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Is an epigenetic switch the key to persistent extinction?

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Abstract

Many studies of learning have demonstrated that conditioned behavior can be eliminated when previously established relations between stimuli are severed. This extinction process has been extremely important for the development of learning theories and, more recently, for delineating the neurobiological mechanisms that underlie memory. A key finding from behavioral studies of extinction is that extinction eliminates behavior without eliminating the original memory; extinguished behavior often returns with time or with a return to the context in which the original learning occurred. This persistence of the original memory after extinction creates a challenge for clinical applications that use extinction as part of a treatment intervention. Consequently, a goal of recent neurobiological research on extinction is to identify potential pharmacological targets that may result in persistent extinction. Drugs that promote epigenetic changes are particularly promising because they can result in a long-term molecular signal that, combined with the appropriate behavioral treatment, can cause persistent changes in behavior induced by extinction. We will review evidence demonstrating extinction enhancements by drugs that target epigenetic mechanisms and will describe some of the challenges that epigenetic approaches face in promoting persistent suppression of memories.

Much of what is known about epigenetic mechanisms in memory comes from the study of initial memory formation (reviewed in Barrett & Wood, 2008). Evidence from different preparations is converging on the idea that these mechanisms, such as histone acetylation and DNA methylation, are critical for long-term memory storage. These are exciting findings because they suggest potential targets for pharmacological manipulations that are designed to promote memory in humans who show cognitive decline (e.g., Fischer et al., 2007). The ultimate goal of approaches like these is to develop therapeutics that can enhance the long-term persistence of newly formed memories. Recent evidence also suggests that targeting epigenetic mechanisms may be useful in developing therapeutics that can enhance the long-term suppression of previously formed memories by acting on processes that occur during extinction.

Extinction as a learning process has been of critical importance in developing behavioral theories of learning (e.g., Pavlov, 1927; Konorski, 1948, 1967; Rescorla, 2000) and is a fundamental process of normal human development and experience. The primary reason that extinction has been so important from a theoretical perspective is that it is a clear case in which there is a change in behavior that does not necessarily reflect a change in the state of

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the original memory. Thus, behavior can be eliminated, but the organism still retains the memory that was formed during initial acquisition.

Extinction is widely used in clinical interventions for many human disorders, with the goal of changing the behaviors that occur in certain environmental situations. The spontaneous recovery that sometimes follows extinction treatments is a major challenge for these interventions. Although there are behavioral approaches that can reduce recovery and related phenomena (e.g., Chan, et al. 2010; Dibbets, Havermans, & Arntz, 2008), recent approaches have attempted to identify pharmacological treatments that can result in persistent extinction, reducing spontaneous recovery and related phenomena (reviewed in Holmes & Quirk, 2010; Myers, Carlezon, & Davis, 2010).

The general idea behind a pharmacotherapeutic approach to extinction is to examine pharmacological treatments that target cellular and molecular processes that have a documented role in memory formation. At a molecular level, drugs that enhance memory likely do so by promoting transcription and translation, either by direct action or through indirect action. This is where an epigenetic approach holds strong promise because inducing long-term changes in gene expression may cause persistent changes in behavior. By targeting mechanisms involved in regulating transcriptional machinery, epigenetic approaches can act directly on the mechanisms that are thought to be involved in long-term memory storage.

In this paper, we review evidence suggesting that targeting epigenetic mechanisms can produce lasting suppression of memories. We suggest possible epigenetic mechanisms that allow such suppression to occur and review evidence suggesting areas in which caution must be taken in developing clinical applications of an epigenetic approach to extinction.

Epigenetic mechanisms underlying memory formation

Research has shown that the generation of persistent memories relies on long-lasting changes in neural structure and function. Persistent memory is the direct result of a diverse array of receptor systems and signaling cascades which converge on the genome to induce changes in gene expression, and, in turn, long-term changes associated with memory consolidation. These mechanisms include modifications of DNA as well as proteins involved in regulating the expression of genes required for memory formation. Such modifications have been linked to memory formation by their ability to mediate a host of changes from the molecular level (gene expression) to the cellular level (i.e., long-term potentiation; Levenson et al., 2004; Vecsey et al., 2007).

