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Journal
Neurobiology of Learning and Memory, 142(Pt A)

ISSN
1074-7427

Authors
Hemstedt, Thekla J
Lattal, K Matthew
Wood, Marcelo A

Publication Date
2017-07-01

DOI
10.1016/j.nlm.2017.01.007

Peer reviewed

HHS Public Access

Author manuscript

Neurobiol Learn Mem. Author manuscript; available in PMC 2018 July 01.

Published in final edited form as:

Neurobiol Learn Mem. 2017 July ; 142(Pt A): 55–65. doi:10.1016/j.nlm.2017.01.007.

Reconsolidation and extinction: using epigenetic signatures to challenge conventional wisdom

Thekla J Hemstedt[1,2], **K Matthew Lattal**[3], and **Marcelo A Wood**[1,2,*]

[1]Department of Neurobiology and Behavior, University of California, Irvine, California, USA

[2]Center for the Neurobiology of Learning and Memory, Irvine, California, USA

[3]Department of Behavioral Neuroscience, Oregon Health & Science University, Portland, Oregon

Abstract

Epigenetic mechanisms have the potential to give rise to lasting changes in cell function that ultimately can affect behavior persistently. This concept is especially interesting with respect to fear reconsolidation and fear memory extinction. These two behavioral approaches are used in the laboratory to investigate how fear memory can be attenuated, which becomes important when searching for therapeutic intervention to treat anxiety disorders and post-traumatic stress disorder. Here we review the role of several key epigenetic mechanisms in reconsolidation and extinction of learned fear and their potential to persistently alter behavioral responses to conditioned cues. We also briefly discuss how epigenetic mechanisms may establish persistent behaviors that challenge our definitions of extinction and reconsolidation.

Introduction

The ability to form fear memories is essential for animals and humans to detect and react to danger. When these memories are recalled, several processes can be engaged that may determine how the organism reacts to subsequent encounters with cues associated with those memories. At the broadest level, retrieval of memories causes plasticity that is both similar to and different from the plasticity that follows initial memory formation. How this retrieval-induced plasticity impacts long-term fearful behaviors depends on several factors, including the prediction error between what the organism expects and what it receives, the ability of the memory to be restabilized following retrieval, and the ability of the fear response to be extinguished. A key to understanding how these different processes lead to long-term changes in memory and behavior is to understand the molecular events that lead to persistent changes in memory.

*Address correspondence to: Marcelo A. Wood, PhD, University of California, Irvine, Department of Neurobiology & Behavior, Center for the Neurobiology of Learning & Memory, 301 Qureshey Research Lab Irvine, CA 926973800, mwood@uci.edu.

Epigenetics may provide important insight into numerous aspects of fear memories because epigenetic mechanisms are known to give rise to persistent changes at the cellular level that may ultimately lead to long-term changes at the behavioral level (Barrett and Wood, 2008; Roth and Sweatt, 2009). Processes such as histone modification, DNA and RNA modification, and nucleosome remodeling are among the most important epigenetic regulators of gene expression. Early-life events that have long-term effects on the epigenome of a cell can persistently affect gene expression in that cell, or even circuits (Feng et al., 2007; Dulac, 2010). Recent work has shown that retrieval of fear memories recruits various epigenetic mechanisms and that may give rise to long-term changes in fear-related memory processes. The dysregulation of these memories leads to excessive and persistent anxiety, which are key symptoms in patients suffering from anxiety disorders and post-traumatic stress disorder (PTSD) (Lang et al., 2000; Morrison and Ressler, 2014). PTSD is elicited by a traumatic event and the likelihood of developing PTSD after a traumatic event is influenced by a variety of factors including early-life experiences and subsequent exposures to mild stressors (Heim and Nemeroff, 2001; Daskalakis et al., 2013). Current behavioral treatments mainly focus on exposure therapies to the fear-evoked stimulus and its beneficial effect has been shown to be enhanced when combined with pharmacological approaches that facilitate extinction learning. Hence, the identification of molecular targets that can persistently reduce the response to the fear-evoked stimulus has been the focus of many research laboratories.

Lasting changes in cell function can presumably enhance fear learning resulting in persistent fear in response to mild stressors and hence provide a possible mechanisms of the increased risk to develop PTSD in patients with early life stress (McGowan, 2013; Zovkic et al., 2013; Zannas et al., 2015). In addition to predisposing some individuals to developing PTSD, the epigenome may also serve as a powerful target for therapeutic intervention once PTSD has developed. One of the main behavioral approaches to treat PTSD patients is exposure therapy, which exposes a patient to the fearful stimulus, leading to a weakening of the fear response. Long-lasting changes in the epigenome may have the ability to persistently suppress the original fear memory and hence may positively support exposure therapy. Though there is currently no treatment for PTSD available that targets a specific epigenetic mechanism, a variety of animal studies point to the potential of epigenetic mechanisms to persistently influence the original fear memory (reviewed in Lattal and Wood, 2013; Kwapis and Wood, 2014; Pizzimenti and Lattal, 2015). This review will focus on epigenetic mechanisms involved in fear memory processes with a focus on reconsolidation and extinction.

Fear conditioning

Experimental analysis of Pavlovian fear conditioning is a common method in the laboratory used to study different aspects of fear learning and memory (Maren, 2001). This section will briefly describe the main stages of fear memory processing including fear acquisition, consolidation, and retrieval as well as fear reconsolidation and extinction.

During acquisition of fear conditioning, a specific context or cue (light/sound; conditioned stimulus) is paired with a foot shock (unconditioned stimulus). This results in a fear

response of the animal when the context or cue is presented in the absence of the foot shock, which is assessed in the retrieval session. If the retrieval session is tested within 1-2 hours after the acquisition session, then it is generally considered to involve short-term memory mechanisms. In contrast, if the retrieval session takes place at a longer time point away from conditioning (*e.g.* 24 hours), then long-term memory mechanisms are thought to be engaged (reviewed in Johansen et al., 2011; Kandel et al., 2014; Schafe et al., 2001).

