



## Review

## Targeting extinction and reconsolidation mechanisms to combat the impact of drug cues on addiction

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## ABSTRACT

Drug addiction is a progressive and compulsive disorder, where recurrent craving and relapse to drug-seeking occur even after long periods of abstinence. A major contributing factor to relapse is drug-associated cues. Here we review behavioral and pharmacological studies outlining novel methods of effective and persistent reductions in cue-induced relapse behavior in animal models. We focus on extinction and reconsolidation of cue-drug associations as the memory processes that are the most likely targets for interventions. Extinction involves the formation of new inhibitory memories rather than memory erasure; thus, it should be possible to facilitate the extinction of cue-drug memories to reduce relapse. We propose that context-dependency of extinction might be altered by mnemonic agents, thereby enhancing the efficacy of cue-exposure therapy as treatment strategy. In contrast, interfering with memory reconsolidation processes can disrupt the integrity or strength of specific cue-drug memories. Reconsolidation is argued to be a distinct process that occurs over a brief time period after memory is reactivated/retrieved – when the memory becomes labile and vulnerable to disruption. Reconsolidation is thought to be an independent, perhaps opposing, process to extinction and disruption of reconsolidation has recently been shown to directly affect subsequent cue-drug memory retrieval in an animal model of relapse. We hypothesize that a combined approach aimed at both enhancing the consolidation of cue-drug extinction and interfering with the reconsolidation of cue-drug memories will have a greater potential for persistently inhibiting cue-induced relapse than either treatment alone.

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### 1. Introduction

Cue-induced craving often precedes and accompanies compulsive drug use and is a major challenge to the successful treatment of addiction. Drug-associated cues acquire powerful conditioned reinforcing properties that promote drug-seeking and -taking that are not easily disrupted. These cues are highly persistent in their ability to induce relapse and, critically, may not readily extinguish when these stimuli are no longer predictive of the actions of addictive drugs. Despite therapeutic interventions and techniques aimed at behaviorally inducing cue extinction in addicts, these methods have not yet proven efficacious in promoting abstinence.

Here we review a new focus for the National Institutes on Drug Abuse (NIDA) research that should aim to identify combinations of

behavioral and pharmacological methods to effectively and persistently reduce the ability of drug-associated cues to induce relapse – largely focusing on cocaine as a prototypical addictive drug. Pre-clinical models and translational studies should capitalize not only on the vast and diverse knowledge gained from the past 35 years of NIDA research on drug-induced neuroadaptations and the neurocircuitry associated with relapse, but also on fundamental learning and memory processes. The integration of such information would obviously be advantageous for the development of novel treatment strategies to combat addiction. Specifically, we review recent research that systemic and brain specific manipulations known to alter opposing mnemonic processes – consolidation of extinction and reconsolidation – can be targeted to reduce the impact of drug cues in addiction. We also argue that the mechanisms that subserve cue-induced relapse to drug-seeking are associated with drug-induced adaptations in DA/glutamate-regulated signaling cascades. This may produce resistance to extinction (associated with altered cortical regulation of drug-associated cues) but also favor enhancements in reconsolidation of drug cues. As such, drug-induced neuroadaptations may contribute to the persistence and impact of drug-associated memories.

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The neurobiological mechanisms of extinction and reconsolidation of natural and drug-related appetitive cues are being identified in part from the wealth of knowledge established from years of research on aversive/fear-related Pavlovian processes. With this arsenal of information we can challenge ourselves to develop a number of hypothesis-based treatment strategies to identify novel behavioral and pharmacological methods to effectively and persistently reduce cue-induced relapse in addiction. We argue here that a promising approach would be to (1) enhance cue extinction learning with agents that are known or predicted to have mnemonic effects, (2) extinguish cues in multiple contexts to reduce the context-dependency of extinction, (3) alter contextual processes that depend on the hippocampus, (4) inhibit reconsolidation, and finally, (5) do a combination of the above.

In 1974, with the establishment of NIDA, a “war on drugs” was waged. In the past 35 years of funded research, NIDA’s program initiatives and investigators have significantly advanced our understanding of neurobiological mechanisms and neuro-behavioral phenomena that underlie addiction. We have learned that there may be no “magic bullet” to “just say no” to drugs. Instead, it will “take a village” – social/societal/genetic/psychological/neural information – to combat addiction. We now have the “audacity of hope” – the knowledge and expertise – to find an effective treatment using a combination of approaches spear-headed by NIDA’s scientific mission. This began with the fundamental premise and the acknowledgement that addiction be considered a brain disease – an idea initiated and promoted by NIDA’s Directors. Like other diseases, addiction is a chronic and relapsing disorder that involves complex biological, environmental and social factors. With this history of NIDA support for research, we are prepared to approach future investigations into reversing the destruction that addiction produces. NIDA’s most important achievement, consequently, has been the use of science to delineate critical concepts underlying the etiology, pathophysiology and treatment of drug addiction.

