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Neuroepigenetic Regulation of Pathogenic Memories

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Abstract

Our unique collection of memories determines our individuality and shapes our future interactions with the world. Remarkable advances into the neurobiological basis of memory have identified key epigenetic mechanisms that support the stability of memory. Various forms of epigenetic regulation at the levels of DNA methylation, histone modification, and non-coding RNAs (ncRNAs) can modulate transcriptional and translational events required for memory processes. By changing the cellular profile in the brain's emotional, reward, and memory circuits, these epigenetic modifications have also been linked to perseverant, pathogenic memories. In this review, we will delve into the relevance of epigenetic dysregulation to pathogenic memory mechanisms by focusing on two neuropsychiatric disorders perpetuated by aberrant memory associations: substance use disorder (SUD) and post-traumatic stress disorder (PTSD). As our understanding improves, neuroepigenetic mechanisms may someday be harnessed to develop novel therapeutic targets for the treatment of these chronic, relapsing disorders.

Memory formation requires the complex refinement of synaptic structures to yield long-lasting changes in plasticity that support and maintain a memory trace. Nuclear histone modifications are poised to regulate such processes because they receive cellular signals and integrate this molecular information into transcriptional and translational events that modulate synaptic plasticity. Rodent learning and memory paradigms result in hyperacetylation of histone proteins in an ERK/MAPK-dependent manner, illustrating this principle of signal integration and demonstrating that histone acetylation is a hallmark feature of memory formation [1, 2]. Dampening histone acetylation by decreasing histone acetyltransferases (HATs) or over-expressing histone deacetylases (HDACs) produces deficits in contextual fear learning, synaptic plasticity, dendritic synapse structure, and long-term memory [3–7]. Conversely, HDAC inhibitors promote histone acetylation and have been hypothesized to change the synaptic architecture of dendrites, allowing for new synapses to take shape during memory formation [8]; thus, ameliorating impairments of

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neuronal plasticity and memory, boosting cognitive function and increasing synapse number [2–4, 6, 9–12].

Interestingly, pretreatment with an HDAC inhibitor can counteract and overcome the memory disrupting effects of DNA methyltransferase (DNMT) inhibition, indicating that multiple epigenetic signals are integrated to produce a behavioral outcome [13]. Epigenetic regulation by methylation of genomic DNA contributes to the support of stable memory consolidation, as well as dynamic synaptic processes during new memory formation, demonstrating its utility as a reversible post-translational modification [14–16]. Indeed, DNA methylation is a critical contributor to memory consolidation and learning-induced synaptic plasticity, events that can be blocked by DNMT inhibition [13, 17]. At the transcriptional level, alteration of DNA methylation within the hippocampus at the time of learning has bidirectional consequences on gene expression, inducing genes that support memory formation, while silencing memory-suppressing genes [15, 18]. Interestingly, hippocampal methylation induced by learning at gene promoters that have been assayed appears to be transient, returning to baseline within 24 hours [15]. However, cortical integration occurs during consolidation of memories, shifting a hippocampus-dependent memory to rely on the cortex and, ultimately, resulting in a lasting cortical hypermethylation pattern in the cortex that contributes to preservation of the memory trace [19]. Thus, integrative DNA methylation represents both dynamic and stable processes of memory formation. For additional information on the general mechanisms discussed above, a number of more extensive, excellent reviews have been written on histone modifications and DNA methylation involved in learning and memory [20–22].

Beyond these traditional modifications, ncRNAs have emerged as potent epigenetic regulators that can ubiquitously repress and/or activate a broad repertoire of targets. MicroRNAs (miRNAs) are non-coding, endogenous RNAs that act as translational repressors through direct binding to the 3′-UTR of target mRNAs and non-cleavage degradation of the target mRNA via deadenylation [23–25]. Since a single miRNA has hundreds of predicted targets based on seed region complementarity, this wide-genomic range likely affords it the ability to efficiently coordinate complex processes, such as those required to form and maintain a memory [26]. Indeed, miRNAs have been studied for their involvement in basic mechanisms of learning and memory, synaptic plasticity, and cognitive dysfunction (For review see [27]). For example, the brain specific miR-134 is enriched in the synapto-dendritic compartment of cultured hippocampal neurons, where it targets actin-related proteins that regulate spine development [28]. Because actin is the major cytoskeletal component of dendritic spines [29], and its polymerization is required for the regulation of structural and functional plasticity and memory formation [30–34], miRNAs like miR-134 are well-suited to exert strict regulatory control over structural plasticity [35–38]. Indeed, exposure to conditioned fear learning paradigms regulates the expression of several miRNAs [26, 39, 40] and manipulation of a single miRNA can prevent memory consolidation and inhibit learning-induced dendritic spine changes [26, 39–43].

