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Regulation of Chromatin Structure in Memory Formation

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Summary

This brief review focuses on the role of epigenetic mechanisms in plasticity and memory formation, and their identification as targets of activity-dependent regulation in neurons. Epigenetic modifications of chromatin, namely post-translational modifications of nuclear proteins and covalent modification of DNA, result in potent regulation of gene readout. Recent data have demonstrated that epigenetic mechanisms play a significant role in regulating synaptic plasticity and memory. In this review, we focus on this theme, describing some basic background concerning epigenetic molecular mechanisms, and describing recent results concerning plasticity and memory formation. As an understanding of these novel mechanisms of transcriptional regulation promises to invigorate many areas of investigation, we end by speculating upon some of the open questions ripe for discovery.

Keywords

memory; hippocampus; demethylation; histone; HDAC; DNA methylation; epigenetic; gene transcription; fear conditioning

Introduction – An Epigenetic Code for Memory?

Recent studies have demonstrated that nuclear targets of neuronal signaling pathways, in particular the histone proteins and DNA that comprise the core chromatin particle, are also an integral component of memory processes [reviewed in [1-3]]. We and others have proposed that an *epigenetic code* might be involved in memory formation, whereby specific patterns of post-translational histone modifications and DNA methylation might help encode the salience of cell-surface signals and their contingencies [[4-5]]. This general hypothesis of an epigenetic code for memory is new and rather speculative, and stems from an earlier idea of a *histone code* proposed by Allis and colleagues [[6]].

A better understanding of the epigenetic code concept as it might apply to memory requires an appreciation of the basic biochemistry regulating chromatin structure. Here we define *epigenetics* as the covalent modification of chromatin that influences activity-dependent changes in gene expression necessary for cognition. These changes can be short-term and transient, or likely long-term and thus capable of perpetuating lasting changes in gene activity

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states. In this vein, there are two basic *molecular* epigenetic mechanisms that are currently studied – post-translational histone modifications and DNA methylation. For background, we will briefly review these mechanisms in the next two sections (see [1, 2] for a more detailed recent treatment).

Epigenetic histone marks

Histones are highly basic proteins that organize DNA within the nucleus. The interaction between histones, which form the core of the chromatin particle, and DNA, is mediated in part by the *N-terminal tail* of histone proteins. One can imagine chromatin as a core of eight histone proteins (histones 2A, 2B, 3, and 4, with two copies of each molecule) with DNA wrapped around similar to twine on a spool. Structural studies indicate the N-terminal tails of histones protrude beyond the DNA and are available for post-translational modifications [7] (Figure 1A-B).

Several sites for modifications exist within the N-terminal tails of histone proteins, and covalent chemical modification of these sites, namely *acetylation*, *phosphorylation*, *methylation*, *ubiquitination* and *sumoylation*, regulates the overall structure of chromatin [8]. These modifications, along with methylation of cytosine residues in DNA are the principal "epigenetic tags" impacting genome readout. As it has been best-characterized in the context of memory formation, we will focus this discussion on histone acetylation.

Acetylation of histones occurs at lysine residues, specifically on their side-chain amino group, effectively neutralizing their positive charge, decreasing the affinity between the protein tail and DNA, and thus relaxing the chromatin structure and allowing the recruitment of transcriptional machinery. Acetylated histone tails also provide a platform for the binding of additional co-activators with domains that recognize acetylated lysines. *Histone acetyltransferases* (*HAT*s) catalyze the direct transfer of an acetyl group from acetyl-CoA to the ε-NH^+ group of the lysine residues within a histone [9]. Histone acetylation is generally associated with transcriptional activation and is widely regarded as one of the epigenetic marks associated with active chromatin (*euchromatin*). CREB Binding Protein (CBP) is one known HAT regulating local chromatin structure as part of CREB-dependent activation of gene transcription in memory [10-13, 14•].

Histone acetylation is a reversible process, and the enzymes that catalyze the reversal of histone acetylation are known as *histone deacetylases* (HDACs). There are a total of eleven different *classical* HDAC isoforms, most of which are expressed in the CNS (Table 1). HDAC inhibitors are the principal way to manipulate the epigenome pharmacologically, and hold promise for therapeutic value [15-18]. Trichostatin A, sodium butyrate, valproic acid, and Suberoylanilide Hydroxamic Acid (SAHA) are commercially available HDAC inhibitors, each having varying degrees of selectivity for the classical HDAC isoforms (Table 1). Isoform-selective HDAC inhibitors are under development but are not yet broadly available. Finally, we should note that the SIR2 family of HDACs (the "*Sirtuins*") is another major category of HDAC, which operate by a completely different catalytic mechanism than the classical HDAC isoforms [19].