One of the most exciting areas of fear memory research that can impact how we understand and treat PTSD and other anxiety related disorders involves aspects of memory recall. Following successful acquisition and consolidation of a memory, recall of that memory engages new processes including reconsolidation and extinction. Reconsolidation and extinction are important memory processes because their ability to change the expression of the original fear memory makes them essential for therapeutic interventions (Tronson and Taylor, 2007; Quirk et al., 2010; Parsons and Ressler, 2013).

During memory retrieval, the animal is exposed to the conditioned stimulus and conditioned fear is measured. With brief retrieval trials, the organism expresses the fear response, but is removed from the apparatus before extinction of fear emerges in behavior. With long (or more) retrieval trials, the organism is removed after the fear response has extinguished. Some studies have found that the duration of the retrieval trial may lead to the engagement of different theoretical processes, with short trials showing effects on reconsolidation processes and long trials showing effects on extinction processes (*e.g.*, Lee, 2009). The two processes are thought to result from retrieval-induced plasticity, in which reconsolidation restabilizes and maintains the labile fearful memory while extinction adds suppressive processes to that memory (Almeida-Correra and Amaral, 2014; Baldi and Bucherelli, 2015). During reconsolidation, a memory is thought to be reactivated, which brings it into a transient labile state before becoming stabilized again. This process, as with consolidation of the original memory, requires new protein synthesis (Nader et al., 2000). Hence, the temporary labile state opens a time window in which some aspect of the fear memory is vulnerable to manipulations that interfere with protein synthesis. Inhibiting protein synthesis during the reconsolidation window therefore leads to a weakening of the fear response. However, many studies have shown that inhibition of protein synthesis after retrieval reduces the fear response only when tested 24 hours after the retrieval session, but the fear response returns as longer periods of time pass following memory retrieval (e.g., Lattal and Abel, 2004; Stafford and Lattal, 2009; Judge and Quartermain, 1982). The mechanisms that lead to the recovery of the fear response remain to be understood.

Reconsolidation and extinction processes interact with other retrieval-induced processes, such as the organism's ability to detect the difference between the outcome that was expected (shock) and the outcome that occurred (no shock). This prediction error occurs early in retrieval and has the biggest impact on behavior in those first brief exposures to the CS (McNally et al., 2011; Li and McNally, 2014). Behavioral and theoretical work on prediction error going back to the Rescorla-Wagner (1972) and earlier models has consistently found that the very first nonreinforced exposure has the biggest impact on extinction (*e.g.*, Rescorla and Wagner, 1972; Rescorla, 2001). Given this finding, one might expect that this distinction between reconsolidation and extinction should not be as clean cut

as is currently defined in the field. Indeed, extinction is usually defined by behavioral evidence showing that the original memory can still be accessed by uncovering phenomena such as reinstatement, renewal and spontaneous recovery (Bouton, 2004; Myers and Davis, 2007; Quirk and Mueller, 2008). The reinstatement paradigm shows that the original memory reoccurs when the US is given unexpectedly (Rescorla and Heth, 1975), whereas renewal shows that the original memory is recalled when the CS is given outside the extinction context (Bouton and King, 1983). Spontaneous recovery reflects that the original memory can come back with the passage of time (Pavlov, 1927). Given that extinction learning requires the formation of a new memory it is not surprising that this learning shares a variety of mechanisms with the formation of the original memory. Among these mechanisms is the synthesis of new proteins (Lin et al., 2003; Szapiro et al., 2003; Orsini and Maren, 2012). Blocking protein synthesis during extinction memory consolidation prevents the formation of the new memory and hence keeps the old memory intact. In contrast, an increase in synthesis of proteins involved in extinction memory consolidation strengthens the newly formed memory and in turn represses the fear response that reflects the old memory to a greater extent.

Thus, many pharmacological manipulations affect reconsolidation as well as extinction and therefore the impact of these two memory processes on the original memory becomes difficult to distinguish. It may be that the salient features of retrieval (the expression of the fear response with brief trials and the extinction of that response with long trials) determine which process is engaged, but this is complicated by the many findings that extinction can be engaged by brief trials. Further, widely used behavioral criteria for distinguishing reconsolidation and extinction – such as the persistent attenuation of the response – are not helpful because satisfying these criteria is necessary for both impaired reconsolidation and enhanced extinction (Stafford and Lattal, 2011; Lattal and Wood, 2013). For example, epigenetic/molecular mechanisms may give rise to extremely persistent extinction memories that would not be subject to uncovering phenomena. Thus, epigenetic mechanisms may challenge the conventional distinction between reconsolidation and extinction. We will touch base on this question near the end of this review. The role of epigenetic mechanisms in reconsolidation and extinction will be discussed next.

Overview of epigenetic mechanisms studied in fear processes

Epigenetic mechanisms are known to regulate gene expression without changing the DNA sequence itself. During the last decade, epigenetic mechanisms have been the focus of studies examining long-term adaptations such as memory formation as they have the potential to make persistent changes at the cellular level that may ultimately lead to long-term behavioral changes (Sweatt, 2009; Fischer, 2014; Jarome and Lubin, 2014; Oliveira, 2016). The main epigenetic mechanisms that directly affect chromatin structure examined in the learning and memory field to date are histone modification (Barrett and Wood, 2008), DNA modification (Baker-Andresen et al., 2013b; Alaghband et al., 2015; Oliveira, 2016) and nucleosome remodeling (Vogel-Ciernia and Wood, 2014; López and Wood, 2015). However, the latter only recently gained attention in the fields of cognitive neuroepigenetics, learning and memory, and addiction. There are other epigenetic mechanisms as well, including RNA modification and RNAi mechanisms (Qureshi and Mehler, 2012;

Woldemichael and Mansuy, 2016), but these do not directly affect chromatin structure *per se*. In this review, we will focus on histone modification and DNA methylation because these are the best studied with regard to retrieval-induced plasticity.