## 2. Clinical evidence for cue learning in addiction

Drug addiction is a progressive, chronic relapsing disorder, where craving and relapse to drug-seeking and -taking behavior persist even after long periods of abstinence. Environmental conditioned cues previously associated with drugs are major contributors to relapse. These cues evoke salient and pervasive memories of the drug experience that induce craving and precipitate relapse to drug-seeking and -taking. Neuroimaging studies in human addicts reveal that drug-associated cues produce neural activation in the same mesocorticolimbic circuitry known to produce the reinforcing properties of addictive drugs, and that the magnitude of activation of these regions is predictive of craving (Grant et al., 1996; Childress et al., 1999; Garavan et al., 2000; Kilts et al., 2001; Bonson et al., 2002) and the probability of relapse (Sinha and Li, 2007; Kilts et al., 2001; Maas et al., 1998). Likewise, dopamine release in the dorsal striatum is enhanced in cocaine dependent individuals viewing cocaine cues and the increase in dopamine is positively correlated with self-reported craving (Volkow et al., 2006). In addition, clinical studies have shown that discrete cues paired with smoked cocaine or alcohol can elicit conditioned responses including changes in heart rate, skin conductance, and reported craving after fairly limited training (Foltin and Haney, 2000; Field and Duka, 2002). Foltin and Haney (2000) reported that these conditioned responses are reduced over several extinction sessions, but it is not known how enduring the conditioned effects of environmental cues are when repeatedly paired with drug in a chronic addict. Therefore, treatment strategies that reduce the motivational properties of drug cues have great potential to reduce craving and relapse in addicts.

## 3. Cue learning in addiction

Several researchers have proposed that addiction develops due to aberrant neuroplasticity in the mesocorticolimbic dopaminergic circuitry that mediates reward-related learning (Kalivas and O’Brien, 2007; Hyman et al., 2006; Everitt and Robbins, 2005; Jones and Bonci, 2005; Self, 2004; Kelley, 2004; Di Chiara, 1999; Jentsch and Taylor, 1999). A primary component of reward-related learning and the development of addiction are the strong associations that develop between stimuli in the environment that are predictive of reward (cues) and the reward itself (e.g., drugs). As learning about reward-associated stimuli develops such cues gain progressively greater control over behavior (Jentsch and Taylor, 1999) and this may be associated with time-dependent changes in dopamine release in response to drug-associated cues in the nucleus accumbens and prefrontal cortex (PFC; Torregrossa and Kalivas, 2008). Cues associated with drugs of abuse can increase drug self-administration and precipitate ‘relapse’ in animal models of addiction (de Wit and Stewart, 1981; Shaham et al., 2003; Epstein et al., 2006; See, 2002, 2005). Indeed, in these models the motivational properties of drug-paired discrete and contextual cues can even be augmented over time, or “incubate” (Grimm et al., 2001), which highlights the necessity to directly target drug-associated cues as a component of therapeutic interventions.

Several studies have demonstrated that the amygdala is involved in incentive learning and contributes to the representation of the incentive value of conditioned stimuli (reviewed in Everitt et al., 2003; Balleine and Killcross, 2006). At least two discrete nuclear complexes within the rodent amygdala have been implicated in these processes, the central nucleus (CeA) and the basolateral complex (BLA). The CeA is connected with hypothalamic and brainstem regions that are involved in mediating autonomic and consummatory responses to stimuli with incentive value. Lesions of the CeA block the acquisition of Pavlovian stimulus-reward conditioning and the effects of Pavlovian conditioned motivational influences on instrumental actions (see Everitt et al., 1999; Cardinal et al., 2002). Specifically, lesions of the CeA but not BLA abolish Pavlovian to instrumental transfer (PIT) and Pavlovian approach (Killcross et al., 1998; Hall et al., 2001; but see Blundell et al., 2001). Moreover, lesions of the CeA, but not the BLA, block the potentiation of conditioned reinforcement by psychostimulants (Burns et al., 1993).

The BLA, however, does regulate other aspects of cue-related learning. For example, Hatfield et al. (1996) and Whitelaw et al. (1996) have demonstrated that lesions of the BLA, but not the CeA, block second-order conditioning and impair reinforcer devaluation. Lesions of the BLA also reduce the reinforcing properties of established conditioned reinforcers (Burns et al., 1993), and prevent cue-induced reinstatement of cocaine-seeking (Meil and See, 1997). Damage within the BLA thus produces impairments in reinforcer valuation and in the ability of conditioned stimuli to affect instrumental responding (Killcross et al., 1997; Malkova et al., 1997; Holland and Gallagher, 1999). These data suggest that the BLA is involved in the stimulus-reward associations critical for the representation and transfer of information about the motivational value of conditioned stimuli to instrumental or motor responses, presumably via its projections to the ventral striatum and PFC. Interestingly, lesions of the BLA abolish the outcome-specific effects of Pavlovian stimuli on instrumental behavior, while lesions of the CeA disrupt the general motivational properties of reward-associated cues (Corbit and Balleine, 2005), providing further information regarding the dissociable contribution of the CeA and BLA to behavior motivated by reward-associated stimuli, and increasingly, data suggest that these amygdala subregions make important and dissociable contributions to cue-drug-motivated behavior.

#### 4. Extinction versus reconsolidation

Learning and memory of stimulus–reward associations have been hypothesized to be composed of several phases that may involve distinct neurobiological processes. These phases include acquisition, consolidation, retrieval, reconsolidation of the memory after retrieval, and extinction, which involves learning of a stimulus–no reward association (Alberini et al., 2006; Bouton, 2004). Of these, memory extinction and reconsolidation offer the most realistic opportunities to influence the strength of a drug-associated cue memory. After pairing of a cue such as a tone or light with an unconditioned stimulus such as a footshock or drug, the cue comes to elicit an array of behavioral and physiological conditioned responses (e.g., freezing or approach; changes in heart rate; changes in respiration). With repeated presentations of the non-reinforced cue, these conditioned responses dissipate or “extinguish”. Extinction is widely accepted to involve new learning that inhibits or overrides initial learning rather than forgetting (Bouton, 2004). Responses to an extinguished cue can re-emerge with the passage of time (spontaneous recovery), changing contexts (renewal), or presentation of the unconditioned stimulus (reinstatement). On the other hand, reconsolidation is the process of restabilizing the memory trace after it is retrieved or “reactivated”, possibly strengthening it and returning the memory to long-term storage (Tronson and Taylor, 2007). While no one has directly proven that reconsolidation strengthens cue–drug memories, the expression of conditioned fear is somewhat enhanced after reactivation, and is further enhanced by PKA activation in the amygdala compared to non-reactivated controls (Tronson et al., 2006). Spatial memory in the Morris water maze also is enhanced after memory reactivation by re-exposure to the context (Flint et al., 2007). Therefore, reconsolidation of cues may later enhance cue-motivated behavior.

