Cognitive epigenetic priming: leveraging histone acetylation for memory amelioration
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Multiple studies have found that increasing histone acetylation by means of histone deacetylase inhibitor (HDACi) treatment can ameliorate memory and rescue cognitive impairments, but their mode of action is not fully understood. In particular, it is unclear how HDACis, applied systemically and devoid of genomic target selectivity, would specifically improve memory-related molecular processes. One theory for such specificity is called cognitive epigenetic priming (CEP), according to which HDACis promote memory by facilitating the expression of neuroplasticity-related genes that have been stimulated by learning itself. In this review, we summarize the experimental evidence in support of CEP, describe newly discovered off-target effects of HDACis and highlight similarities between drug-induced and naturally occurring CEP. Understanding the underlying mechanisms of CEP is important in light of the preclinical premise of HDACis as cognitive enhancers.

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Current Opinion in Neurobiology 2021, 67:75–84
This review comes from a themed issue on Neurobiology of learning and plasticity
Edited by Tara Keck and Sheena A Josselyn
For a complete overview see the Issue and the Editorial
Available online 26th October 2020
https://doi.org/10.1016/j.conb.2020.08.011
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Introduction
Memory formation relies both on synapse-to-synapse communication and synapse-to-nucleus signaling. While short-term memory is primarily the result of the former and independent of the latter, long-term memory depends on synaptic messages being integrated via downstream signaling cascades to induce transcription in the nucleus [1]. Transcriptional induction requires the access of the transcriptional machinery and regulatory transcription factors to the chromatin. For this, chromatin conformation must be in an ‘open’ state, which is controlled by stimulus and time-specific epigenetic mechanisms. Some epigenetic markers, such as DNA methylation, are primarily associated with closed and un-transcribed regions of the chromatin [2]. Others, like histone acetylation – the primary focus of this review – are associated with open regions and an increase in gene transcription at the affected locations.

Histone acetylation is maintained by ‘writing’ enzymes, known as histone acetyltransferases (HATs), ‘erasing’ enzymes, called histone deacetylases (HDACs), and ‘reading’ enzymes that contain bromodomains that recognize and localize to acetylated lysine residues. The ratios of ‘writer’ and ‘eraser’ activity can be artificially manipulated by treating animals with HDAC inhibitors (HDACis), leading to alterations in histone acetylation. These histone acetylation changes not only open the chromatin to be more accessible but also re-allocate the targeting of ‘readers’ such as the transcriptional co-activators, bromodomain-containing protein 4 (Brd4) and cAMP response element-binding protein (CBP) [3], thereby increasing gene transcription.

In the brain, hippocampal histone acetylation has been shown to positively correlate with contextual fear conditioning, novel object recognition, and spatial memory formation [4–7]. Conversely, disorders defined by reduced cognitive abilities, such as Alzheimer’s disease (AD) and age-related cognitive decline are associated with reduced histone acetylation in the hippocampus in both pre-clinical models and in human post-mortem brain samples [8,9,10].

Correspondingly, HDACis were found to improve performance in contextual fear conditioning and extinction learning, as well as to rescue memory impairments in neurodegenerative disorders [4,11–14,15,16–19]. Taking into account these positive effects, several HDACis are currently being tested in clinical trials to treat memory disorders in arachnophobia (NCT02789813), schizophrenia (NCT03263533), and AD (NCT03056495). Despite promising results for HDACis in the treatment of pre-clinical models of neurodegeneration and memory loss, the mechanisms by which HDAC inhibition improves memory formation are still not fully elucidated. This is important to understand as in some cases HDACis were found to exacerbate negative symptoms of neurodegenerative disorders such as aggression and agitation [20].

Cognitive epigenetic priming
‘Cognitive epigenetic priming’ (CEP) is a recently proposed theory that aims to explain how, when paired with a stimulus such as learning, HDAC inhibition ameliorates
memory formation [21]. This model is derived from the experimentally well-established concept of ‘epigenetic priming’ in development and cellular differentiation, which describes three conformationally defined chromatin states: closed states, that are tightly wound and allow limited access to underlying genes; permissive or primed states, in which pioneer transcription factors and histone modifications allow for initial relaxation of chromatin; and open states, that are easily accessible to the transcription machinery [22]. In development, this theory characterizes the coordinated epigenetic and transcriptional signals needed to transition through different states during cell lineage diversification [23] (Box 1).