Histone modifications

DNA is wrapped around an octamer of histone proteins that contains two copies of histone H2A, H2B, H3 and H4 and the DNA-protein complex is referred to as chromatin. As histones have a positively charged N-terminus and DNA is negatively charged, the chromatin structure is condensed limiting accessibility of the transcription machinery. The tails of each histone can undergo a variety of post-translational modifications (PTM), including acetylation, methylation, phosphorylation, sumoylation and ubiquination (Zhang et al., 2016). Some of these modifications open the chromatin, therefore giving accessibility to transcription factors that bind to the DNA and induce transcription. In addition, histone modifications can also lead to a more condensed chromatin structure, which results in gene repression. Acetylation of histones is mainly associated with gene activation, as this modification neutralizes the interaction between the negatively charged DNA and the positively charged lysine residues on histone tails, resulting in a less condensed chromatin structure (Zhang et al., 2015). Prominent acetylation marks that are studied include H3K4 and H3K14 (Levenson et al., 2004; Fischer et al., 2007; Peleg et al., 2010). In contrast, histone methylation can bidirectionally modify gene expression, depending on the histone residue modified and the number of methyl groups present on a given residue. For example, histone tri-methylation is linked to gene repression at H3K9 (H3K9me3), but associated to gene activation at H3K4 (H3K4me3) (Li et al., 2007; Akbarian and Huang, 2009; Zhang et al., 2015).

Histone modifications are catalyzed by various enzymes and the modifications are reversible. Among the best-studied enzymes are histone acetyltransferases (HAT) and histone deacetylase complexes (HDACs). HATs transfer an acetyl group to lysine residues, whereas HDACs remove acetyl groups. A few prominent HATs examined in learning and memory include CBP, p300 and PCAF, which all have a role in memory formation (Barrett and Wood, 2008; Peixoto and Abel, 2013). The HDACs are divided into different categories (HDAC I, HDAC IIa, HDAC IIB, HDAC IV and Sirtuins) depending on their structure, enzymatic function, subcellular localization and expression patterns (Haberland et al., 2009). The importance of HDACs with regard to memory formation has been confirmed in a variety of studies (reviewed in Barrett and Wood, 2008; Gräff and Tsai, 2013). Though less frequently studied, another important group of enzymes inducing PTM are histone methyltransferases (HMTs) and histone demethylases (HDMs), which add or remove a methyl group to the histone tail, respectively. Their involvement in memory consolidation has also been confirmed in several studies (Gupta-Agarwal et al., 2014; Jakovcevski et al., 2015; Snigdha et al., 2016). To date, our knowledge is limited on how the various histone modification enzymes and consequently histone modifications themselves interact with each other during memory consolidation. Given that various histone modifications have been reported to be important for memory consolidation, it seems likely that there is a strong interdependence between them beyond their simple co-occurance. Their exact pattern likely gives rise to exquisite control of coordinate gene expression patterns for specific cell

function, an idea originally called the histone code (Strahl and Allis, 2000) that remains to be proven.

DNA methylation

DNA methylation is an epigenetic mark that affects gene expression by directly modifying the DNA. Traditionally, DNA methylation is associated with gene repression, however recent studies suggest that DNA methylation can also lead to gene activation. DNA methylation is catalyzed by DNA methyltransferases (DNMTs) by adding a methyl group to the 5′ position of a cytosine in the CpG nucleotide (5-mC). S-adenosyl-L-methionine serves as a methyl group donor in this process (Jeltsch, 2002). Among the DNMTs that are known to have catalytic activity are DNMT1, DNMT3b and DNMT3a (Margot et al., 2003). DNMT1 is also referred to as the maintenance DNMT as it preferentially methylates hemimethylated DNA. In contrast, DNMT3a and DNMT3b are called *de novo* methyltransferases as they create new methylation marks. Several isoforms that result from alternative splicing exist for DNMT3b (Robertson et al., 1999; Xie et al., 1999). DNMT3a has currently only two known isoforms, namely DNMT3a1 and DNMT3a2. Interestingly, DNMT3a1 localizes mainly to transcriptionally silent heterochromatin, whereas DNMT3a2 localizes to transcriptionally active euchromatin (Chen et al., 2002).

DNA methylation can repress gene transcription via direct interference of transcription factor binding (Watt and Molloy, 1988) or via methyl-CpG binding domain (MBD) proteins (Boyes and Bird, 1991; Jones et al., 1998; Nan et al., 1998). MeCP2, a MBD protein, can for example recruit HDACs and therefore lead to deacetylation of histones. As described above, this condenses chromatin and consequently results in transcriptional silencing (Jones et al., 1998; Nan et al., 1998). However, it has been also shown that MeCP2 can recruit transcriptional activators, such as CREB1, opening chromatin structure to promote gene activation (Chahrour et al., 2008). Furthermore, DNA methylation in gene bodies has been shown to increase gene transcription (Wu et al., 2010; Jones, 2012). This indicates that changes in the level of 5-mC might have opposing effects, gene activation versus gene repression, depending on where in the genome it occurs (i.e. promoter or gene body). The importance of DNTMs in memory formation has been shown in a variety of studies (*e.g.* Miller and Sweatt, 2007; Feng et al., 2010; Oliveira et al., 2012)

In contrast, the growth arrest and DNA damage-inducible protein 45b (Gadd45b) and ten-eleven-translocation (TET) proteins are DNA demethylation enzymes that have been shown to be critical for memory formation (Ma et al., 2009; Leach et al., 2012; Sultan et al., 2012; Kaas et al., 2013; Alaghband et al., 2015). Interestingly, 5-hydroxymethylcytosine (5-hmC) has recently been shown to not only be a DNA demethylation intermediate, but also to be a stable epigenetic mark itself (Branco et al., 2012; Hahn et al., 2013). The crucial players for hydroxylation of 5-mC to 5-hmC are currently believed to be the TET-family methylcytosine dioxygenases, comprising TET1-3 (Tahiliani et al., 2009; Li et al., 2013). 5-hmC can further be converted by the TET enzymes to 5-formylcytosine (5-fC) and 5-carboxylcytosine (5-caC), however not much is known about their role in brain function. Similar to 5-mC, changes in the level of 5-hmC occur in different regions of the genome, including promoters, gene bodies, and at transcription factor binding sites (Mellén et al., 2012; Hahn et al., 2013).

The functional relevance of the occurrence of 5-mC and 5-hmC in various parts of the genome is almost unexplored and its impact on gene transcription vs. repression and on cognitive function needs to be addressed in future studies.

