CS may be present but the medication may substantially modify the interoceptive stimuli so that exteroceptive context no longer evokes the memory trace. Consequently, the blocking effects of a medication treatment are drug state dependent and as a result, the CS–CR bond remains unaffected. As a result, the conditioned drug reaction may be maintained once the pharmaceutical treatment is removed. When the CS is viewed as evoking the memory trace, then it is necessary to have the treatment implemented after the CS has activated the memory trace. At this time point, the treatment can potentially modify the memory trace directly and alter the CS–CR bond.

2. Conditioned fear response and its extinction in anxiety

2.1. Definitions of conditioned fear and its extinction

An extensive literature describes the phenomena of fear conditioning and its extinction in animal models and clinical anxiety disorders (Delgado et al., 2006; Quirk and Mueller, 2008; Myers and Davis, 2007). Conditioned responding to aversive stimuli develops when a cue or context is associated with a threatening UCS. After repeated exposures, subjects learn that a conditioned CS predicts aversive consequences and initiates a conditioned fear response (CR) such as freezing or avoidance behaviors (Radulovic et al., 1998). Pavlovian fear conditioning is an involuntary learning process that is long lasting and allows an organism to anticipate and prepare for potentially dangerous conditions (Maren, 2005). Fear conditioning is one of the central features of posttraumatic stress disorder (PTSD) as demonstrated by cue and context induced re-experiencing responses (e.g. flashbacks) or behavioral responses such as freezing (Quirk and Mueller, 2008).

As in the reward, extinction of conditioned fear requires that the subject is repeatedly exposed to the CS after the removal of the UCS. Similarly, extinction learning results in a decrease in the frequency or intensity of conditioned fear. In fear conditioning, re-exposing the subject to the original CS produces one of two processes, reconsolidation or extinction of the CR (Peters et al., 2009; Quirk and Mueller, 2008). Through longer stimulus re-exposure or its repetition (without the UCS), extinction learning develops and conditioned fear responses decrease. The persistence of phobic and anxiety disorders may be caused by a failure to acquire or consolidate fear extinction (Rauch et al., 2006). There are also non-Pavlovian elements of extinction that modulate this learning including UCS devaluation and response fatigue (Myers and Davis, 2007).

2.2. Neural circuitry and mechanisms mediating fear conditioning and its extinction

It is widely accepted that the amygdala, PFC, and hippocampus are key sites of synaptic plasticity and mediate the acquisition of fear conditioning (Corcoran and Quirk, 2007). Fear related sensory information is transmitted to the amygdala through its basal and lateral (BLA) nuclei. PTSD can be conceptualized as a cue- and context-associated fear conditioning process that results from amygdalar hyperresponsivity and an inability to extinguish these neural responses. The hippocampus is critical in associative learning, memory consolidation and in the retrieval of episodic memories. The sites of extinction learning may be distributed across several structures, especially the PFC and its corticolimbic projections to the amygdala (Fig. 2). Glutamatergic excitatory projections from the PL extend to the sites of fear memory storage in the BLA and central nucleus of the amygdala (CNA) and activate downstream fear circuitry. Projections from the BLA to the CNA are thought to activate fear responses through outputs to the hypothalamus and brainstem. The IL cortex appears to be the primary candidate key pathway to suppress fear responses via extinction learning. Single unit recordings have shown that IL neurons respond to conditioned stimuli only after extinction learning has developed (Milad et al., 2006). Agents that activate IL pathways suppress conditioned fear (Vidal-Gonzalez et al, 2006). The IL projects to GABAergic neurons between the BLA and CNA called the intercalated cell masses (ITC) positioned between these two amygdalar subregions. Activation of the ITC inhibits output from the CNA and reduces fear responses. It has been hypothesized that fear extinction entails an increase in excitatory drive to the ITC and produces reductions in output from the CNA (Peters et al., 2009).