Similarly, CEP defines cell states during memory formation, albeit with more flexible epigenetic modifications owing to the faster timescale required for learning. In particular, this theory focuses on histone acetylation induced by HDAC inhibition during memory formation and states that the HDACi-induced epigenetic changes sensitize memory-related genes so that they are more likely to be transcribed in response to a targeting stimulus, such as neuronal activation [21]. Indeed, most HDACi treatments are administered orally during clinical trials or interperitoneally (i.p.) in animal experiments, from which follows that they affect, in principle, histone acetylation indiscriminately between brain areas, cell types and gene loci. Accordingly, HDACis would relax the overall chromatin conformation, thus priming genes for potential activation. However, genes that are already characterized by histone acetylation, namely by learning-induced neuronal activity, would be more likely to reach the threshold necessary for transcription. In turn, this would lead to a targeted activation of plasticity-related pathways and thereby to enhanced cognition (Figure 1).

CEP was first described in extinction learning [15**], where pairing CI-994, a benzamide-type class I HDACi (Box 2), with an otherwise inefficient extinction protocol, helped to reduce long-lasting traumatic memories in mice. Importantly, the effects of HDAC inhibition were stimulus dependent, as HDACi treatment without memory recall did not ameliorate the traumatic memory. Since then, other studies have revealed similar memory-promoting effects using different HDACis in conjunction with learning, both in healthy conditions and those characterized by cognitive impairment, and have thereby helped to not only elucidate the mechanisms of action of HDACis as cognitive enhancers but also to assess the experimental evidence for CEP.

Potential mechanisms of HDAC inhibition
The molecular and physiological mechanisms underlying CEP have predominantly been studied at three levels. First, as the epigenetic changes induced by HDACis and their priming effects on the chromatin landscape; second, as the ensuing changes in gene transcription and activity; and third, as the corresponding alterations in synaptic plasticity, in particular long-term potentiation (LTP) (Figure 2).

HDAC inhibition increases histone acetylation
Combining HDAC inhibition with learning paradigms has repeatedly been found to increase histone acetylation in multiple conditions. When paired with extinction training, CI-994 (i.p.) not only improved the consolidation of extinction memories, but also increased total hippocampal H3 acetylation as revealed by immunohistochemistry (IHC) [15**]. Importantly, no histone acetylation changes were observed when the HDACi was applied without extinction training, which provides evidence for the stimulus-dependency of CEP (Figure 1b). Further studies have found that the class I HDACi, MS-275 (i.p.), also enhances the consolidation of recent fear memory extinction, and concomitantly increases total H4 acetylation in the cortex and amygdala as revealed by IHC [16]. Beyond extinction training, global histone acetylation increases were also observed, via western blot analysis, in the hippocampus of healthy animals following learning, where chronic sodium butyrate (NaB) (i.p.) administration enhanced and maintained memory for up to one month after contextual fear conditioning compared to vehicle treated animals [24].

Another intriguing application of HDAC inhibition lies in the amelioration of cognitive disorders in preclinical models of AD and age-related cognitive decline, both of which are characterized by an impairment in spatial memory and a depreciation in these task’s ability to induce histone acetylation [9,25**]. In 3xTg AD and APP/PS1 mice, two models of AD, chronic SAHA treatment (oral) rescued their memory impairments [25**], an effect that was recapitulated by the more specific HDACis RGFP-966 (i.p.) [8**] and M344 (i.p.) [26]. Furthermore, SAHA administration was found to reverse the
dominant histone hypo-acetylation (revealed by chromatin immunoprecipitation followed by sequencing, ChIP-seq) in hippocampal area CA1 of these mouse models [25**], which was also observed in western blots for RGFP-966 in HEK/APPsw cell lines [8**] and for M344 in wild-type mice [26]. Finally, SAHA (intra-hippocampal and oral administration) also improved the cognitive defects and the H4K12ac reductions in the hippocampus of aged mice [9,25**].