Potential of epigenetic mechanisms to persistently attenuate fear memory

In the last decade it has become evident that epigenetic mechanisms play a crucial role in regulating (fear) memory processes. Manipulations that alter the epigenome have been reported to influence memory consolidation and change gene expression profiles during memory consolidation. Several recent reviews discuss the literature regarding the contributions of epigenetic mechanisms on fear memory consolidation (Maddox et al., 2013b; Zovkic and Sweatt, 2013; Kwapis and Wood, 2014). This review will focus on how epigenetic mechanisms can persistently impact the original fear memory by the two seemingly opposing mechanisms: reconsolidation and extinction. The specific epigenetic mechanisms involved in reconsolidation and extinction will first be discussed separately and then will be brought together at the end.

Histone modifications in fear reconsolidation

The first evidence that histone modifications are involved in memory reconsolidation came from a study by Lubin and colleagues (Lubin and Sweatt, 2007). In this study they showed that interference with the nuclear-factor kappa B (NF-kB) signaling pathway, previously shown to be important for memory consolidation of the original memory, leads to deficits in memory reconsolidation and changes in PTM of H3. More specifically, the authors demonstrated that recall of contextual memory induces changes in the level of H3 phosphorylation and acetylation in the CA1 region of the rat hippocampus, whereas H4 acetylation levels were not affected. H4 acetylation levels were determined by Western Blot using an antibody that detects acetylation at K5/K8/K12 and K16. Therefore, it should not be ruled out that H4 acetylation at other acetylation sites or at specific genes were altered.

Similar findings have been reported in the lateral amygdala, in which H3 acetylation was induced 90 min after memory reactivation (Maddox and Schafe, 2011). The time-window in which an increase of H3 acetylation was observed was narrow, as no increase was observed 60 min or 120min after reactivation. Intra-lateral amygdala (LA) infusion of the HDAC inhibitor TSA 60 min after reactivation and tissue collection 30 min after TSA delivery revealed an increase of H3 acetylation as well as an increase in H4 acetylation. Additionally, intra-LA infusion of TSA 60 min, but not six hours, after memory reactivation prevented the extinction of fear seen in the vehicle control group, which was interpreted as an enhancement in reconsolidation, but could also be interpreted as an impairment of extinction. Whatever the theoretical process, that study nicely shows that retrieval engages histone acetylation and to successfully impact retrieval-induced plasticity, the HDAC inhibitors have to be applied during a restricted time interval when memory reconsolidation takes place.

In addition to the observed changes of H3 phosphorylation and acetylation after memory reactivation, Lubin et al. reported a NF-kB/I_kB Kinase (IKK)-dependent increase of H3

phosphorylation and acetylation at the promoter of the memory-associated gene *zif268* (also known as early growth response 1 (*Egr1*)) during reconsolidation (identified performing chromatin immunoprecipitation (ChIP) analysis). As inhibition of NF-kB signaling leads to alterations in both memory reconsolidation and H3 acetylation, they performed a rescue experiment in which inhibition of the NF-kB signaling pathway was preceded by treatment of the HDAC inhibitor, sodium butyrate (NaB). Treatment of NaB rescued deficits in memory reconsolidation induced by NF-kB inhibition. A more recent study shows data consistent with this finding. Si et al., (2012) demonstrated that infusion of an IKK inhibitor into the basolateral amygdala (BLA) caused impairments in memory reconsolidation in auditory fear conditioning. The deficits in memory reconsolidation were reversed by systemic administration of the HDAC inhibitor NaB. Though they have not reported possible molecular mechanisms through which NaB reverses the impairments in memory reconsolidation, it is tempting to speculate that the IKK inhibitor inhibits the expression of genes required for memory reconsolidation and that necessary transcriptional events can either be restored by HDAC inhibition or bypassed by expression of other genes involved in memory processes.

Opposite findings on the effect of HDAC inhibitors on memory reconsolidation are reported in studies using the inhibitory avoidance task. In inhibitory avoidance, infusion of trichostatin A (TSA) one hour after memory retrieval had no effect on memory reconsolidation as step-down latencies were similar between the vehicle and TSA-infused groups in a test session conducted 24 hrs after the retrieval (Blank et al., 2014). The same group showed that the HDAC inhibitor NaB reversed impairments in memory consolidation (of the original memory) that were due to inhibition of the brain-derived neurotrophic factor (BDNF) tyrosine receptor kinase B (TrkB). However, deficits in memory reconsolidation induced by TrkB inhibition were not reversed by NaB (Blank et al., 2016). A possible explanation for this discrepancy in the finding is that the effect of HDAC inhibition on facilitating memory reconsolidation is restricted to fear conditioning and does not hold for inhibitory avoidance. Inhibitory avoidance is different than classical conditioning in that the animal has to emit an instrumental response to avoid the shock (Izquierdo et al., 2016). Studies on memory consolidation suggest, that these two learning paradigms share common mechanisms but also differ in some aspects; *e.g.* the involvement of the amygdala differs between those tasks (Tinsley et al., 2004). In inhibitory avoidance, different brain circuits and molecular mechanisms may be recruited that influence the effect of HDAC inhibitors on memory reconsolidation. However, differences in the results could also be explained by other experimental factors, such as the concentration of the HDAC inhibitor that is required and the time point the drug is administered. Interestingly, studies on inhibitory avoidance have shown, that stepping down onto the platform is necessary to initiate extinction of the inhibitory avoidance response (Cammarota et al., 2004). Therefore, an experimental design in which the animal is not allowed to step down in the reactivation session, would recruit mechanisms of reconsolidation but not extinction. This paradigm may help to address the question whether epigenetic mechanisms lead to persistent extinction versus the disruption of reconsolidation.

Gräff and colleagues showed that recall-induced H3K9/14 acetylation and HDAC2 binding at the promoter of *c-Fos* are differentially regulated for recent and remote memories (Gräff

et al., 2014). H3K9/14 acetylation at the promoter *c-Fos* is less abundant after recall of remote memories compared to recent memories, whereas HDAC2 binding at the promoter region of *c-Fos* is induced. In addition, the study demonstrated that HDAC2 nitrosylation that promotes the release of HDAC2 from chromatin, was increased after recall for recent but not for remote memories.