While recent work in the field of neuroepigenetics has provided us with insight into the effects of epigenetic dysregulation during memory processes, we have only reached the tip of the iceberg. It is well established that stressful, pathogenic events such as abuse, early-life

trauma and combat exposure induce epigenetic modifications [44–48] that have been linked to neuropsychiatric disease susceptibility [49–51]. However, much remains elusive regarding the role of epigenetics in *maintaining* long-lasting pathogenic memories such as those experienced by substance abusers and PTSD patients. Moreover, a better grasp of the ability of epigenetic mechanisms to modulate pathogenic memories will allow for the identification of potential targets for therapeutic use in the treatment of deeply engrained associations capable of perpetuating SUD and PTSD.

Epigenetic mechanisms in pathogenic memory: Drug-associated memories

Learned associations between environmental stimuli and the rewarding effects of drugs of abuse serve as lasting, potent memories capable of triggering a conditioned, physiological response and feelings of intense craving in abstinent drug users. These memories are highly resistant to extinction and contribute to the high rate of relapse among addicts. Therefore, a common approach in the field is to identify mechanisms capable of accelerating the extinction or blocking the reconsolidation of these deeply engrained memories. Our understanding of epigenetic contributions to these memories is limited and far more is known about the mechanisms contributing to the formation of drug-associated memories than the mechanisms involved in their expression, extinction or reconsolidation.

Currently, everything known about epigenetic contributions to drug-associated memories comes from studies utilizing conditioned place preference (CPP), a behavior task in which animals learn to associate the rewarding effects of a drug with the environmental context in which it is administered and later show a preference for that environment. Histone acetylation and methylation, as well as DNA methylation have been implicated in the formation and extinction of drug-context associations. For instance, elevating histone acetylation via HDAC inhibition (HDACi) enhances cocaine, morphine and heroin place preferences, but decreases nicotine CPP [52–58]. Similarly, HDACi accelerates the extinction of cocaine and morphine CPP [54, 59, 60] and prevents the blockade of morphine CPP reconsolidation induced by an inhibitor of nuclear factor-kB (NF-kB) [61]. However, HDACi was shown in another study to delay cocaine CPP extinction [62]. Under certain conditions, rodents develop conditioned place aversions to ethanol and morphine, and rather than the accelerated extinction seen with place preferences, HDACi seems to delay the extinction of these aversive memories [63, 64].

Because there are 11 HDAC isoforms, excluding the non-histone related sirtuins, that can be subdivided into four classes, a major goal within the field of neuroepigenetics is to identify which HDACs contribute to the behavioral effects identified with somewhat broadly acting HDAC inhibitors. To that end, overexpression of HDAC4 in the striatum has been found to disrupt a cocaine place preference [57]. This same type of association is enhanced by genetic knockdown of HDAC3 within the brain's reward center, the nucleus accumbens (NAc) [65]. Further, reducing the nuclear accumulation of HDAC5 in the NAc via dephosphorylation and focal knockdown of the HAT, *CBP*, in the NAc both disrupt cocaine CPP [66, 67]. New HDAC inhibitors are becoming available with increased selectivity and one such compound, RGFP966, bears a high degree of specificity for HDAC3, a member of the Class I family

of HDACs. Consistent with the effect of more broadly acting HDACi's, inhibition limited to HDAC3 was also capable of enhancing cocaine CPP [68].

By adding methyl groups to lysine 9 on histone H3 (H3K9), the histone methyltransferase (HMT), *G9a*, is capable of inhibiting transcription. Consistent with this function, intra-NAc knockdown of *G9a* enhanced cocaine CPP, while overexpression disrupted a place preference for morphine CPP [69, 70]. Recent technical advances are allowing researchers to target subpopulations of neurons. This is particularly advantageous in the striatum, a brain region populated by neurons with very different downstream projections. These neurons can be delineated by their expression of either the D1 receptor (*Drd1*) or D2 receptor (*Drd2*). A recent study employing one such cell type-specific technique found that *G9a* knockdown in D1-containing striatal neurons decreased cocaine CPP, while knockdown in D2 neurons enhanced the strength of the association [71]. Similarly, knockdown of the transcriptionally permissive H3K4 HMT, *Mll1*, in the NAc prevented the formation of a methamphetamine place preference [72]. H3K4 methyl moieties can be removed by the histone demethylase, *Kdm5c*, driving transcriptional repression. Interestingly, intra-NAc knockdown of this enzyme has no effect of the formation of a methamphetamine association, but prevents its storage and/or expression [72].