Notwithstanding, in order to better understand whether and to which extent genomic regions transition from a
Box 2 Class I versus pan-HDACs

There are currently 11 known HDAC proteins that are divided into 4 different subgroups based on their DNA sequence. Historically, the most commonly used HDACis inhibit several subgroups, which could lead to an increase in off-target effects and may account for some of the changes seen in tau aggregation in response to HDAC inhibition [39].

Many of the cognitive enhancements that are caused by HDAC inhibition can also be seen when individual Class I HDACs, such as HDAC2 [66] and HDAC3 [8**,18,33,67], are inhibited, suggesting that Class-I specific inhibitors are sufficient for memory enhancing effects. Future clinical trials should use more targeted HDACis in order to reduce unwanted effects.

| HDAC inhibitor | Class of inhibition | Phase of memory | Reference |
|----------------|---------------------|-----------------|-----------|
| TSA            | Pan                 | Formation, Rescue | [4,14,34,39,57]* |
| Vorinostat (SAHA) | Pan             | Formation, Rescue | [9,19,25]**,39,44,66 |
| Valproic acid   | Pan                 | Extinction, Rescue | [17,39] |
| M344 CI-994     | Class I             | Formation, Extinction, Rescue | [15**,39,68] |
| Sodium butyrate | Class I             | Formation, Reconsolidation | [4,5,11,24] |
| RGFP963 MS-275  | Class I             | Extinction, Rescue | [13,16] |
| RGFP966 HDAC3 inhibitor | Class I      | Extinction, Rescue | [8**,18] |

HDAC inhibition enhances transcription

According to the CEP hypothesis, the genes epigenetically primed by HDACi treatment will subsequently be more readily activated by the targeting stimulus, that is, learning. In the following studies, this was indeed the case. After remote fear extinction training, the IEGs showing increased promoter histone acetylation were also transcriptionally upregulated. What is more, genome-wide, learning and synaptic-related pathways were among the most upregulated ontologies, suggesting that such specific activation may have been facilitated by the HDACi treatment [1**]. Further evidence for such a targeting effect in CEP comes from a study comparing divergent transcriptional profiles in two conditions of cognitive impairment, AD and aging. While AD was found to inhibit genes involved in synaptic plasticity [8,25**,26], downregulated genes in aging were mainly involved in RNA transcription, protein modification and cellular metabolism [9,25**]. Intriguingly, in both ailments, SAHA was found to selectively rescue the mis-regulated genes [25**], likely as a consequence of HDACis having a stronger effect on genes that are already defined by hypoacetylation. The HDACi-induced global reallocation of histone acetylation likely alters transcription by redistributing the binding of acetylation ‘readers’, such as Brd4, a protein that binds regions of acetylated histones and recruits elongation factors involved in transcriptional induction [28]. In line, inhibiting Brd4 with the small-molecule inhibitor, JQ1, also ameliorated memory formation in AD-like animals [30], suggesting that memory enhancement might also be driven by the recruitment and localization of the transcriptional machinery in addition to acetylation-induced chromatin conformation changes per se.

Nevertheless, multiple studies have reported a surprisingly high number of downregulated genes as shown in RNA-sequencing experiments following HDACi-supported contextual fear conditioning and extinction training [15**,27]. The mechanisms and roles played by HDACi inhibition in this unexpected decrease in transcription are not clear, but could be the result of compensatory mechanisms regulating transcriptional homeostasis [25**], in particular since little specificity was found among the gene ontologies of the downregulated genes [27]. In line, one study showed that in human cell lines, HDACi treatment prevented histone deacetylation at gene bodies and intergenic regions, and that this indiscriminating increase in acetylation may mask other genetic elements such as promoters and enhancers for stimulus-specific histone acetylation increments [28].