To date, several studies have focused on examining histone modification during reconsolidation using HDAC inhibitors, but little is known about the effect of HAT inhibitors during reconsolidation. Maddox et al. used the naturally occurring HAT inhibitor garcinol that is derived from the rind of the fruit of the Kokum tree, to study the effect of HAT inhibitors on memory reconsolidation (Maddox et al., 2013c). HAT activity of p300 and p300/CBP-associated factor (PCAF) in HeLa cells was reported to be inhibited by garcinol (Balasubramanyam et al., 2004). Additionally, Maddox and colleagues used the HAT inhibitor c646 to interfere with HAT activity of CREB-binding protein (CBP) and p300 (Maddox et al., 2013a). They demonstrated that the memory recall test-induced H3 acetylation in the LA was diminished by intra-LA infusion of garcinol and c646, as well as systemic injection of garcinol. The loss of activity-dependent H3 acetylation coincided with impaired freezing levels in the post-retrieval test session. However, the impairment was only observed when the mice were tested 24 hours after the reactivation session, but not when tested three hours after, indicating that only post-reconsolidation long-term memory was affected. It is important to note, that the same rats were used for post-reconsolidation short-term and long-term memory testing, hence the short-term memory test might have affected the long-term memory test. Maddox and colleagues also demonstrated that treatment with garcinol and c646 reduced freezing for remote memories acquired two weeks before the retrieval session, compared to the 24-hour time point that is commonly studied. This is a crucial finding with respect to possible treatments for anxiety disorders, as they usually develop over a longer time period. Importantly, the weakened fear response that was observed after treatment of garcinol or c646 in the reconsolidation window, was not susceptible to spontaneous recovery, reinstatement and contextual shift indicating that the weakening of the fear response was persistent. In this study, these three tests were conducted sequentially within the same animals, which can confound interpretation. In any case, the results from Maddox et al have important implications for the potential use of HAT inhibitors to weaken or block retrieval-induced plasticity.

Together, the studies briefly discussed above suggest that histone acetylation is enriched at promoters of plasticity-related genes during reconsolidation and that enzymes catalyzing histone modifications can alter the retrieval-induced plasticity associated with the original memory. The studies of Gräff et al and Maddox et al show that by using different behavioral approaches HDAC and HAT inhibitors, respectively, can attenuate the original fear memory persistently when administered during fear memory reconsolidation. In addition, a variety of studies have shown that impairments in memory reconsolidation can be restored by HDAC inhibitors, presumably via restoring the expression of important plasticity-related genes, or perhaps by engaging alternative pathways.

Histone modifications in fear extinction

A variety of pharmacological approaches have shown that HDAC inhibitors can facilitate extinction with brief retrieval trials (Lattal et al., 2007; Itzhak et al., 2012; Stafford et al., 2012; Heinrichs et al., 2013; Bowers et al., 2015). Bredy and colleauges demonstrated that extinction induced increases in the levels of H4 acetylation at the *Bdnf* P4 promoter and mRNA levels of *Bdnf* exon I and IV in the PFC (Bredy et al., 2007). The importance of BDNF in memory formation has previously been reported in a variety of studies (*e.g.* Mu et al., 1999; Heldt et al., 2007). In addition, they used a weak extinction learning protocol that does not induce changes in behavior or in H3 and H4 acetylation at the *Bdnf* promoters P1 and P4. However, intraperitoneal administration of the HDAC inhibitor valproic acid (VPA) resulted in increased H4, but not H3, acetylation levels around the *Bdnf* P1 and P4 promoter and further resulted in increased mRNA levels of *Bdnf* exon 4 after extinction learning. In addition, treatment with either VPA or the HDAC inhibitor NaB allowed for the formation of fear extinction memory in the weak extinction paradigm.

Stafford et al showed that intrahippocampal infusion of NaB enhanced H3K14 acetylation in the hippocampus following weak or strong extinction training (Stafford et al., 2012). As the hippocampal circuit has previously been shown to be essential for extinction learning (Peters et al., 2010), they further investigated if acetylation levels in the infralimbic cortex are affected by intrahippocampal injections of NaB. They reported that intrahippocampal injections of NaB accelerated H3K14 acetylation levels in the infralimbic cortex only after weak extinction training. NaB directly infused into the infralimbic cortex further resulted in persistent extinction memory enhancements. Increased acetylation levels after HDAC inhibition were also reported at the *Nr2b* promoter in a study by Fujita et al (2012). NR2B is a subunit of the N-methyl-D-aspartate receptor (NMDAR) and NMDAR agonists are already used in therapy to facilitate fear extinction in PTSD patients. Fujita et al reported that systemic injections of the HDAC inhibitor vorinostat leads to facilitated fear extinction, which further coincides with higher levels of global H3 and H4 acetylation and increased mRNA levels of *Nr2b* in the hippocampus. ChIP analysis revealed that histone H3 and H4 acetylation was increased around the *Nr2b* promoter and that p-CREB binding was significantly enhanced at the *Nr2b* promoter in vorinostat injected mice compared to control mice. Together, these studies demonstrate that HDAC inhibitors can convert a weak extinction learning experience into extinction memory and that extinction learning induces acetylation of histone tails at promoters of plasticity-related genes. However, the use of non-specific pharmacological approaches is limited as it does not allow one to differentiate between the contributions of the various HDAC isoforms in extinction. Additionally, in the studies in which HDAC inhibitors are given systemically, secondary effects that contribute to the outcome cannot be excluded as acetylation is affected globally. Given the non-specific mechanism of action of HDAC inhibitors, it is even more surprising that these compounds all appear to promote extinction.