As in addiction, consolidation of extinction learning involves NMDA receptor-mediated burst firing in the infralimbic (IL) portion of the PFC. Impairment of the ventromedial PFC by lesions or pharmacological inactivation reduces fear extinction and its retrieval (Burgos-Robles et al., 2007). Interference with PFC glutamatergic pathways via the administration of NMDA receptor antagonist drugs blocks the development or expression of fear extinction. The mechanisms underlying fear conditioning and its extinction have been studied most extensively in the thalamo- and cortico-amygdalar pathways where glutamate α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) receptor subunits are involved. After extinction is consolidated and the fear CS is presented, cortical GABA is released and diminishes the firing of glutamatergic neurons that generate fear responses. Neuroimaging studies in humans also support involvement of both amygdala and PFC regions in fear extinction (Gottfried and Dolan, 2004).

2.3. Translation of extinction learning into treatment for anxiety

One effective psychotherapeutic approach for neutralizing fear conditioning in PTSD is prolonged exposure (PE) therapy, a form of extinction learning that has similarities to CET. Following the experience of a traumatic event 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. If trauma victims restrict their routines and avoid reminders of the traumatic event, then symptoms of PTSD are more likely to become chronic. PE produces extinction of trauma-related thoughts, feelings, and behaviors. The therapy utilizes a set of techniques in which patients use imaginal imagery, trauma-driven scripts, and *in vivo* exposure to reduce emotional reactions to feared objects and situations in a safe setting. Patients learn to understand that their fears and reactions to these stimuli are unrealistic (Foa, 2006). In a controlled study (Marks et al., 1998), patients with chronic PTSD were randomized to one of four treatments: PE (imaginal and live) alone; cognitive restructuring alone; combined PE and cognitive restructuring; or relaxation without PE or cognitive restructuring. Exposure therapy and cognitive restructuring therapy, alone or together, improved PTSD at the end of treatment and at follow-up. In a large randomized controlled trial of female veterans with PTSD, patients were randomly assigned to receive PE or control treatment (Schnurr et al., 2007). Women who received PE experienced a greater reduction of PTSD symptoms. The prolonged exposure group was more likely to no longer meet PTSD diagnostic criteria and to achieve remission. Thus, fear extinction therapies have been found to be efficacious in the treatment of PTSD (Foa, 2006). Similarly, treatment studies for specific phobias using extinction training using *in vivo* exposure, desensitization, and virtual reality are acutely effective for different types of phobias (Choy et al., 2007).