Epigenetic marks on chromatin and DNA can be directly manipulated by pharmacological agents that target the specific enzymes regulating these marks. The best studied of these in memory formation are histone deacetylase (HDAC) enzymes which add or remove acetyl groups from lysine residues on histone tails (Morris et al., 2010). For example, pharmacological HDAC inhibition leads to increases in histone acetylation. This increased acetylation helps set the stage for increases in the expression of genes critical for memory formation (e.g., BDNF, NR4A1) through increased access to the genome, as well as the recruitment of transcription factors and other epigenomic modifiers (Barrett & Wood, 2008). Importantly, HDAC inhibitors have repeatedly been shown to enhance new memory formation in a variety of preparations from fear to drug learning using both systemic and brain region specific treatment (Vecsey et al., 2007; Stefanko et al., 2009; Kumar et al., 2005). More recently, other enzymes that are responsible for histone phosphorylation as well as histone and/or DNA methylation have been shown to play an important part in new memory formation (Gupta et al., 2010; Koshibu et al., 2009; Miller & Sweatt, 2007)

Evidence for epigenetic mechanisms in extinction

After an initial memory has been formed, the subsequent retrieval of that memory engages many of the same mechanisms that are involved in new memory formation (e.g., Lattal et al., 2006). However, the consequences of a retrieval trial can be different, depending on the conditions in which the memory is retrieved. The loss of behavior that occurs after extinction is the most widely documented effect of memory retrieval, but surprisingly little is known about the influence of epigenetics on extinction memory formation.

Although there has been elegant work on the involvement of transcriptional regulation of CREB and other transcription factors in extinction (e.g., Mamiya et al., 2009), relatively little is known about epigenetic mechanisms of gene regulation in extinction, as they relate to chromatin biology and direct modification of DNA (e.g., methylation; for an overview of the other transcriptional processes involved in extinction see Radulovic & Tronson, 2010). What we do know about epigenetic mechanisms in extinction comes almost exclusively from studies of histone acetylation, including pharmacological methods of altering histone acetylation. Like studies of new memory formation, many of these studies have focused on understanding the effect of HDAC inhibitors on memory retrieval and extinction. The general conclusion is that HDAC inhibitor treatment generates persistent decreases in behavior (extinction enhancements) when paired with memory retrieval (Bredy & Barad., 2007; Lattal et al., 2007; Malvaez et al., 2010; Wang et al., 2010; but see also Lubin et al., 2007; Bredy et al., 2008). This has been shown in a variety of preparations including extinction of cued and contextual fear as well as the extinction of a conditioned place preference (CPP) for both cocaine and morphine (Table 1).

Although these extinction enhancements are becoming well-documented, it is not always clear which memory processes are affected by HDAC inhibitor treatment during extinction. Specifically, little is known about whether these enhancements are due to enhancements in extinction acquisition (learning) or extinction memory consolidation. Indeed, the majority of studies showing extinction enhancements administered the HDAC inhibitor prior to extinction/memory retrieval. Given the pharmacokinetics and pharmacodynamics of these HDAC inhibitors, administration even a few hours prior to extinction would mean that their effects are present during both the acquisition and memory consolidation phases of extinction. Although some recent studies have shown that post-session HDAC inhibitor treatment enhances fear extinction (Malvaez et al., 2010; Stafford, Ryabinin & Lattal, *in revision*), the precise effects of HDAC inhibitors on acquisition and consolidation of extinction requires further work.

In addition to determining how chromatin modifications, such as histone acetylation, promote acquisition or consolidation, a major unresolved issue in extinction enhancements is which HDAC enzymes mediate these long-term effects. While HDAC inhibitor mediated extinction enhancements have been demonstrated with different HDAC inhibitors, such as sodium butyrate (NaB), valproic acid (VPA), and trichostatin A (TSA), it is still unclear what HDACs are involved in extinction memory formation (Bredy et al., 2007; Lattal et al., 2007). Recent evidence suggests that certain HDAC isozymes such as HDAC 2 and 3 have a critical role in regulating new memory formation (Guan et al., 2009; McQuown et al., 2011), but little is known about extinction. Part of the difficulty in making specific conclusions from many of the extinction studies is that there are multiple targets of pan-HDAC inhibitors such as HDAC isozymes 1, 2, 3 and 6 (Bradner et al., 2010; Kilgore et al., 2010). In addition, characterizing the non-HDAC enzyme targets of these HDAC inhibitors is of critical importance as they interact with other non-histone and non-nuclear proteins involved in a variety of cellular functions (e.g., Choudhary et al., 2009). Further understanding these non-specific effects as well as which HDAC enzymes are involved in extinction processes

will be necessary in deducing the exact mechanisms by which acetylation generates persistent memory extinction.