Hait and colleagues investigated the function of HDACs in regulating memory extinction using the FDA approved drug FTY720 (Hait et al., 2014). FTY720 is a mimetic of the endogenous HDAC inhibitor sphingosine-1-phosphate (S1P) that is known to bind to HDAC1 and HDAC2 and therefore increases histone acetylation levels. Similar to the

endogenous S1P, FTY720 binds HDACs upon phosphorylation (p-FTY720) by sphingosine kinase 2 (SphK2) in the nucleus and hence inhibits enzymatic activity of HDACs. FY720 was further shown to increase acetylation of H3K9, H4K5 and H2BK12. To study the effect of FTY720 in fear extinction, they used severe combined immune deficient (SCID) mice that are known to have cognitive impairments. Oral administration of FTY720 reversed extinction deficits in SCID mice and increased H3K9, H4K5 and H2K12 acetylation in the hippocampus. Additionally, a variety of memory-associated genes, among others vascular endothelial growth factor D (*VegfD*), nuclear receptor subfamily 4 group A member 2 (*Nr4a2*) and *c-fos*, were upregulated in FTY720 treated SCID mice. They further report decreased hippocampal acetylation levels of H3K9, H4K5 and H2K12 and extinction memory deficits in mice with a deletion of SphK2. As SphK2 is the main isoform phosphorylating FTY720, these deficits could not be reversed by overexpression of FTY720 in *SphK2* -/- mice. However, expression of the HDAC inhibitor suberanilohydroxamic acid (SAHA, earlier referred to as Vorinostat) restored acetylation levels and extinction in *SphK2*-/- mice. Because FTY720 is FDA-approved, there is potential to treat PTSD patients when given together with exposure therapy. Understanding the persistence of the behavioral and molecular effects will be critical to using this drug in clinical applications.

The studies listed so far have all used pharmacological approaches, which have the benefit of being more easily and rapidly translated into therapeutic interventions. However, most of the drugs have an impact on several HDACs and limited information is available on the role of individual HDACs with regard to cognitive performance. To understand the specific role of HDAC1, whose increase has been associated with a variety of neuropsychiatric diseases, Bahari-Javan and co-workers developed a virus-mediated approach (Bahari-Javan et al., 2012). They overexpressed HDAC1 in the mouse hippocampus and observed facilitated fear extinction compared to vehicle-injected animals. Further, analysis of hippocampal tissue dissected one hour after the third extinction session revealed decreased *c-fos* mRNA in HDAC1-overexpressing mice. This decrease of *c-fos* expression was correlated with increased HDAC1 levels, decreased H3K9 acetylation levels, but increased H3K9 tri-methylation levels at the *c-fos* promoter. In addition, the histone methyltransferase suppressor of variegation 3–9 homolog (SUV39H1), silent mating type information regulation 2 homolog (SIRT1) and mSin3b were increased at the *c-fos* promoter after day 3 of extinction learning, providing a mechanism by which *c-fos* expression is reduced. SUV39H1 is a known H3K9 methyltransferase that gets activated by SIRT1 and has been reported to interact with HDAC1. In addition, HDAC1 builds a corepressor complex together with mSin3b. In contrast, inhibition of HDAC1 activity via MS-275 or infusion of HDAC1-siRNA revealed elevated levels of H3K9 acetylation, decreased levels of H3K9 tri-methylation at the *c-fos* promoter and consequently induced level of *c-fos* mRNA. Further, blockage or knockdown of HDAC1 resulted in fear extinction deficits and they report a negative correlation between the activity-regulated gene *c-fos* and successful extinction. These data are important because they offer a constraint on the idea that HDACs in general negatively regulate extinction. This study was the first to specifically investigate the function of HDAC1 and hence other HDACs may contribute to the regulation of fear extinction in an opposite manner. Indeed, Morris and colleagues showed that *Hdac2* knockout (KO) mice exhibit facilitated fear extinction, although they did not see any changes in fear extinction

comparing *Hdac1* KO mice with wild-type mice (Morris et al., 2013). One concern that should be taken into account when studying KO mice is that it cannot be ruled out that unobserved developmental effects contribute to the behavioral phenotype or compensatory mechanisms confound interpretation.

As extinction learning in the animal model is used to model aspects of exposure therapy in anxiety disorders, some studies have investigated whether HDAC inhibitors can facilitate fear extinction in animal stress models that are generally more resistant to fear extinction. Matsumoto et al used a single prolonged stress approach that induces stress in mice and impairs fear extinction, as reported at a post-extinction test. Matsumoto and coworkers showed that the HDAC inhibitor vorinostat improved fear extinction (Matsumoto et al., 2013). They also demonstrated that mice injected with vorinostat showed increased levels of H3 and H4 acetylation compared to vehicle-injected animals. Further, NR2B and CAMKIIα and CAMKIIβ protein levels were similarly upregulated. As previously mentioned NR2B is part of the NMDA receptor and the NMDAR-CaMKII signaling pathway is important for memory extinction (Szapiro et al., 2003; Sotres-Bayon et al., 2007), so this increase suggests that extinction signaling pathways are activated by vorinostat. Additionally, it was reported that the 129S1/SvImJ mouse strain (which is generally resistant to extinction and thus reflects a major hallmark of PTSD patients) is capable of extinguishing fear if VPA is administered before the extinction trial (Whittle et al., 2013). In addition, administration of MS-275 improved fear extinction memory when given directly after the extinction session. The molecular mechanisms by which HDAC inhibitors facilitate fear extinction remain to be investigated. As protein levels of the calcium-induced signaling pathways have been shown to be influenced by HDAC inhibition it is tempting to speculate that epigenetic mechanisms have the potential to impact calcium signaling which in turn influences activity-dependent gene expression and by this may further facilitate and strengthen memory extinction.

Surprisingly, a study investigating the role of HAT activity in fear extinction found that inhibition of HAT activity by infusion of the p300 inhibitor c646 into the infralimbic prefrontal cortex (ILPFC) facilitated fear memory extinction, in addition to enhancing LTP (Marek et al., 2011). The mechanisms by which p300 inhibition by c646 facilitates fear extinction remain to be investigated. One issue to consider for this and any other pharmacological study with HDAC or HAT inhibitors, is that the native protein-protein complexes may be disrupted by the small molecule inhibitors leading to unintended effects on other enzymes within the complex, which would confound interpretation of mechanism.

With regard to histone methylation, a recent study by Balemans and colleagues however demonstrated that the euchromatin histone methyltransferase 1 (EHMT1) is critical for fear memory extinction using *Ehmt1*+/- heterozygous mice (Balemans et al., 2013). EHMT1 catalyzes mono and dimethylation of histone H3K9 and is associated with transcriptional repression. Besides its impact on fear memory extinction they also showed that *Ehmt1*+/- mice have alterations in dendritic morphology and synaptic transmission. To rule out the possibility that the observed impairments come from developmental deficits, additional approaches that interfere with EHTM1 expression acutely (e.g. pharmacological or viral-mediated approaches) rather than chronically should be used in future studies to verify these results. In any case, this study shows that other PTMs besides histone acetylation are

involved in the regulation of fear extinction. The field needs additional studies in this area to more fully understand the key histone modification mechanisms necessary for the regulation of extinction.