While retrieval of a previously consolidated memory can induce a period of lability during which the reconsolidation of that memory can be manipulated, the retrieval of a cue in the absence of reinforcement can also lead to extinction. Thus, the same experience (non-reinforced exposure to a learned cue) can result in two distinct behavioral outcomes: (1) stabilization of the conditioned response through the process of reconsolidation or (2) reduction in the conditioned response through the process of extinction. Recent studies have suggested that brief and/or weak exposures to a conditioned cue lead to reconsolidation whereas more prolonged or repeated retrieval events, or weaker conditioning, results in extinction (Pedreira and Maldonado, 2003; Eisenberg et al., 2003; Suzuki et al., 2004; Power et al., 2006; Tronson et al., 2006). Therefore, deficits in performance following manipulations at the time of retrieval could be interpreted either as a blockade of reconsolidation or a facilitation of extinction. However, when these same manipulations produce no observable changes in the rate of extinction with a more prolonged retrieval event, it is more likely that altered reconsolidation has occurred (Tronson et al., 2006). Further, demonstrations of memory enhancements following manipulations at the time of retrieval are less easily explained by an altered extinction account. Regardless of the psychological mechanisms it is important that both short-term and long-term consequences of post-retrieval manipulations be examined. Alterations in reconsolidation or extinction that produce only transient mnemonic effects are less likely to be relevant to the very long-lasting role that drug-associated cues play in craving and relapse.

#### 5. Treatment strategies

Cue-exposure therapy has been tested and used as an adjunct to pharmacological and cognitive-behavioral therapies in human addicts (O'Brien et al., 1990) and is based on extinction of drug-paired cues in a setting other than that where drugs have been

taken (e.g., rehabilitation facility). Unfortunately, extinguishing these cue memories has not proven efficacious in reducing relapse in either humans (Conklin and Tiffany, 2002) or rats (Crombag and Shaham, 2002), illuminating the need for alternative strategies or extinction ‘supplements’ (behavioral and/or pharmacological). The lack of effectiveness of extinction therapies to treat addiction is likely due to the highly context-dependent nature of extinction. When extinction of the drug-associated cue occurs in the treatment facility the conditioned responses to the cue (e.g., increased heart rate; craving) may be reduced, but it is unlikely that these effects will transfer to the drug-taking environment. In animal models, extensive extinction training in a non-drug-taking context of both the instrumental response and either a discriminative stimulus (SD) or discrete cue (CS+) associated with drug, does not significantly reduce renewal of drug-seeking (Kearns and Weiss, 2007; Crombag and Shaham, 2002; Crombag et al., 2002). Cue exposure in the drug-taking environment is less practical, but may be more efficacious than extinction in a rehabilitation facility. There is one report of cue exposure in an immersive virtual reality environment, which was more effective in eliciting conditioned responses than traditional slides or videos, and may therefore be a more effective way of achieving effective cue extinction within a rehabilitation setting (Kuntze et al., 2001).

Another strategy for reducing the motivational impact of drug cues is to disrupt reconsolidation of drug cue memories. Recently, disruption of fear memory reconsolidation has received much attention, both in pre-clinical and clinical research, as a means of treating anxiety disorders such as post-traumatic stress disorder (PTSD) and phobias (McCleery and Harvey, 2004; Debiec and LeDoux, 2006; Tronson and Taylor, 2007). Patients with PTSD often have extreme symptoms of anxiety when exposed to stimuli that remind them of the traumatic experience. When these stimuli are presented to patients in the clinical setting to induce fear, the reconsolidation process can be inhibited by glucocorticoid exposure or by propranolol. Glucocorticoid treated PTSD and phobic patients have reported reduced severity of fear and anxiety in response to these stimuli when encountered in the outside environment (de Quervain, 2008; de Quervain and Margraf, 2008), and propranolol-treated subjects have decreased physiological fear responses when later asked to recall the traumatic event (Brunet et al., 2008). In the Brunet et al. (2008) study, propranolol was given after reactivation of the traumatic memory suggesting that reconsolidation processes were specifically targeted; however, the glucocorticoids were given prior to and during memory reactivation, making it difficult to interpret the exact mechanism by which the fear memory was disrupted. Nevertheless, disruption of reconsolidation of a cue-related memory appears to be a feasible clinical treatment strategy. However, the mechanisms by which cue–drug memories are reconsolidated still need to be elucidated and this treatment strategy remains to be explicitly tested in human drug addicts. Pharmacological manipulations can be used to alter the behavioral impact of drug-paired cues by either enhancing the extinction of these cues (Quirk and Mueller, 2008) or disrupting the reconsolidation of the cues following their retrieval/reactivation’ (Nader et al., 2000). Understanding the neural and behavioral mechanisms involved in extinction and reconsolidation of drug-associated cues is likely to have important implications for the treatment of addiction. Further, a combined approach that inhibits reconsolidation and enhances extinction of cue–drug memories could be utilized. The context-specificity of extinction might allow for extinction to be enhanced in one context while reconsolidation is disrupted in another context to produce a greater reduction in the motivational properties of the cues to produce relapse. However, if disrupting reconsolidation effectively “erases” the cue–drug memory (which has not been proven), it may not be necessary to use a combined approach.