Epigenetic Changes within the Extinction Circuit

Over the past ten years, a great deal of insight into the neurobiological circuitry underlying extinction has facilitated more sophisticated studies of the excitatory and inhibitory processes mediating extinction memory formation and expression. For example, a large body of evidence suggests contextual extinction is mediated by hippocampal signaling to the infralimbic cortex which in turn activates GABAergic cells in the amygdala (i.e., intercalated cells), leading to decreased central amygdala firing and behavioral response inhibition (Amano et al., 2010; Quirk and Mueller, 2008). The involvement of different genes supporting extinction within this circuit has also recently come to light (reviewed in Lattal, Radulovic, & Lukowiak, 2006; Quirk & Mueller, 2008). However, surprisingly little is known about how epigenetic factors and transcriptional control of genes within these regions contribute to extinction.

What is known about the involvement of brain region-specific epigenetic control of extinction is limited to studies of HDAC inhibitors. One of the first studies to implicate brain region specific epigenetic control over gene expression involved in fear extinction investigated the involvement of histone acetylation and BDNF expression in extinction. This study by Bredy et al. (2007) showed that systemic HDAC inhibitor treatment (VPA) enhanced extinction through its ability to enhance acetylation around the BDNF promoter in the medial prefrontal cortex, thereby increasing expression of BDNF. Other studies have implicated a role for hippocampal acetylation in extinction by showing that pairing intra-hippocampal infusions of HDAC inhibitors with extinction enhanced long-term contextual fear extinction (Lattal et al., 2007), due potentially to increases in histone acetylation in the infra-limbic cortex (Stafford, Ryabinin & Lattal, *in revision*). Beyond fear, a recent study by Malvaez et al. (2010) identified acetylation in the nucleus accumbens as a candidate for mediating HDAC inhibitor-induced enhancements in extinction of a cocaine conditioned place preference. When taken together, these studies are consistent with those showing that gene expression within these fear and reward pathways is important in mediating extinction of fear and drug-seeking behavior (Quirk & Mueller; 2008; Millan et al., 2011). Future studies will be critical in further understating how epigenetic and transcriptional control within these brain regions lead to persistent decreases in fear and drug-seeking behaviors.

Although studies of HDAC inhibition and extinction memory formation have been extremely valuable in providing evidence for epigenetic mechanisms in extinction, less is known about the role of the diverse epigenetic mechanisms underlying new memory formation (i.e., histone acetylation, DNA methylation, histone methylation, etc.). Studies of these other modifications to chromatin and DNA within the extinction circuit will inform us about the ways that a persistent extinction memory is generated. A recent study exemplifies the power of using this sort of approach in understanding the molecular underpinnings of a long-term fear memory. Miller et al. (2010) showed that 30 days after memory fear memory formation, medial prefrontal DNA methylation marks of the memory suppressor gene calcineurin were positively correlated with fear memory expression. When this DNA methylation was pharmacologically removed, the fear behavior decreased. This suggests that the prefrontal methylation signature may be a long-term biochemical mark for maintaining or suppressing a fear memory. Studies of extinction memory formation could benefit from a similar approach because persistent extinction memory formation may have unique long-lasting epigenomic effects in different brain regions.

The Extinction Engram: Theoretical Implications of Epigenetics

There are two broad hypotheses about the ways in which epigenetic mechanisms may promote extinction: modifications and/or remodeling of chromatin and DNA are 1) an actual component of the long-term extinction engram itself, or are 2) the catalysts for generating the downstream molecular extinction engram (i.e., protein and structural changes). These two hypotheses are not necessarily mutually exclusive as extinction likely reflects interplay between long term epigenetic marks and the downstream functional consequences of these marks.

Given what is currently known about chromatin biology and memory formation, there is mixed evidence for the idea that epigenetic modifications themselves represent the content of the memory. For example, chromatin modifications are often transient, decreasing 24 hours following a learning experience or genomic activating event (Agalioti et al., 2002; Vecsey et al., 2007). This indicates that certain modifications are not persistent enough to be a molecular signature of a memory over the long term. However, there is accumulating evidence that certain histone marks (e.g., histone methylation) may indeed persist following certain transcriptional events (e.g., McGarvey et al, 2006). As very few studies have looked beyond bulk modifications at specific histone tail residues (e.g., lysine acetylation), this highlights the possibility that a long-term chromatin mark or change in the actual structure/organization of chromatin (chromatin remodeling) is representative of the extinction memory.