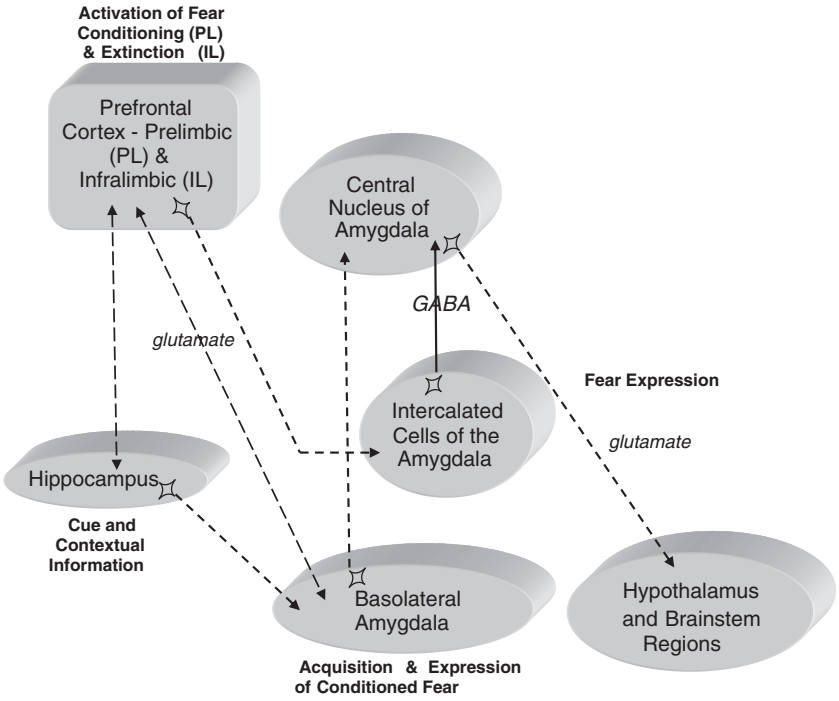

Fig. 2. Neural circuitry of fear conditioning and its extinction. The BLA, PFC, and hippocampus are key sites for the acquisition of fear conditioning. Fear related sensory information enters the amygdala through its basal and lateral nuclei. Projections from the CNA provoke expression of fear responses via downstream projections to the midbrain and hypothalamic regions. The hippocampus is critical in contextual associative learning, memory consolidation and in the retrieval of memories. The sites of extinction learning may be distributed across the PFC and its corticolimbic projections to the amygdala. Glutamatergic excitatory projections from the PL extend to sites of fear conditioning in BLA while the IL is the key pathway for the extinction of memories. The IL projects to both GABAergic neurons between the BLA and CNA called the intercalated cell masses (ITC) positioned between the two amygdalar subregions. Extinction may represent an increase in excitatory drive to the ITC and decreased output from the BLA.

3. Integrated mechanisms and treatment approaches to enhance extinction learning in conditioned fear and drug reward

Exposure therapies are effective in reducing PTSD symptoms (Foa, 2006) and partially effective in the extinction of craving and relapse in addiction (Conklin and Tiffany, 2002). Exposure therapies for both addiction and PTSD utilize imaginal approaches, written scripts, and sometimes live exposure techniques to reduce emotional reactions. Several factors constrain efficacy of extinction learning as presently implemented. The nature of the rewarding or adverse stimuli in addiction and PTSD, respectively, is different. In addiction, the sensory quality of the extinction contexts used in a treatment environment may only weakly approximate the reality of the drug-using environment. Of course, exposure to a naturalistic setting in addiction is potentially dangerous and cannot easily be employed in a treatment setting. Consequently, the efficacy of the extinction protocol is not sufficient to reverse the original conditioning so that extinction reminders are needed in treatment approaches. The relative permanence of the CS and CR bonds in addiction, and its resistance to extinction could account for its partial efficacy in substance use disorders. Differences in reconsolidation and extinction learning may be operative in anxiety and addiction. Operant conditioning is likely to be relevant to addiction so that even if conditioned motivational responses are extinguished, the instrumental act of drug self-administration remains. Assisting addicted individuals with other interventions including cognitive, behavioral, motivational therapy and coping skills appears critical for maintaining abstinence (Rohsenow et al., 2001). The differing nature of rewarding and aversive stimuli and their conditioning mechanisms may produce the differential efficacy of exposure treatment in addiction and anxiety.

Extensive neuroscience research shows a convergence of evidence for the central role of PFC glutamatergic pathways in extinction of conditioned fear and conditioned drug reward behaviors (Peters et al., 2008; Quirk and Mueller, 2008; Taylor et al., 2009). In the medial PFC, the PL appears to serve as an on-switch for both conditioned reward and fear while the IL functions as an off-switch for both. This convergence is particularly striking when viewed in light of the fact that neural circuitry mediating reward (Fig. 1) is different anatomically, neurochemically, and physiologically from substrates of fear conditioning (Fig. 2). Thus, the use of pharmacological treatment approaches may optimize extinction learning. Adjunctive cognitive enhancement using pharmacotherapy approaches may improve the extinction of cue reactivity in addiction and PTSD (Cai et al., 2006). Agents that affect certain neurotransmitter mechanisms may be potentially useful in enhancing extinction. For instance, pharmacotherapy approaches with the N-methyl-D-aspartate receptor partial agonist, D-cycloserine (DCS), and GABA receptor agents along with procedures derived from animal learning research can be more fully implemented in addiction and PTSD or phobia treatment (Berlau and McGaugh, 2006). DCS has been shown to enhance the extinction of fear conditioning and is hypothesized to hasten extinction of cocaine cue reactivity in animal models (Nic Dhonnchadha et al., 2010) and in humans (Price et al., 2009). Initial clinical trials demonstrate that DCS in conjunction with cue and contextual exposure therapies reduce anxiety for patients with social anxiety (Guastella et al., 2008; Hofmann et al., 2006) and phobias (Ressler et al., 2004). The $GABA_B$ receptor agonist, baclofen, improves hyperarousal and avoidance symptoms in chronic PTSD due to combat (Drake et al., 2003). $GABA_B$ agonists also have been shown to enhance the extinction of conditioned drug reward (Heinrichs et al., 2010). In a trial of baclofen for smoking reduction, treatment significantly reduced cigarettes smoked per day and drug craving (Franklin et al., 2009). The timing of drug administration is critically related to effects on memory has been shown to reverse the lowering of reward thresholds by drugs of abuse and reduce cue reactivity in addiction (Maccioni et al., 2008). DCS and