## 6. Mechanisms of cue extinction

Several studies in the aversive and appetitive conditioning literatures have identified key processes involved in extinction. Pre-extinction session manipulations have most commonly been used but do not distinguish between effects on the acquisition versus the consolidation of extinction, which is believed to last for several hours while molecular/cellular processes stabilize the long-term extinction memory. While pre-extinction manipulations may be just as or even more beneficial than post-extinction manipulations due to the enhancement of both acquisition and consolidation of the extinction memory, the specific memory process involved cannot be determined. In addition, pre-extinction session infusions are more likely to result in state-dependent learning effects. In contrast, post-session manipulations do not interfere with acquisition of extinction, only produce state-dependent learning outside of the extinction learning context, and can be used to more precisely investigate consolidation processes that strengthen or stabilize extinction memories.

There is strong evidence from the elegant work of Quirk and colleagues that the infralimbic region of the medial PFC is specifically involved in the consolidation of fear extinction. For example, high frequency bursting of neurons in infralimbic cortex, requiring NMDA-mediated glutamatergic neurotransmission and PKA-signaling, occurs shortly after extinction and predicts subsequent retrieval of extinction (Burgos-Robles et al., 2007). Importantly, extinction consolidation can be strengthened by either electrical stimulation of infralimbic cortex (Milad and Quirk, 2002; Vidal-Gonzalez et al., 2006) or potentiation of AMPA glutamate receptors within this region (Zushida et al., 2007). There have been very few studies examining the role of infralimbic PFC on extinction of appetitive or drug cues, but a report by Koya et al. (in press) demonstrated that inactivation of the ventral (but not dorsal) medial PFC reduced cue-induced reinstatement of lever pressing after 30 days of abstinence from cocaine self-administration, which could be interpreted as enhanced acquisition of cue extinction learning. Therefore, the ventral medial PFC may regulate both aversive and drug-associated extinction memories, though possibly in different ways. The potential roles of other prefrontal cortical regions in the acquisition and maintenance of extinction memories have yet to be determined. The infralimbic cortex likely mediates extinction of conditioned memories through connections to the amygdala, which is the known output structure for the expression of conditioned fear (Muller et al., 1997; Wilensky et al., 2006) and is required for cue-induced reinstatement of cocaine-seeking behavior (Meil and See, 1997; McLaughlin and See, 2003). Indeed, Berretta and colleagues (2005) found that activation of the infralimbic cortex resulted in increased expression of Fos protein (an indicator of increased neuronal activity) in the intercalated neurons of the amygdala. These results provide a mechanism by which activity of the infralimbic cortex could increase glutamatergic input to the intercalated neurons of the amygdala that then send a GABAergic projection to the CeA, resulting in reduced fear expression. While this mechanism may not apply to drug cue-induced behavior, one study has shown that renewal of cocaine-seeking after extinction in an alternate context is associated with increased Fos expression in both the infralimbic cortex and the basolateral amygdala (Hamlin et al., 2008). Therefore, extinction of both aversive and appetitive memories may involve infralimbic cortex-mediated inhibition of amygdalar control of behavior.

## 7. Mechanisms of drug cue extinction

In contrast to the substantial literature on the neurobiological mechanisms of fear extinction, there are few reports on the extinction of reward-related memories. Schroeder and Packard

(2003, 2004) found that extinction of an amphetamine conditioned place preference (CPP) could be enhanced by immediate post-extinction administration of glucose or the muscarinic acetylcholine receptor agonist oxotremorine. The effect was observed when these compounds were administered systemically or directly into the basolateral amygdala (BLA). When the same compounds were administered 2 h after the extinction session, there was no effect, suggesting a selective enhancement of extinction memory consolidation. Likewise, post-session administration of D-cycloserine (DCS), a partial NMDA agonist, either systemically or in the BLA, facilitated extinction of a cocaine-CPP (Botreau et al., 2006).

Two recent reports by See and colleagues suggest that similar amygdala-dependent learning mechanisms may be important for the extinction of discrete drug-paired cue memories (Fuchs et al., 2006; Feltenstein and See, 2007). In these paradigms the animals first self-administered cocaine in the absence of a cue and then received Pavlovian cue-drug pairings in the absence of instrumental responding and the cue's ability to support responding on the drug-associated lever was assessed in an extinction test (no cocaine delivered). Post-test infusions of the sodium channel blocker tetrodotoxin (TTX) or the NMDA antagonist AP-5 into the BLA inhibited the expression of extinction on subsequent days of testing (Fuchs et al., 2006; Feltenstein and See, 2007). While these studies suggest that modulation of extinction consolidation is feasible after cue-drug learning, the passive and discrete (single session) cue-drug pairings, given after repeated self-administration does not recapitulate the repeated cue-drug pairings and drug-taking behavior in addicts. Further, since these manipulations of extinction consolidation were given in the self-administration context they are not easily applicable to clinical interventions. Additionally, a study by Koya et al. (in press) suggests that increased activity of the ventral PFC impairs combined cue and instrumental extinction on the first day of extinction 1 day following cocaine self-administration, while inhibiting this region has no effect, but 30 days after cocaine self-administration inhibition of the ventral PFC reduces responding for the cocaine-paired cue on the first day of extinction, suggesting dynamic regulation of this region after chronic cocaine exposure (see also discussion below).