Covalent modification of DNA – cytosine methylation

The second major mechanism whereby the genome can be epigenetically marked is DNA methylation (see [20, 21] for a more detailed treatment of this mechanism). Methylation of DNA is a *direct chemical modification* of a cytosine side-chain that adds a -CH_3 group through a covalent bond (Figure 1C). Methylation of DNA is catalyzed by a class of enzymes known as *DNA methyltransferases* (*DNMT*s) [20, 21]. DNMTs transfer methyl groups to cytosine residues, specifically at the 5-position of the pyrimidine ring [20, 21]. Not all cytosines can be methylated; cytosines must be immediately followed by a guanine to be methylated [20, 21].

These *CpG* dinucleotide sequences are highly underrepresented in the genome, and often occur in small clusters known as *CpG islands* [20, 21].

There are two variants of DNMTs: *maintenance* DNMTs and *de novo* DNMTs [20, 21]. De novo DNMTs (DNMT3a and DNMT3b) methylate previously unmethylated CpG sites in DNA – sites which have no methyl-cytosine on either DNA strand. The maintenance DNMT isoform (DNMT1, though it appears to regulate *de novo* methylation in some cases) methylates *hemi-methylated DNA* – DNA which has a methylated CpG already present on one strand but no methyl-cytosine on the complementary strand. Maintenance DNMTs perpetuate methylation marks after cell division, regenerating the methyl-cytosine marks on the newly synthesized complementary DNA strand that arises from DNA replication.

DNA methylation, with its stable nature, offers an ideal substrate for the long-term cellular changes necessary for the maintenance and persistence of memory. However, DNA methylation would also have to be an active and reversible process to enable neurons to respond to physiological and environmental stimuli. To date, DNA demethylation has been viewed largely as a passive process in differentiated cells, whereby multiple rounds of cell division without DNMT-mediated remethylation is necessary to erase epigenetic marks. The idea of whether there is active DNA demethylation in post-mitotic cells, such as neurons, is controversial in the field, mainly due to the fact that the identity of a demethylase that can actively remove methyl groups remains elusive. But there is increasing evidence to suggest that there is active methylation and demethylation in mature cells [22, 23•, 24, 25••, 26•, 27]. The DNA methyltransferases DNMT3a and DNMT3b appear to have a hand in this process [23•, 26•], though recent work suggests that Gadd45b may also have a role by promoting active DNA demethylation through nucleotide-excision repair [25••].

The predominant view in the literature is that methylation of DNA is associated with *suppression of gene transcription*, and in many cases extensive DNA methylation triggers complete silencing of the associated gene. The precise molecular processes through which this occurs are complex, but in essence, methylation of cytosines at CpG dinucleotides recruits methyl-DNA binding proteins, at specific sites in the genome [20, 21]. Proteins binding to methylated DNA have both a *methyl-DNA binding domain* (*MBD*) and a *transcription-regulatory domain* (*TRD*). The TRD recruits adapter/scaffolding proteins, which in turn recruit HDACs to the site. The HDACs alter chromatin structure locally through removing acetyl groups from histone core proteins, leading to compaction of chromatin and transcriptional suppression. Thus, methylation of DNA triggers localized regulation of the three-dimensional structure of DNA and its associated histone proteins, resulting in a higher-affinity interaction between DNA and the histone core, and transcriptional repression by allosteric means. It is important to note that while DNA methylation is usually (and historically) associated with transcriptional suppression, recent studies have indicated that DNA methylation can also be associated with transcriptional activation [28•, 29].

Epigenetic marking of histones in memory

A diverse series of studies have demonstrated memory formation is associated with epigenetic marking of the genome. For example, contextual fear memory formation in rodents is associated with acetylation of hippocampal histone H3 [4, 30, 31••]. This epigenetic marking requires NMDA-receptor-dependent synaptic transmission and the ERK/MAPK signaling cascade in the hippocampus, as does the fear conditioning memory itself [31••, 32]. This is one specific example demonstrating epigenetic tagging of the genome during consolidation of hippocampus-dependent memory.