In addition to reallocating the transcriptional and epigenetic machinery, HDACi treatment may also alter transcriptional profiles by ameliorating splicing defects and isoform switching induced by AD. For example, HDACi treatment was found to restate H4K12ac at mis-

primed state to an activated state during CEP, it is important to determine which specific loci are affected. Using ChIP-qPCR approaches, H3K9/14ac was found to be increased at the promoter regions of immediate early genes (IEGs) such as cFos and Npas4 after combined HDAC inhibition and extinction training [15**]. Furthermore, although H4K12ac was reduced en masse at neuronal transcriptional start sites (TSSs) in cognitively impaired animals, this reduction could be rescued by long-term oral administration of SAHA as revealed by ChIP-seq [9,25**].

In addition, several studies indicate that enhancer acetylation is relevant in CEP. Both H3K27ac and H3K9ac are associated with active enhancers, which play a critical role in transcriptional activation [27,28]. Recent work using a CRISPR-based approach, in which the dead mutant of Cas9 was fused to the HAT p300, showed that increasing acetylation in the enhancer region of cFos alone was sufficient to upregulate this IEG and its downstream targets [29]. This suggests that CEP at the level of enhancer histone acetylation could be sufficient to improve memory. Future studies of CEP will need to corroborate this and also measure changes at intergenic regions in order to determine which genes are truly in the primed state.
Mechanisms underlying HDACi-mediated cognitive epigenetic priming (CEP).

(a) To enhance memory, HDAC inhibitors (HDACis) not only alter histone acetylation (pink), but also that of other unexpected substrates (teal), which in turn alters chromatin accessibility as well as transcriptional activation and ultimately results in different gene ontologies being affected. Node size represents the number of publications since 2013 (summarized in this review) that describe the node’s role in learning and memory following HDACi-mediated CEP. Arrows represent interactions between connecting nodes. (b) Experimental evidence of the role of HDAC inhibition at different target levels [15**]. All readouts are measured 2 hours after HDACi and 1 hour after extinction training between HDACi and vehicle-treated animals. From left to right: Histone acetylation in hippocampal area CA1 measured by IHC. RT-PCR confirmation of the transcriptional expression of several neuroplasticity related genes in CA1. LTP measured at Schaffer collaterals. Quantification of synapse number taken from CA1 brain sections by transmission electron microscopy. Differences in freezing behavior between remote fear memory recall and after extinction training, indicating improved extinction memory retention.

regulated exon-intron junctions in a mouse model of neurodegeneration [25**], which coincided with the reestablishment of the proper isoform usage. The role of HDAC inhibition on isoform switching, in particular promoter usage, has not been described in healthy individuals; however, it could be relevant for genes like BDNF, for which different isoforms play distinct roles in synaptic plasticity in the hippocampus [31]. Investigating these mechanisms further could shed light on the role of HDAC inhibition in transcriptional dynamics and the downstream products that play a role in memory formation.

**HDAC inhibition facilitates synaptic plasticity**

The HDACi-mediated upregulation of transcriptional cascades that involve IEGs and synaptic transmission...
Importantly, the positive effects of HDAC inhibition on synaptic potentiation both in AD models and healthy animals were only observed after LTP induction, reinforcing the stimulus-dependency notion of CEP [4,33]. Furthermore, they relied on transcriptional activation and downstream protein synthesis [33]: Co-treating HDACis with the transcriptional inhibitor, actinomycin D [4,34], or a Brd4 inhibitor, JQ1 [35], blocked the HDACi-mediated enhancement of LTP. This could be a consequence of blocked IEG induction and subsequently, reduced activation of genes involved in synaptic plasticity [15**,25**], as for example, ion channel promoters are bound and activated by cFos and other members of the AP-1 complex [36*].

In accordance with the above, HDACis influence histone acetylation and regulate downstream changes in transcription and LTP. Even so, due to the broad functions of HDACs [37], it cannot be discounted that some of the consequences of CEP are due to non-histone acetylation.