GABA receptor agents show promise to enhance extinction learning in drug and fear conditioning and for increasing efficacy of exposure-based psychotherapy (Hofmann, 2007).

Finally, epigenetic mechanisms provide a novel avenue for altering gene expression underlying neural plasticity and behavior. Certain drugs modify transcriptional pathways through epigenetic mechanisms involving histones. Histones are highly basic proteins that organize DNA within the nucleus. Certain chromatin modifying enzymes, such as histone deacetylases, modify histone tails and in turn alter neuronal gene transcription (Roth and Sweatt, 2009). Treatment with histone deacetylase (HDAC) inhibitors induces dendritic sprouting, synaptic connections, and learning reinstatement (Fischer et al., 2007). Valproate modulates brain derived neurotrophic factor expression, increases long-term memory for extinction related to its HDAC inhibitor effects and enhances extinction training fear conditioned subjects (Bredy and Barad, 2008). HDAC inhibitor treatment facilitates extinction of cocaine-induced conditioned reward (Malvaez et al, 2010). In this last study, HDAC inhibitor treatment also increased histone acetylation in the nucleus accumbens following extinction. These results suggest a relationship between histone modification, epigenetic regulation of neurotrophic factors, enhancement of plasticity and long-term memory for extinction of conditioned fear. These studies provide preliminary evidence that histone deacetylase inhibitors are agents for enhancing extinction learning in both addiction and conditioned fear.

4. Conclusions

In summary, learning experience involving drugs of abuse or fear responses is associated with cue and contextual stimuli that produce conditioned responding to such stimuli. Extinction learning is an active process resulting after the devaluation of these conditioned cues and contexts. Extinction treatments have been preliminarily effective in reducing cue and context induced emotions and behaviors and improving outcomes in anxiety and substance abuse disorders. Convergent neurobiological evidence documents the central role of PFC pathways in extinction of conditioned fear and drug reward behaviors. The essential goal of extinction therapies is to enhance long-term extinction responses by increasing resistance to spontaneous recovery, contextual renewal, and post-extinction reinstatement produced by re-exposure to conditioned cues or stress triggers. Future research and treatment needs to better incorporate all these elements into extinction learning. Additionally, comparative analysis of the neural substrates of original and extinction learning in reward and fear contexts provides significant potential for enhancement of therapeutic efficacy. Future pharmacotherapies may harness glutamatergic, GABAergic, or epigenetic mechanisms to facilitate cue and contextual exposure therapy efficacy. Such comparative studies of extinction processes and their neural mechanisms can guide the design of future clinical trials in substance use and anxiety disorders. Improvements in our knowledge of mechanisms relating to the expression and extinction of fear conditioning and drug cue reactivity will inform more comprehensive, standardized, evidence-based pharmacotherapy and behavioral therapies. Such knowledge can be translated into more effective treatment and will better allay the suffering of many afflicted individuals.

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