Together, the studies discussed above provide evidence that extinction learning changes acetylation patterns at the promoter of plasticity-related genes and that modulating histone modifying enzymes can alter extinction memory. Future studies however need to focus on which HDAC variants positively or negatively affect extinction learning, as only a few studies have aimed at investigating the contribution of a specific HDAC variant. Further, as epigenetic mechanisms can change the molecular signature of a cell persistently, the long-term effect of extinction learning on the original memory should be tested more thoroughly (*e.g.* by examining spontaneous recovery, reinstatement and context shifting). Testing extinction memory after longer time points will provide important information about whether epigenetic mechanisms not only facilitate memory extinction, but do so in a persistent fashion.

DNA methylation in fear memory reconsolidation and extinction

Whereas growing evidence exists that transcriptional regulation via DNA methylation is important for memory consolidation (Miller and Sweatt, 2007; Feng et al., 2010; Oliveira et al., 2012), only a few studies have examined DNA methylation during memory reconsolidation. Maddox et al showed that inhibition of DNA methylation via infusion of 5-aza-2-deoxycytidine (5-AZA) or RG108 into the LA during the reconsolidation window impairs fear memory reconsolidation and the retention of memory-related synaptic plasticity (Maddox and Schafe, 2011; Maddox et al., 2014). Further, there was no observation of spontaneous recovery, reinstatement or context shift (renewal). Inhibition of DNA methylation further correlated with reduced levels of H3 acetylation which suggests an interplay between DNA methylation and histone acetylation. Indeed, pretreatment of the HDAC inhibitor TSA ameliorated fear memory reconsolidation impairments induced by the DNA methylation inhibitor 5-AZA. The field needs more studies investigating DNA methylation levels after memory reconsolidation and how enzymes catalyzing DNA (de-) methylation affect gene expression during memory reconsolidation, as well as which brain regions and cell types are most affected by DNA methylation mechanisms.

One of the first studies providing a correlation between DNA methylation and fear extinction came from Baker-Andresen and colleagues who compared fear extinction in male and female mice (Baker-Andresen et al., 2013a). They discovered that female mice are resistant to fear extinction and have higher levels of DNA methylation around the *Bdnf* exon IV promoter in the infralimbic PFC when compared to male mice. Thus, DNA methylation at *Bdnf* exon IV may represent a molecular signature for extinction resistance. Future studies are needed to confirm that this may represent a real causal mechanism, which could potentially guide the field to understand how individuals are resistant or susceptible to extinction based therapies.

Studies manipulating enzymes of the TET family have provided insight into the necessity of epigenetic factors in the regulation of fear memory extinction (reviewed in Alaghband et al.,

2015). *Tet1* KO mice were shown to have impairments in fear extinction (Rudenko et al., 2013). In addition, these mice were reported to have reduced levels of global 5-hmC levels in the hippocampus and cortex. A microarray analysis revealed that a variety of genes are differentially regulated in the hippocampus and cortex of *Tet1* KO mice compared to control mice. Among those genes were well known activity-regulated genes such as *c-fos*, *Arc* and *Npas4*. Sodium bisulfite sequencing further revealed that the *Npas4* promoter-exon 1 region is hypermethylated in the cortex and hippocampus of *Tet1* KO mice presumably contributing to the decreased expression level of *Npas4* mRNA. In addition, after extinction learning, the *Npas4* promoter-exon 1 region remained hypomethylated in control animals. In contrast, the *Npas4* promoter-exon 1 region was hypermethylated after extinction in *Tet1* KO mice to similar amounts as naïve *Tet1* KO animals that did not undergo fear extinction. Li et al reported that fear extinction is not impaired by shRNA-mediated downregulation of TET1 in the ILPFC. However, deficits in fear extinction are observed when TET3 levels are reduced (injecting a shRNA against *Tet3*) (Li et al., 2014). The differences between the results of these two studies may result from different levels of TET1 knockdown (shRNA knockdown is variable animal to animal versus a complete knockout as examined in the Rudenko study) and variations in the fear extinction protocol. Importantly as discussed earlier, chronic inhibition of a gene as in the case of KO mice may elicit developmental abnormalities that confound interpretation in terms of an extinction-specific effect. A successful rescue experiment in which TET1 is overexpressed in the *Tet1* KO mice would strengthen the overall conclusion that TET1 is indeed involved in fear extinction.

Li et al further demonstrate in their study that mRNA levels of *Tet3*, but not *Tet1* are induced by fear extinction learning in cortical neurons. Extinction learning resulted in a global redistribution of 5-hmC patterns and a gene ontology study revealed that 5-hmC peaks existed at a variety of genes associated with synaptic signaling. Among those genes was *gephyrin*, which is known to play an important role in fear extinction by anchoring the gamma-aminobutyric acid (GABA) receptors to the postsynaptic membrane. TET3 occupancy was found at the *gephyrin* promoter and *gephyrin* mRNA levels were increased after fear extinction learning. Therefore, TET enzymes seem to affect fear extinction by changing the pattern of 5-hmC and hence the expression of genes important for extinction, which were further shown to be positively correlated with the expression of the DNA methyltransferase DNMT3a2 (Oliveira et al., 2016). Viral-mediated manipulation of DNMT3a2 levels in the hippocampus revealed that overexpression of DNMT3a2 leads to an increase in *c-fos* and *Arc* mRNA levels during extinction memory consolidation. This increase presumably contributes to the facilitating effects of DNMT3a2 overexpression on fear memory extinction observed in this study. Conversely, DNMT3a2 inhibition impaired fear memory extinction and a rescue experiment showed that those deficits were ameliorated by overexpression of DNMT3a2. Thus, this study reports a critical role of DNMT3a2 in memory extinction and that its expression impacts plasticity-related genes.