Given the paucity of studies aimed at facilitating extinction of cue-drug memories, there is a critical need to determine whether the extinction of responding for a cue associated with self-administered drugs involves the same neural mechanisms as extinction for an experimenter-administered drug. It is also important to determine if facilitation of extinction consolidation using post-session memory enhancers can inhibit spontaneous recovery after periods of abstinence or renewal if extinction takes place in a context other than the self-administration context (e.g., in a rehabilitation facility). To date, studies on facilitation of extinction memories have primarily focused on manipulations specifically within contexts/environments where the original memories were formed. However, extinction of both fear and drug-associated memories is highly context-specific (Bouton and Bolles, 1979; Parker et al., 2006; Kearns and Weiss, 2007) – such that extinction does not generalize to contexts other than that where extinction occurred. Consequently, extinction memories generated in a treatment setting are unlikely to generalize to other environments (i.e., drug-taking contexts) and this likely contributes to the limited success of extinction-based therapies (Drummond, 2000; Bouton, 2002; Kalivas et al., 2006).

Attempts to enhance the generalization of extinction memory to other contexts are highly desirable since extinguishing cue-drug memories in the original drug-associated environment is not clinically feasible (Kearns and Weiss, 2007). The hippocampus is involved in contextual modulation of retrieval/expression of extinction (Corcoran and Maren, 2001, 2004; Hobin et al., 2006), but it is not yet known if manipulations of hippocampal activity

during the acquisition of extinction could later reduce the context-specificity of extinction expression. Alternatively, pharmacological enhancement of extinction consolidation using systemic or infralimbic cortex manipulations may alone increase the context generalization of cue extinction by increasing the strength of the extinction memory, thus, producing a greater inhibition of activity in brain regions that promote cue-motivated behavior. Unfortunately, systemic administration of DCS (the NMDAR partial agonist known to facilitate extinction) did not produce context generalization of extinction for a fear-induced conditioned suppression of lever pressing (Woods and Bouton, 2006). However, no one has examined the ability of pharmacological or brain specific manipulations to enhance the context generalization of extinction for a drug-paired cue. Finally, generalization of cue extinction may be facilitated by conducting extinction in multiple, distinct contexts as has been demonstrated for alcohol associated cues in rats (Chaudhri et al., 2008) and for fear responses in humans (Vansteenwegen et al., 2007). Manipulations shown to enhance the context generalization of cue extinction would be of tremendous value in augmenting extinction therapies, and we believe that more basic and clinical studies should address this issue.

Finally, it is possible that chronic exposure to drugs of abuse results in neuroplasticity in the PFC, BLA, and/or other brain regions that make drug-associated cues resistant to extinction. Notably, Weiss and colleagues (2001) reported that renewal of cocaine-seeking behavior induced by a cocaine-paired cue did not diminish even after 34 days of intermittent, repeated testing when extinction would be expected to occur. Therefore, the persistence of manipulations that enhance extinction of drug cue memories to promote abstinence should also be determined.

## 8. Mechanisms of instrumental extinction

There have been a few studies examining the mechanisms of extinction of the instrumental response that, prior to extinction, produced an infusion of drug. Extinction of the instrumental response required to obtain drug is different from extinction of the drug-paired cue memory, but may share similar neurobiological mechanisms and may be important to understand for the prevention of relapse. Similar to studies on the expression of extinction for conditioned fear, inhibition of infralimbic PFC reinstates responding on the active lever for cocaine after instrumental extinction and during a test of spontaneous recovery (Peters et al., 2008a,b), suggesting that this brain region is important for retrieval of learned extinction memories. However, inactivation of the infralimbic PFC reduces instrumental responding for a cocaine-paired cue on day 1 of extinction after extended abstinence (Koya et al., *in press*). This apparent opposite result from the Peters et al. (2008a,b) studies may be due to the presence of discrete cues during the extinction learning in the Koya et al. study, or because the infralimbic manipulation was conducted prior to the initial acquisition of extinction and not prior to a test of the expression of previously learned extinction as was done in the Peters et al. studies. Therefore, the infralimbic PFC may play a more complicated role in drug-seeking behavior depending on the time elapsed since the last cocaine exposure and during the acquisition versus expression of extinction. In addition, two recent studies suggest that inactivation of the nucleus accumbens shell increases instrumental responding after extinction (Fuchs et al., *in press*; Peters et al., 2008a), and the Fuchs et al. study suggests that inactivation of the nucleus accumbens core may have the same effect. Moreover, simultaneous unilateral inactivation of both the infralimbic PFC and the nucleus accumbens shell reinstates instrumental responding, suggesting that these two brain regions act as part of a neural circuit necessary for the expression of instrumental extinction (Peters et al., 2008b).