DNA methylation and non-coding RNAs have received even less attention in the context of drug-associated memory. DNA methylation is associated with transcriptional silencing and represents another attractive mechanism for mediating long-lasting memories [15, 19]. Changes in DNA methylation can be triggered through activity of the *de novo* methylatransferases, *Dnmt3a* and *Dnmt3b*. Indeed, reduction of the repressive state has been observed in the brain's reward system after a single administration of cocaine through changes in *Dnmt3a* expression and chronic, systemic methyl supplementation with methionine disrupted a place preference for cocaine [73, 74]. Paradoxically, infusion of a DNMT inhibitor directly into Area CA1 of the hippocampus also disrupted the formation of cocaine CPP [75], while DNMT inhibition in the NAc enhanced cocaine CPP [73]. Additionally, the expression of cocaine CPP was prevented by DNMT inhibition within the prelimbic cortex [75]. Together, these results indicate a clear need to identify the gene- and region-specific roles of DNA methylation, as well as this epigenetic modification's contribution to the long-term storage of drug-associated memories.

Non-coding RNAs have been implicated in transcriptional and translational regulation. Recent studies suggest that cocaine and heroin can induce changes in long, non-coding RNA (lncRNA) expression [76, 77]. For example, the expression profiles of lncRNAs and associated mRNA are changed in the NAc 24 hours after expression of cocaine CPP [76]. miRNAs are also changed after cocaine locomotor sensitization, a process involving substantial synaptic plasticity [78]. Specific miRNAs have also been implicated in the regulation of the transcription factor CREB, as well as BDNF [79, 80], both of which are key participants in synaptic plasticity. Although further investigation will be required to determine if differential profiles of lncRNAs and miRNAs occur during the different phases of memory, as well as identification of the underlying mechanisms, the existing data suggest they may be capable of participating in the formation, and perhaps, post-consolidation regulation of drug-associated memories.

Together, these findings suggest that substances of abuse have the capacity to prime neural circuits to increase susceptibility to relapse by mediating long-lasting memories through either facilitating a permissive state or inhibiting a repressive state. However, a challenge presented by CPP acquisition studies involves interpretation of the findings, as they are used as both a measure of drug reward and learning ability. Indeed, the majority of authors have interpreted their acquisition phase findings, particularly those related to the NAc, as epigenetic-induced changes to the rewarding properties of drugs of abuse. This interpretation is supported by the numerous, concomitant reports of changes in locomotor sensitization with epigenetic modification. The likelihood of influences on reward, rather than learning, is further indicated by the finding that HDAC inhibition with sodium butyrate (NaB) increases cocaine self-administration during the protocol's maintenance phase [81]. Though, another study found that systemic HDAC inhibition with trichostatin A (TSA) or phenylbutyrate (PB) decreased cocaine self-administration and correlated with decreased HDAC activity within the prefrontal cortex (PFC), a key member of the neural circuitry governing drug-associated memory [82]. This may represent epigenetic-mediated compensatory actions in the PFC, such as activation of BDNF [83]. Interestingly, the discrepancy of findings between the two studies examining the effects of HDAC inhibition on cocaine self-administration may lie in the selectivity of the particular inhibitors that were utilized. While TSA and PB are broad spectrum HDAC inhibitors, hitting members of every HDAC Class, NaB's targets are limited to Class I HDACs (HDAC1, 2, 3 and 8) [11]. Regardless, there is clearly a need to further characterize the region-specific contribution of epigenetic modifiers to drug-associated and other pathological memory associations, particularly in terms of how these memories are stored, expressed and subsequently modified.

Epigenetic mechanisms in pathogenic memory: Implications for PTSD

During PTSD, an individual experiences or witnesses a traumatic event or events that later lead to substantial dysfunction in fear processing, including hyperactivation of the amygdala (AMY), upon exposure to fearful stimuli and generalization of fearful responses to nonfearful stimuli. The AMY, the brains emotional memory center, plays a critical role in many forms of cognition, including psychiatric disorders with a memory component [84, 85]. Unlike hippocampus-dependent memories, which shift to the cortex as long-term memory develops [19, 86, 87], AMY-dependent memories continue to rely on the AMY weeks after learning [88, 89]. Understanding the mechanisms through which the AMY maintains these painful memories in a stable state for months to years has significant clinical importance. Given the powerful transcriptional and translational effects of epigenetic modifications, as well as their long-lasting potential, epigenetics represent a promising avenue of research for PTSD.