It is important to note that a change in chromatin structure/organization, termed chromatin remodeling (e.g., nucleosome sliding), is very different from chromatin modification (e.g., histone tail modification). It is true that chromatin modifications may play a role in chromatin remodeling through recruitment of remodeling complexes (e.g., SWI/SNF); however, chromatin modifications are not always required for these remodeling events to occur (Koutroubas et al., 2008). Beyond histone modifications, recent studies suggest that DNA methylation may be a long-term mark for memory depending on the brain structure evaluated (Miller et al., 2010); thus, one possibility is that long-term methylation changes could be associated with persistent extinction.

The second hypothesis--that epigenetic mechanisms promote protein and structural changes that reflect the memory--fits well with current models of extinction, which indicate that extinction is the result of a new inhibitory memory being formed (Bouton, 2004). This is because epigenetic changes likely catalyze the changes in mRNA expression, protein expression, and potentially structural changes underlying the formation of new extinction memories. It would therefore be likely that those downstream results of chromatin or DNA modification are the actual components of the long-term extinction engram. Drugs that promote histone acetylation, for example, may cause these downstream effects by either prolonging the duration of the transcriptional events or by increasing the number of neurons in which these events occur.

These hypotheses may not be mutually exclusive as the long-lasting epigenetic extinction engram likely includes a variety of components, including persistent epigenetic marks and structural changes in the circuit representing the memory. The actual keys to persistent extinction may also include players beyond the genome and epigenome as recent evidence indicates that memory formation includes receptor insertion and structural changes which may not rely on changes in gene expression *per se* (Fischer et al., 2004; Rex et al., 2001; Derkach et al., 2007).

An answer to the question of what mechanisms are involved in extinction memory formation will likely require looking beyond the involvement of acetylation in extinction and towards

some of the other epigenetic events. These sorts of investigations will lead to better understanding of how changes in chromatin (modifications and remodeling) as well as modifications of DNA fit into the cellular and neurobiological events underlying persistent extinction memories.

Extinction, reconsolidation, and memory erasure

Just as there are a variety of molecular events that may underlie persistent changes in behavior, there are a number of higher level cognitive processes that may be involved in long-term effects on memory. Thus, the systemic delivery of a drug, such as an HDAC inhibitor, around the time of memory retrieval may affect any number of cognitive processes. We have focused on the effects on extinction, with the inference being that the loss of behavior that follows the pairing of a drug with memory retrieval reflects enhancements in some aspect of the new memory that is formed during extinction. It also is possible that under certain conditions, the drug may (1) impair extinction, (2) promote some aspect of the original memory, or (3) weaken or even erase the original memory. In fact, recent research has focused on conditions (e.g., varying memory retrieval duration/strength) under which pharmacological manipulation may differentially affect these different retrieval mediated processes (e.g., Lee, Milton, & Everitt, 2006). Separating these processes is challenging as the behavioral and molecular signatures of many of these processes are identical (e.g., enhanced extinction and memory erasure will both involve the persistent loss of behavior).

A clear example of a case in which multiple explanations are available for similar effects on behavior comes from studies examining the role of NF- κ B in retrieval and extinction. Lubin et al. (2007) found that inhibiting the NF- κ B pathway following fear memory retrieval caused deficits in fear memory expression the next day as well as decreases in histone marks typically associated with memory formation. The authors concluded that they had blocked the reconsolidation of the memory, as its behavioral and molecular expression were both reduced by blocking NF- κ B. Similarly, Merlo and Romano (2008) also found that NF- κ B inhibition was associated with loss of fear memory expression. However, they interpreted their results to mean that NF- κ B inhibition was required for extinction rather than blockade of memory reconsolidation. There are many other examples in the literature of this issue, in which different studies show similar behavioral effects resulting from similar molecular manipulations, but interpret these results in terms of reconsolidation impairments or extinction enhancements (e.g., Isiegas et al., 2006; Tronson & Taylor, 2006; reviewed in Bernardi, et al., 2009). Until a clear picture is developed of the behavioral, systems, and molecular consequences of epigenetic manipulations, there will always be multiple possible interpretations for any behavioral result. In certain cases, these two alternatives are viable and distinguishing them will require some well-developed theories that make explicitly different predictions about behavior and molecular effects.