Notably, extinction training has been reported to reverse cocaine-induced decreases in the expression of the GluR1 and GluR2/3 subunits of AMPA glutamate receptors in the nucleus accumbens shell. In addition, viral over-expression of GluR1 and GluR2 in the nucleus accumbens enhances extinction of cocaine self-administration (Sutton et al., 2003; Self and Choi, 2004). However, over-expression of these AMPA receptor subunits did not alter extinction of responding on a sucrose-paired lever, suggesting that cocaine exposure may produce neuroadaptations that result in altered extinction learning circuitry (Sutton et al., 2003). Moreover, *N*-acetyl cysteine has been reported to modulate glutamatergic neurotransmission in the nucleus accumbens and to reduce extinction responding on a lever previously paired with heroin self-administration (Zhou and Kalivas, 2008). Therefore, an increased understanding of how drugs of abuse alter learning and memory processes for reward-associated stimuli will be advantageous for determining mechanisms to facilitate extinction for the treatment of addiction.

## 9. Mechanisms of drug cue reconsolidation

While understanding the mnemonic mechanisms of extinction has been an area of intensive neuropsychiatric research, within the past several years there has been an increased focus on investigations of amygdala-dependent reconsolidation processes (Tronson and Taylor, 2007). Studies have yielded important findings showing that reconsolidation, like consolidation, depends upon *de novo* protein synthesis (e.g., Nader et al., 2000; Dudai, 2004; Alberini, 2005) and several other parallel signaling mechanisms (Kida et al., 2002; Bozon et al., 2003). Likewise, we have recently shown that reconsolidation of fear memory requires amygdalar PKA activation and, interestingly, that a fear memory can be facilitated by direct activation of PKA immediately after the fear retrieval event (Tronson et al., 2006).

The fear reconsolidation literature suggests that disruption of reconsolidation of cue-drug memories might be a powerful method for intervention in addiction. In addition, reconsolidation processes are context-independent, likely increasing the applicability and utility of manipulations of reconsolidation processes to the clinical setting. Several recently published studies have demonstrated a role for reconsolidation in the maintenance of drug-paired cue memories. In a series of elegant studies, Lee and Everitt demonstrated that after extended cocaine self-administration, cue-induced reinstatement of cocaine-seeking, cue-maintained cocaine-seeking under a second-order schedule of reinforcement, and the acquisition of a new response with drug-associated conditioned reinforcers (e.g., Lee et al., 2005, 2006) could all be disrupted by knockdown of the immediate-early gene *Zif268* at the time of cue retrieval. These novel, and pioneering, studies suggest that amygdala-dependent cue-drug memories can be disrupted by a single reactivation-dependent infusion of *Zif268* antisense oligodeoxynucleotides and that the disruption is long-lasting (27 days). The expression of *Zif268* is also known to be up-regulated in the BLA following re-exposure to discrete cues associated with either footshock (Hall et al., 2001a) or self-administered cocaine (Thomas et al., 2003). While these studies identify a role for genes regulated by *Zif268* in cue-drug memory reconsolidation (Lee et al., 2004) little is known with regards to other potential molecular and behavioral mechanisms under which persistent modulation of drug memories can be achieved. However, a recent report suggests that systemic propranolol could disrupt the ability of both cocaine- and food-paired cues to act as conditioned reinforcers in rats (Milton et al., 2008). In addition, propranolol has been shown to block reconsolidation of both cocaine and morphine CPP (Bernardi et al., 2006; Robinson and Franklin, 2007). Together these studies suggest that adrenergic signaling is important for reconsolidation of

appetitive memories, much like that which has been shown for fear reconsolidation (Debiec and LeDoux, 2006). Importantly, we have recently shown that, similar to fear reconsolidation, drug-paired cue reconsolidation depends upon amygdalar PKA activity following retrieval (Sanchez et al., 2008). This observation is particularly intriguing given that the persistent up-regulation of PKA activity following chronic cocaine exposure (see below) may result in a progressive strengthening of cue-drug memories through such memory reconsolidation processes. One possible caveat of manipulations of reconsolidation processes for the treatment of addiction is the possibility that inhibiting reconsolidation could effectively result in memory erasure. While studies to date using conditioned fear and cue-drug associations have not shown a complete loss of behavior induced by fear or drug-associated cues after manipulating reconsolidation, it is possible that a “maximal” inhibition of reconsolidation could ultimately result in memory erasure. Indeed, inhibition of the protein kinase C (PKC) isoform PKMzeta has been shown to persistently reduce the expression of a long-term memory (Shema et al., 2007). While a complete erasure of memory may not be ideal in the clinical treatment setting, manipulations that profoundly weaken cue-drug associations could be efficacious in reducing craving and relapse induced by drug-associated cues.

In addition, several other signaling molecules have been implicated in the reconsolidation of memories of contextual drug associations using the CPP paradigm. Matrix metalloproteinases (Brown et al., 2007), muscarinic acetylcholine and NMDA receptors (Kelley et al., 2007; Sadler et al., 2007; Sakurai et al., 2007; Zhai et al., 2008), neuronal nitric oxide synthase (Itzhak and Anderson, 2007), and calcium/calmodulin-dependent protein kinase II (CaMKII; Sakurai et al., 2007) have all been shown to modulate the reconsolidation of CPP memories as inhibition of all of these proteins reduces the expression of CPP. In some instances, the drug of abuse must be administered when the animal is placed into the conditioned context to see an effect of a particular protein on reconsolidation processes (e.g., matrix metalloproteinases), suggesting that reconsolidation of contextual associations with a drug may involve distinct processes depending on whether the individual is under the influence of that drug.