Non-histone targets of HDACis

Although the range of action of HATs and HDACs are mostly associated with histone acetylation, these enzymes can also substantially modify non-histone proteins [38]. To illustrate this, pan-HDACis, such as TSA and SAHA, were found to increase cytoplasmic tau acetylation and aggregation, hallmarks of several neurodegenerative diseases [39]. This is surprising considering that HDACi treatment ameliorated the behavioral deficits in AD-like pathologies [8**,25**,26]. These discrepancies may be explained by the evidence that more specific HDACis, such as RGFP-966 and M344 (see Box 2), decrease levels of phosphorylated tau and the toxic form of amyloid beta in the cytoplasm, this latter likely via altering the expression of amyloid precursor protein (APP)-processing genes [8**,26]. Nevertheless, as even the pan-HDACi VPA was found to ameliorate levels of reactive oxygen species (ROS) and pro-inflammatory cytokines in post-traumatic stress disorder (PTSD) and AD-like animal models [17], it remains unclear whether using more specific HDACis represents a viable strategy to eliminate off-target, that is, non-histone acetylation-mediated effects.

What is more, even within the nucleus, HDACis can target non-histone proteins. HATs and HDACs have been found to modify acetylation on the C-terminal domain (CTD) of RNA polymerase II (RNA Pol II) in mouse embryonic stem cells (ESCs), inducing the transition from polymerase pausing to elongation, particularly at IEGs [40]. TSA impedes the deacetylation of the RNA Pol II CTD, and thus likely maintains a higher ratio of activated polymerases, which in turn reduces pausing and increases levels of transcription. This particular example illustrates that in addition to, or even bypassing the epigenome, HDAC inhibition can affect transcriptional activation. Furthermore, there is a plethora of evidence outside of the brain suggesting that HDACs can target pathways that are involved in DNA damage repair, cell division, protein folding and metabolism, processes that also play a role in learning and memory [41]. Future studies must explore whether these findings are also relevant to HDACis in the brain.

CEP beyond HDAC inhibition

Considering the experimental evidence gathered thus far, HDACi-supported CEP appears to promote memory formation by imitating epigenetic processes that occur naturally following neuronal activation. For example, histone acetylation, chromatin opening, and transcription are increased in the hippocampus within an hour after contextual learning or following electroconvulsive seizures [4,36*,42], and these epigenetic changes are further enhanced by HDACi treatments [16,24]. Likewise, extinction learning per se induces hippocampal histone acetylation, an effect that is reinforced by HDACi application [15**,43]. Therefore, it is not surprising that other external stimuli may be able to improve subsequent learning when inducing similar epigenetic changes to those elicited by HDACis. Indeed, both environmental enrichment and nicotine exposure enhance hippocampal histone acetylation, LTP, and long-term memory in response to either cocaine or contextual learning alone [44–46], and thus acts as ‘natural’ CEP stimuli. While in the case of environmental enrichment, the CEP effect was beneficial to fight cognitive decline occurring in neurodegeneration [11], priming via drugs of abuse was found to lead to greater drug dependency [46].

Beyond HDAC inhibition, histone acetylation can also be altered by increasing or decreasing levels of HAT activity. For example, activating the HAT CBP/p300 using the HAT activator CSP-TTK21, reinstated levels of H2B acetylation, rescued transcription of genes involved in ion transport and learning and restored spatial memory in a mouse model for tauopathy, THY-Tau22 [47]. Interestingly, enhancing HAT activity may have an even broader priming effect than HDAC inhibition, as HDAC activity was found to be limited only to locations that had previously been acetylated by HATs in human CD4+ T cells [48], however this has not yet been assessed in the brain.

Moreover, CEP effects may not be unique to histone acetylation alone. For example, mice that lack certain
histone methyltransferases exhibit impairments in contextual and motor learning [49], suggesting an important role for histone methylation in learning and memory. Likewise, memory formation also induces changes in DNA methylation at genes involved in synaptic transmission [42,50], while inhibition of DNA methylation via DNA methyltransferase (DNMT) inhibitors can impede memory enhancements induced by a subthreshold pre-training in Aplysia [51]. Lastly, the control of activity-dependent gene transcription and its role on downstream learning and memory may also rely on protein turnover and the incorporation of histone variants that alter chromatin conformation [52,53]. Although, these epigenetic modifications beyond histone acetylation are out of the scope of this review, these examples of non-acetylation-based CEP may provide further insight into the mechanisms of drug-induced and natural epigenetic priming and could help improve future therapies both for healthy and cognitively impaired individuals.