Either a weakening of the original memory or a strengthening of the extinction memory is a potentially plausible account for the loss of behavior induced by an HDAC inhibitor during extinction. Many recent papers have appealed to memory erasure to explain the loss of behavior that follows an extinction trial paired with a certain neurobiological manipulation, with the idea being that the manipulation prevented the reconsolidation of the original memory (e.g., Cao et al., 2008; Mao, Hsiao, & Gean, 2006). This is an exciting idea at a theoretical level and has profound implications for clinical applications, but erasure accounts in general seem unlikely absent a major neurobiological manipulation because many studies of humans have demonstrated a distinction between the loss of performance and the loss of the memory (e.g., Kindt et al., 2009; Norrholm et al., 2006; Norrholm et al., 2008). In the case of HDAC inhibitors, one would need a mechanism through which increases in

acetylation caused the erasure of the previously formed memory. This would be counterintuitive, based on current knowledge about transcriptional events in memory consolidation, but one possibility would be that increased expression of memory suppressor genes (e.g., PP1) may alter some aspect of the previously formed memory (Abel & Kandel, 1998; Malleret et al., 2002; Koshibu et al., 2009).

Independent of their effects on previously formed memories, increased expression of memory suppressor genes during extinction may interfere with the development of new memories that form during extinction. Indeed, Bredy and Barad (2008) found that, under certain conditions, the HDAC inhibitor VPA actually impaired extinction, as revealed through more contextual renewal after extinction in VPA-treated mice compared to vehicle-treated mice. Increased expression of these suppressor genes as a mechanism of an impairment in extinction is a strong possibility because studies have shown that memory suppressor genes are often methylated during memory formation and HDAC inhibitors frequently initiate molecular cascades that reverse DNA methylation (Dong et al., 2007; Miller et al., 2010). The implication in extinction is that by enhancing expression of a memory suppressor gene the HDAC inhibitor may suppress the ability of a new extinction memory to be formed.

A behavioral explanation for HDAC inhibitors impairing extinction memory formation is also possible, independent of effects on memory suppressor genes. For example, the HDAC inhibitor may act through non-associative mechanisms to strengthen the representation of the US (e.g., by promoting transcriptional events in the reward pathways in the case of substance abuse). Thus, when the CS activates a strengthened US representation, the behavioral response evoked by that CS is stronger than it would have been in the absence of the HDAC inhibitor. Changes in the status of the components of the original memory (whether a context, CS, US, or CS-US representation) have been shown to promote or impair performance (see Delamater, 2004; Tronel et al., 2005). In fact, there is some suggestion that HDAC inhibitors may not only impair extinction, but may also enhance expression of the original memory following retrieval (Lubin & Sweatt, 2007; Bredy & Barad, 2008). For example, Bredy and Barad (2008) demonstrated that an HDAC inhibitor could promote or weaken responding depending on the conditions of memory retrieval. However, in the absence of control groups that did not receive retrieval, it is difficult to interpret group differences as enhancements in reconsolidation or impairments in extinction, among other possibilities (see Lattal & Stafford, 2008; Tronel, et al. 2005).

Thus, there are many possible behavioral results that may occur with epigenetic manipulations during extinction and there are many theoretical interpretations for any given result. Until the field has a better understanding of the behavioral and molecular conditions that promote or weaken behavior, these results will continue to be open to many interpretations.

Moving from the laboratory to the clinic

Epigenetic approaches to extinction have the potential to offer new pharmacotherapeutic interventions to a wide range of human psychiatric disorders that involve failures in inhibition, including substance abuse, anxiety disorders, and developmental disorders. Although the literature is relatively small, there are now several studies that demonstrate that drugs that promote epigenetic changes can promote the development and persistence of extinction. These studies demonstrate exciting possibilities for treatments that depend on long-term maintenance of extinction. Future studies that identify specific epigenetic mechanisms and targets (e.g., histone modifying enzymes) involved in extinction will allow

for more targeted therapies for psychiatric disease ranging from anxiety disorders to drug abuse.