The majority of research on drug memory reconsolidation processes has been conducted using CPP (as described above), and several important plasticity-regulated molecules have been identified that regulate drug-cue/context reconsolidation processes. For example, cocaine-CPP has been shown to activate extracellular regulated protein kinase (ERK) activity in the nucleus accumbens core, and inhibition of ERK in the core after reactivation inhibits subsequent expression of CPP for up to 14 days (Miller and Marshall, 2005). Likewise, systemic inhibition of ERK or protein synthesis after cocaine or morphine CPP reactivation is sufficient to reduce subsequent expression of CPP (Valjent et al., 2006). While CPP is a useful paradigm to study mechanisms of cocaine reinforcement and have highlighted a role for reconsolidation in the maintenance of appetitive memories, the relatively short (and passive) context/cue associations do not mimic the habitual nature of drug-seeking and -taking behaviors that, arguably, can be achieved only with drug self-administration procedures. Therefore, we believe that repeated drug self-administration procedures are best suited to study behavioral and pharmacological therapies aimed at reducing the impact of environmental cues on drug relapse.

## 10. Neuroadaptations in PKA/ERK/CREB associated with drug exposure and reward-associated learning

Drug-paired cue memories may be especially pervasive, and potentially resistant to extinction, due to pathological neurobiological changes resulting from long-term exposure to the drug

itself. We have speculated that persistent, drug-induced neuroadaptations may predispose these cue memories to undergo reconsolidation, as opposed to extinction, following retrieval. This may further exacerbate the development and persistence of maladaptive drug-associated memories and their ability to precipitate craving and drug-taking (Tronson and Taylor, 2007). Indeed, many of the neuroadaptive changes that occur within the cortico-limbic-striatal network are essential for the acquisition and expression of cue- or context-associated memories, including PKA, ERK, CREB and BDNF.

Among the strongest evidence for neurobiological alterations in systems associated with reward-related learning and memory comes from a series of reports showing that chronic psychostimulant exposure increases activity of the dopamine-regulated cAMP/protein kinase A (PKA) pathway in cortico-limbic-striatal circuits (Nestler, 2004). Although these neuroadaptations and their consequences have been best characterized in striatal regions such as the nucleus accumbens (Terwilliger et al., 1991; Self et al., 1998; Sutton et al., 2000; Beninger et al., 2003; Lu et al., 2003; Lynch and Taylor, 2005; Mattson et al., 2005; Lynch et al., 2007), similar alterations occur within the amygdala (Terwilliger et al., 1991; Pollandt et al., 2006). We have demonstrated that inhibition of amygdala PKA activity impairs the acquisition of appetitive stimulus-reward learning (Jentsch et al., 2002) and reconsolidation of a cocaine-associated cue (Sanchez et al., 2008). Moreover, stimulation of PKA within the amygdala facilitates stimulus-reward learning and, indeed, mimics the facilitation of stimulus-reward learning reported after prior chronic cocaine, amphetamine or nicotine exposure in rodents (Harmer and Phillips, 1998; Taylor and Jentsch, 2001; Olsson et al., 2003). Additionally, stimulation of PKA in the BLA augments the reconsolidation of a fear-associated stimulus (Tronson et al., 2006), and also using aversive conditioning, blockade of PKA activity in the amygdala results in enhancements in extinction learning (Koh and Bernstein, 2003). Together, these observations indicate that enhanced amygdalar PKA activity following chronic drug exposure can augment the formation and strength of stimulus-reward associations such as those formed between cues and the reinforcing effects of drugs. This could occur by both consolidation and reconsolidation mechanisms and, possibly, reductions in extinction. Such information now needs to be confirmed in drug self-administration paradigms and should be integrated into efforts to develop behavioral therapies to combat cue-induced craving and relapse in human addicts.

The cellular effects of cocaine-induced enhancement of PKA activity are likely to involve an increased activity of ERK and the downstream transcription factor CREB. Accordingly, chronic cocaine exposure has been repeatedly shown to increase CREB phosphorylation or activity (Konradi et al., 1994; Shaw-Lutchman et al., 2003; Mattson et al., 2005; Brenhouse et al., 2007). However, Mattson and colleagues (2005) determined that the cocaine-induced increase in CREB phosphorylation in the nucleus accumbens is mediated through augmented activity of ERK rather than PKA, as the increase was blocked by an ERK inhibitor, but not the PKA antagonist Rp-cAMPS. Whether the same signaling pathway is also responsible for the increased CREB phosphorylation observed in the amygdala remains to be determined. However, it is clear that the activation of CREB in the nucleus accumbens and amygdala may have opposing effects on drug-motivated behavior as accumbens CREB has repeatedly been found to reduce behavior and learning associated with psychostimulant exposure (Carlezon et al., 1998; Walters and Blendy, 2001). CREB is, however, required for the rewarding properties of nicotine (Walters et al., 2005), suggesting an important role of this transcription in other brain regions such as amygdala.

Both ERK and CREB-regulated gene transcription is essential for virtually all forms of memory consolidation (Kida et al., 2002; Lonze