Discussion

There is now considerable evidence supporting the theory of CEP as a mechanism by which HDAC inhibition improves learning in a stimulus-dependent manner. However, there are still a number of details that must be elucidated. At the cellular level, some studies suggest that, in the brain, neurodegeneration and HDAC inhibition specifically alter acetylation in neurons while having no effect on non-neuronal cell types [16,25*]. Future research will also need to decipher these effects in other neuronal cell types such as astrocytes, which are crucial for proper memory formation [54], and bona fide memory-related cell populations, so-called engrams [55,56]. At the molecular level, it will be important to investigate which acetylation residues and genomic locations are most affected by each HDACi. For example, one study has used IHC to show that one hour after i.p. administration and before any conditioning, the HDACis RGFP-966 and RGFP-963 reduce total H3ac and H4ac levels in the hippocampus, whereas they increase H3ac and have no effect on H4ac in the amygdala [18]. Future experiments will need to more quantitatively determine whether HDACis can indeed penetrate brain regions differentially and whether certain HDACis have differential effects on histone marks within and between brain regions.

In addition, the sequence of molecular events taking place in response to combined HDAC inhibition and learning must be better determined. It is clear that both HDACis and learning first alter histone acetylation. However, it is less evident whether this in turn alters chromatin conformation to permit transcription factor localization and activation or whether acetylation-induced transcription precedes changes in chromatin conformation. Although this has not yet been tested in the brain, one study showed that HDAC inhibition alone can induce changes in histone acetylation and transcription that precede moderate changes in chromatin accessibility in Drosophila S2 cell lines [57*]. Nevertheless, given the well-established interplay between acetylation and chromatin conformation the more likely scenario is that changes in chromatin conformation precede transcriptional changes [21,58]. This also fits with the recently proposed theory of ‘genomic metaplasticity’, in which activity-induced changes in epigenetic marks prime genetic locations for the transcriptional activity induced by later neuronal activation [59]. After contextual fear conditioning, many of the newly accessible regions overlap with enhancers and promoters of IEGs and channel proteins involved in synaptic signaling. While transcription of these genes usually endures for less than 24 hours [36*,60*], a subset of neuronal activity-induced opened chromatin sites, so-called gained open sites, were found to be maintained for at least 48 hours. These gained-open regions overlapped with the AP-1-binding motif, and were enriched for binding of members of the AP-1-binding transcription factors, such as cFos, FosB, and Jun [36*,60*]. Consequently, cFos overexpression was partially able to mimic the neuronal activity-induced natural chromatin opening, and genes upregulated by cFos-induced chromatin opening were similar to those induced by neuronal activation [36*]. In turn, such long-term maintenance of opened regions and chromatin binding may act to prime their underlying architecture for facilitated transcriptional reactivation in response to a recall event, thus facilitating memory retention, but this remains to be experimentally determined. In future studies, it is, therefore, important to disentangle these processes in learning and memory in order to clearly separate ‘primed’ and ‘active’ locations and their role in consolidation.

Finally, despite isolated reports of HDACis’ inability to penetrate the blood brain barrier in vivo [61] and some reported toxicity in clinical trials [62], preclinical research agrees that HDAC inhibition alters neuronal acetylation in vivo, which leads to memory enhancements in both healthy and cognitively impaired conditions. These improvements are likely not only due to CEP, but also to its combined interaction with the acetylation of other proteins that enhance transcription. Future studies that further elucidate our understanding of these mechanisms will help us understand how we learn and how we can harness those mechanisms to improve our own memory.

Conflict of interest statement

Nothing declared.

Note added in proof

During the proofreading of this review, an important article appeared illustrating that natural learning indeed induces a primed state epigenome-widely in engram cells, but that recall further channels this primed state
into an effector state via, among others, specific enhancer-promoter interactions [70].

Acknowledgements

Work in the laboratory of J.G. is supported by the Swiss National Science Foundation, the National Competence Center for Research ‘Synapsy’, the Vallee Foundation, and the ERC.

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