These studies also offer important caveats in the use of epigenetic therapies to treat clinical disorders. First, as Bredy and Barad (2008) demonstrated, an HDAC inhibitor may retard or reverse the positive effects of extinction, depending on the behavioral approach. This emphasizes the need for a clear understanding of how these drugs interact with a range of behavioral events. Second, many studies have documented distinct and common mechanisms between acquisition and extinction in different learning preparations (e.g., fear conditioning and extinction, Quirk et al., 2008; Millan et al., 2011). This suggests that there may be unintended consequences when HDAC inhibitors and related drugs are used for treatment. If, for example, a patient receives an HDAC inhibitor as part of a treatment program for post-traumatic stress disorder, that patient may be more vulnerable to the addicting effects of abused substances, because the amount of drug needed to be reinforcing will be lowered (e.g., Kumar et al., 2005). These unintended effects, once established, may themselves be more resistant to future extinction treatments (Lockett et al., 2010; Kwon & Houpt, 2010). As we understand more about the epigenetic processes involved in extinction and develop drugs that target specific HDAC enzymes, new treatment strategies will emerge that may selectively affect extinction. Until then, the potential power of these drugs to mediate memory and extinction in a variety of settings suggests the implementation of these treatments needs to occur under conditions that are closely monitored by the clinician administering the drug.

Is an epigenetic switch the key to persistent extinction?

As the literature currently stands, it is clear that epigenetic changes have great potential to provide the long-term switch that promotes persistent extinction. There are many possible epigenetic mechanisms that underlie the formation and retention of long-term memories. Answering the specific question about epigenetic mechanisms as the key to persistent extinction, however, is going to have to be nuanced for some time to come. An understanding of the long-term epigenetic changes that underlie extinction will be most informative only after the field understands the interplay between inhibitory and excitatory behavioral and molecular processes in extinction. Epigenetic mechanisms may underlie persistent enhancements in extinction, but they also likely underlie persistent impairments in extinction in cases in which extinction fails at the behavioral level (e.g., Bredy & Barad, 2008).

Epigenetic mechanisms confer both transcriptional repression and transcriptional activation, sometimes in harmony, making it a very likely candidate to understand memory extinction from the bottom up. Further analysis of the complete epigenome and its interaction with other cellular extinction mechanisms will therefore yield a unique opportunity to understand the mechanisms that cause persistent extinction at molecular, systems, and psychological levels.

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Table 1

Recent studies manipulating epigenetic mechanisms during extinction.

Study	Manipulation	Molecular Effect	Behavioral Effect	Theoretical account
Bredy & Barad, 2007	Systemic HDAC inhibitor (VPA and NaB) before cued fear retrieval	Systemic VPA treatment increased mPFC histone H4 acetylation driven BDNF expression following retrieval	Decreased freezing 7D after retrieval	HDAC inhibitor enhanced extinction due to effects on mPFC acetylation and BDNF expression
Lattal, Barrett, & Wood, 2007	Systemic (NaB) or hippocampal (TSA) treatment before contextual fear memory retrieval	None measured	Decreased freezing 1D after retrieval	Hippocampus involved in ability of HDAC inhibitor to enhance extinction
Lubin & Sweatt, 2007	Systemic HDAC inhibitor (NaB) before and NF-kB inhibition (DDTC) after retrieval	Nf-kB and IκB involved in conferring hippocampal histone modifications (acetylation, phosphorylation) following retrieval	NF-kB inhibition-induced decreased freezing was prevented 1D following retrieval	HDAC inhibitor prevented NF-kB induced reconsolidation deficit
Bredy & Barad, 2008	Systemic HDAC inhibitor (VPA) treatment before cued fear retrieval	None measured	<ol style="list-style-type: none"> 1 pre- retrieval VPA enhances freezing in training context 2 VPA prior to massed CS presentations enhances freezing at 10D but not 3 D in training context 3 VPA prior to spaced CS presentations decreases freezing 3D and 10D later in both retrieval and training contexts 	VPA enhanced extinction or reconsolidation, depending on conditions of retrieval
Malvaez, Sanchis-Segura, Vo, Lattal, & Wood, 2010	Systemic HDAC inhibitor (NaB) after cocaine CPP retrieval	NaB enhanced histone H3 acetylation in the nucleus accumbens	Decreased CPP and attenuated cocaine-induced CPP reinstatement	NaB enhanced extinction
Wang et al., 2010	Systemic HDAC inhibitor (NaB) before morphine CPP retrieval	None Measured	Decreased CPP and attenuated morphine-induced place preference reinstatement	NaB enhanced extinction
Yang et al., 2010	Systemic HDAC inhibitor (NaB) and NF-kB inhibition (SN50) before morphine CPP retrieval	None Measured	NaB prevented NF-kB mediated deficits in morphine CPP	NaB prevented NF-kB mediated morphine CPP reconsolidation impairments