The above studies demonstrate that enzymes catalyzing DNA methylation and demethylation have a crucial role in regulating gene expression required for fear memory extinction. However, we are just at the beginning of understanding their contribution to fear extinction. Future studies need to evaluate the role of other DNA (de-) methyltransferases and need to address the discrepancies of the findings to date. In addition, the redistribution

of 5-mC and 5-hmC during fear memory extinction throughout the genome will be interesting to investigate in future experiments, as their occurrence may have opposite outcomes on gene activation and repression depending on where in the genome they are located.

Summary

Understanding the molecular and cellular mechanisms underlying memory reconsolidation and memory extinction is of great importance as these memory processes relate directly to PTSD and other anxiety disorders. The current literature provides strong evidence that epigenetic processes are important factors in regulating fear memory reconsolidation and fear memory extinction and hence these mechanisms may serve as potential targets to facilitate cognitive behavioral therapy (CBT) approaches. Thus, it is critical that we continue to make progress in this area of research. A few important issues for consideration as the field moves forward are described below.

Behavioral definitions—It will be important to understand the role of epigenetics in establishing persistent extinction versus the disruption of reconsolidation. The process of extinction is thought to be in play when uncovering phenomena (spontaneous recovery, reinstatement and renewal) reveal the behavior associated with the original learning experience. However, as Pavlov observed, extinction can be enhanced ‘beyond the zero’, meaning that although the behavior has hit a floor, continued extinction training leads to strengthened extinction that is observed in the resistance to spontaneous recovery (Pavlov, 1927). Thus, it is easily conceivable that epigenetic mechanisms, which can establish extremely persistent cell function changes, can generate unusually robust forms of extinction memory. Because an unusually strong extinction memory would be resistant to uncovering phenomena, the results could be misinterpreted as a disruption of reconsolidation (Lattal and Wood, 2013). Thus, our behavioral definitions should be used with caution.

Timing—Short retrieval durations are associated with memory reconsolidation, whereas longer retrieval times are believed to shift the reconsolidation process towards an extinction process. Studies using short retrieval times often discuss their results with regard to engaging reconsolidation mechanisms. However, epigenetic mechanisms have the potential to transform a subthreshold learning experience into a robust long-term memory. Thus, epigenetic manipulations may shift the dynamics between reconsolidation and extinction so that short retrieval paradigms may allow for a faster recruitment of the extinction machinery (Figure 1).

Individual epigenome—A third major issue to consider, especially as the field makes progress towards clinical application of translational basic research, is the individual epigenome. The epigenome encodes a depth of information that we have barely come to understand, especially with regard to previous experience. Thus, it will be critical to determine the state of an individual's epigenome, and specifically identified markers, to understand individual susceptibility or resistance to maladaptive fear memory formation, persistence, and recall processes. Similarly, understanding what kinds of previous

experience, like early-life stress, impact the epigenome and subsequently alter fear-related learning and memory will be important.

Acknowledgments

This work was supported by the National Institute of Mental Health (NIMH) and National Institute on Aging (NIA) grants (MH101491, AG051807, AG050787) to MAW, US Department of the Army/DOD-TATRC W81XWH-14-2-0143 and MH106284 to KML, and a George E. Hewitt Foundation for Medical Research Fellowship to TJH. We would like to thank Dr. Janine L. Kwapis for providing critical comments on the manuscript.

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Highlights

Here we review the role of several key epigenetic mechanisms in reconsolidation and extinction of learned fear and their potential to persistently alter behavioral responses to conditioned cues.

We also briefly discuss how epigenetic mechanisms may establish persistent behaviors that challenge our definitions of extinction and reconsolidation.

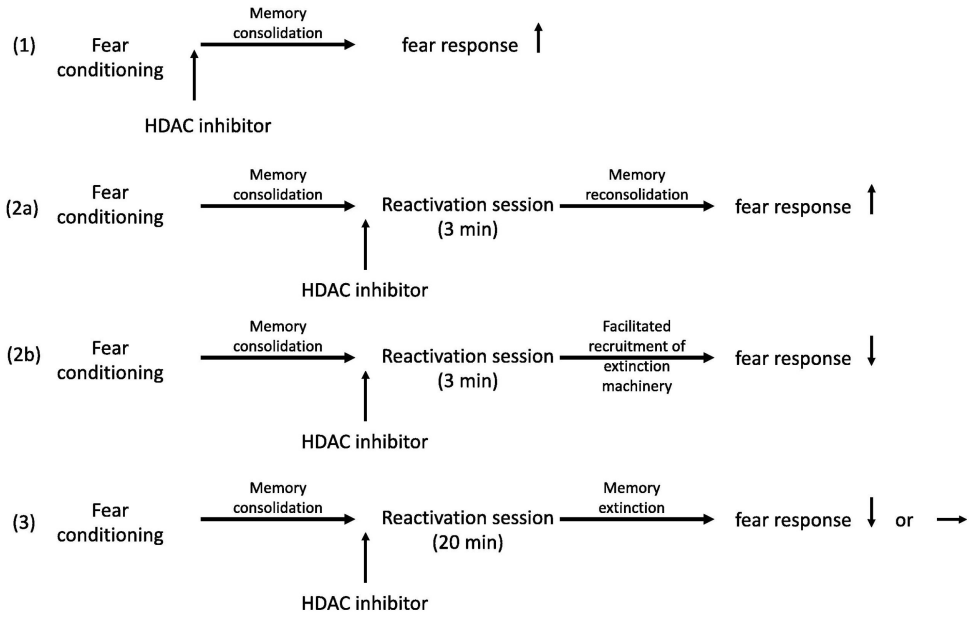

Figure 1. The effect of HDAC inhibitors on different behavioral paradigms

(1) Injecting HDAC inhibitors before memory consolidation increases the fear response. (2a) HDAC inhibitors injected before a 3 min reactivation session may lead to an increase in the fear response if the reconsolidation machinery is recruited. (2b) However, administration of HDAC inhibitors before a short reactivation session may also facilitate the recruitment of the extinction machinery therefore enhancing extinction memory (decrease of fear response). (3) Administration of HDAC inhibitors before a 20 min reactivation session can enhance extinction memory (decreased fear response), however if the extinction protocol alone induces a high level of acetylation, then a ceiling effect may be reached obscuring further effects by an HDAC inhibitor.