and Ginty, 2002; Sweatt, 2004; Carlezon et al., 2005; Josselyn and Nguyen, 2005), including amygdala-dependent forms of memory (Lamprecht et al., 1997; Schafe et al., 2000; Thiels and Klann, 2001; Josselyn et al., 2001, 2004; Jasnow et al., 2005; Paul et al., 2007). Even short-term drug-induced increases in PKA/ERK signaling events could contribute to the ability of stimuli to acquire enhanced conditioned reinforcing properties and altered extinction learning. The role for ERK and CREB in reward-related learning and conditioned reinforcement remains to be precisely defined. This work is currently underway, and has initially been focused on the nucleus accumbens. These studies have demonstrated that ERK activity in the nucleus accumbens is required for the conditioned reinforcing effects of food-associated stimuli in drug-naïve animals (Shiflett et al., 2008) and is also sufficient to block reconsolidation of a cocaine-associated memory in the CPP model (Miller and Marshall, 2005). Furthermore, nucleus accumbens infusion of BDNF, a growth factor known to activate ERK/CREB through stimulation of TrkB receptors, potentiates responding for a conditioned reinforcer, and this effect is augmented by cocaine administration (Horger et al., 1999). Few studies have, however, identified a direct link between persistent drug-induced neuroadaptive changes and altered processing of reward-related stimuli. One exception is the association between a time-dependent increase in the reinforcing effects of cocaine cues (i.e., incubation) and increases in ERK activity in the CeA and an increase in BDNF within mesolimbic dopamine areas (Grimm et al., 2003; Lu et al., 2005a,b). In these ways, drug-induced increases in PKA/ERK/CREB/BDNF activity within the amygdala and associated circuitry could directly contribute to the fundamental aspects of addiction involving behaviors maintained by drug-associated cues and incentive aspects of motivation (Jentsch and Taylor, 1999).

## 11. Summary

In conclusion, NIDA researchers have identified an array of drug-induced neuroadaptations that may underlie changes in learning and memory processes that result in enhanced control of behavior by reward-associated stimuli. Given the ability of cues to elicit craving and relapse after long periods of abstinence it is critical to identify treatments that can reduce the motivational properties of drug-associated cues. To date, there has been interest in manipulations that block initial acquisition or extinction of drug-paired cue memories, yet few studies have attempted to facilitate extinction and/or disrupt reconsolidation. Here, with the support of current literature, we have proposed that a combined approach involving both enhanced consolidation of extinction and disrupted reconsolidation of drug-paired cue memories could be used as a novel and potentially powerful treatment strategy to reduce cue-induced relapse. Manipulations with mnemonic agents given together with non-reinforced cue-exposure therapies may be used to selectively alter these processes. We have proposed that facilitated extinction of cocaine-associated cues can be achieved with systemic pharmacological manipulations or by behavioral therapies aimed at increasing the contextual generalization of extinction memories. A number of currently used pharmacological agents that may be used to reduce the strength of drug cue memories have been identified, including the systemic (e.g., MK801, propranolol) or amygdalar (e.g., PKA inhibitors) manipulations known to disrupt memory reconsolidation of drug cues. We found that amygdala infusions of PKA inhibitors after reactivation of cocaine-paired cues can reduce cue reinstatement and conditioned reinforcement (Sanchez et al., 2008), consistent with previous reports that cocaine-seeking behavior can be reduced by disrupting reconsolidation of cue-drug memories. Importantly, our disruption of reconsolidation had immediate effects and can be given in an

environment other than the drug self-administration context – features that are highly advantageous from a treatment perspective. The impact and persistence of these manipulations on newly acquired or older cue memories are being investigated as are the potential for reducing the context-dependency of cue extinction. We have had some preliminary success (Torregrossa et al., 2008). In addition, a combined approach to enhance consolidation of extinction and disrupt reconsolidation to reduce the motivational impact of cocaine-associated stimuli on behavior might be the most advantageous and clinically applicable strategy to achieve a robust and persistent suppression of relapse behaviors. NIDA funded research clearly can, and will, identify precise neurobiological mechanisms involved in drug-paired cue memories that are relevant to relapse in order to develop new behavioral and pharmacological strategies amenable for clinical use.

## 12. Where do we go from here?

The neuroadaptations induced by drug exposures reviewed above might also be viewed as targets that can be exploited to promote abstinence, rather than the consequence of an addict succumbing to relapse. Much recent research has focused on the transition to addiction, both in behavioral and neurobiological terms. Pre-existing propensities towards impulsive behavior and/or poor inhibitory (self) control may be required for the shift from casual to compulsive, chronically relapsing drug-seeking and -taking behavior and must be considered a critical avenue for future research on addiction (see recent report by Belin et al., 2008). Nonetheless, it is known that drugs also can inflict devastating alterations in adaptive behavior dependent on prefrontal cortical circuits that normally serve to regulate limbic–striatal functions. The hypothesized conversion from impulsive to compulsive (Everitt and Robbins, 2005; Jentsch and Taylor, 1999) behavior can be exploited in reverse. Indeed, might extinction processes be more resistant and/or context-dependent in people with predisposing hypofunction of prefrontal cortical circuits mediating inhibitory control? These factors might be associated with sensation-seeking and polymorphisms in genes regulating dopaminergic function (such as COMT). To date, few studies have examined the role for prefrontal subregions in the regulation of cue-associated memories. Could enhancements in reconsolidation of drug-paired cues also be more pervasive after drug exposures due to a shift in the balance between prefrontal executive control and subcortical stimulus-driven behavior? Are the strong and persistent drug-associated memories that contribute to the phenomenon of drug “incubation”, which involve glutamatergic AMPA receptor trafficking (Conrad et al., 2008), be dependent on enhanced reconsolidation and/or reduced extinction? Finally, as in other fields, we should look at a role for resiliency rather than just vulnerability factors in the balance between extinction and reconsolidation processes. A fundamental paradigm shift would therefore be to focus, as we have argued, on behavioral and pharmacological methods that could enhance prefrontal control processes. In other words, is the transition to addiction actually constrained or prevented by flexible prefrontal executive control processes. With the essential behavioral and neurobiological advances of the past 35 years sponsored by NIDA’s research program, leadership, portfolio and new investigators we are prepared to continue the battle against addiction.

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