Stress has been shown to induce epigenetic modifications [90, 91]. Taken together with the fact that manipulation of the chromatin state or abundance of regulatory miRNAs can affect how the brain forms and recalls a memory, one can postulate that a stressful event that precipitates PTSD will produce epigenetic changes in brain regions that differentially process that memory, as well as the subsequent behavioral responses to reminders of the stressful event. In accordance with this notion, the pathogenic memories of PTSD are resistant to prolonged exposure therapy (i.e. extinction). Therefore, the focus of many

researchers in the field has been to identify molecular targets that accelerate the extinction process.

Evidence that epigenetic mechanisms contribute to the perseverant memory state that is characteristic of PTSD is beginning to accumulate [92–94]. As mentioned above, traditional fear conditioning in rodents has provided insight into the epigenetic mechanisms of memory, thus laying the groundwork for traumatic fear memory studies in models of PTSD with strong face validity [95, 96]. Most studies on pathogenic memory research have employed animal models of PTSD that include a test of “traumatic memory” in a conditioned fear paradigm. For instance, in rodents, a “normal” fear memory can be converted to a traumatic, extinction-resistant memory by pre-exposure to a stressor [97]. Subsequent fear conditioning results in a fear memory that displays greater resistance to extinction than one formed in the absence of prior stress [97, 98]. Treatment with an HDAC inhibitor ameliorates fear extinction deficits in such a paradigm, presumably because it increases histone acetylation to support the formation of new extinction memories [99]. Under basal conditions, this model produces enhanced consolidation after contextual fear conditioning and increased acetylation of histones H3 and H4 at the promoter of *bdnf* [100]. When taking into consideration the fact that histone acetylation contributes to basic memory processes, these studies suggest that histone acetylation contributes to the formation of a very strong initial fear memory in PTSD, but that it can also be exploited for the formation of extinction memories that aid in the inhibition of pathogenic fear memory responses.

While many studies have reported altered DNA methylation patterns in PTSD patients or animal models of PTSD (for review see [101, 102]), the contribution of these epigenetic changes to the development or maintenance of PTSD traumatic memories has not been described. Likewise, the role of miRNAs in PTSD remains a complete mystery. In recent years, animal models of PTSD with good face validity have been described, in which key facets of the disorder, such as fear extinction resistance and generalization of fear, are recapitulated, [95, 96]. Therefore, it is highly likely that future studies will employ these models to delve into the roles of epigenetic modifications in pathogenic memory processes. Finally, it should be noted that the development of PTSD is considered a maladaptive response to a stressful event. Exposure to stress throughout life is unavoidable; yet most individuals are resilient and do not develop PTSD [50, 103]. The interaction between vulnerable genetic factors and exposure-based epigenetic modifications that one incurs throughout life is believed to be a crucial contributor to the individual variability seen in the development of disorders such as PTSD [94]. Thus, pathogenic epigenetic modifications induced by stress in some individuals may dysregulate the mechanisms recruited for the formation, storage and/or retrieval of a subsequent, particularly salient stressful event. This could also lead to resistance of the “traumatic” memory to extinction and inappropriately sensitized behavioral responses to seemingly non-stressful stimuli.

Conclusion

Understanding the contribution of epigenetic mechanisms to how pathological memories associated with SUD and PTSD are stored, expressed and subsequently modified will have the potential to uncover novel therapeutic targets. However, the current status of the

literature highlights the need to refine the models in which these disorders are investigated. In the context of SUD, conditioned place preference studies represent a first line approach to identifying novel therapeutic targets, but the next step will be to test them in gold standard reinstatement models of self-administration. Similarly, while traditional fear conditioning paradigms have laid the ground work for epigenetic studies into pathogenic memory, the use of models that aim to include multiple components of PTSD may uncover more relevant epigenetic targets that will be critical to mitigate this relapsing disorder. Nonetheless, it will be interesting to see how the current work with rodent fear conditioning paradigms maps onto future PTSD studies. By utilizing the most appropriate tools and animal models of SUD and PTSD, future studies will allow us to gain critical insight into the therapeutic window of targets and biomarkers of pathogenic memory disorders.

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