Considering the previous statement, one would predict disruption of HAT activity would interfere with long-term memory formation. As previously mentioned, CREB Binding Protein

(CBP) is a HAT, and several studies have investigated long-term memory formation in genetically manipulated mice with impaired CBP function and have demonstrated that CBP/HAT-deficient mice have both L-LTP and long-term memory deficits [10, 11, 13, 33].

Thus, histone acetylation is regulated in long-term memory, and disruption of HAT activity impairs long-term memory. Together, these observations suggest that perturbations in the processes regulating chromatin structure can influence long-term memory formation in the behaving animal *in vivo*. Then, can augmentation of histone acetylation *enhance* memory formation? Several studies have investigated the effect of HDAC inhibitors on long-term memory formation, and found that indeed HDAC inhibition improves memory formation (4, 10, 14•, 30, 34, 35••).

Overall, there is extensive and varied data demonstrating that histone acetylation is regulated during memory consolidation, and this regulation contributes to an animal's capacity to form memories.

DNA Methylation in Memory

Studies have also begun to investigate the capacity of DNA methylation to regulate synaptic plasticity and memory in adult animals [31••, 36, 37•, 38, 39••]. Inhibitors of DNMTs alter DNA methylation in adult CNS tissue and block hippocampal Long-term Potentiation (LTP) [36, 37•, 38]. DNMT inhibition blocks hippocampus-dependent memory formation in a contextual fear conditioning paradigm [31••, 39••]. Data also demonstrate fear conditioning is associated with rapid methylation and transcriptional silencing of the memory suppressor gene *Protein Phosphatase 1* (PP1), while demethylation and transcriptional activation of the synaptic plasticity gene *reelin* [39••]. Finally, DNA methylation controls site-specific initiation of *bdnf* gene transcription during memory formation [31••]. These findings have the surprising implication that both DNA methylation and demethylation are involved in long-term memory.

It is important to briefly point out here that much of what we know regarding the role of DNA methylation in synaptic physiology and memory is from pharmacological studies using drugs whose mechanisms we do not fully understand. Because both 5-aza-C and zebularine are nucleoside analogs that need to be incorporated into DNA to trap DNMT and block DNA methylation, the mechanism of how these drugs are able to alter methylation in post-mitotic neurons is not clear. They may do so by actively demethylating DNA in non-dividing cells through a replication-independent event, such as a DNA repair process, but this has not been tested. There is only one behavior study to-date that has used a non-nucleoside compound (RG108) to directly inhibit DNMT enzyme activity, and importantly, results indicated that RG108 had similar effects on memory as that of zebularine [31••].

Overall, results suggest that DNA methylation is dynamically regulated in the adult nervous system and this cellular mechanism is a crucial step in memory formation. Importantly, these studies implicating a role for altered DNA methylation in memory suggest an expansion of the original *histone code* concept into a broader *epigenetic code* concept, wherein a variety of marks associated with chromatin regulation may contribute combinatorial readout and control of memory formation.

Summary and Speculations

Thus far we have presented an emerging new view of the epigenome and its role in regulating memory formation. Indeed, this is a rapidly expanding area in neurobiology and studies are being published at a rapid pace demonstrating that epigenetic mechanisms are involved in mediating diverse experience-driven changes in the CNS. The effects of such changes are manifest at the molecular, cellular, circuit, and behavioral levels. These diverse observations

support the view that the epigenome resides at the interface of the environment and the genome. Future studies geared toward understanding the role of the epigenome in experience-dependent behavioral modification will clearly be important for, and relevant to the memory field.

We would like to conclude by mentioning what we feel to be a few interesting open questions and implications raised by the emerging role of epigenetic mechanisms in memory formation.

As we have described, epigenetic molecular mechanisms are emerging as an important component of gene regulation in memory. This role in memory reprises their role as cellular information storage devices in development, and suggests an important conservation of function as molecular information storage devices. One idea we find intriguing is that utilization of epigenetic mechanisms for information storage may represent a unifying model in biology, with epigenetic mechanisms being utilized for cellular memory at levels from cellular differentiation to development to behavioral memory. However, it is important to keep in mind the only data currently available investigated the hypothesis that there are changes in epigenetic markings in response to stimuli that *induce* changes in cellular physiology or behavior (i.e. learning). The question of whether these epigenetic changes contribute to the maintenance and persistence of memory is still by-and-large open. The best evidence for such an idea comes from studies demonstrating that epigenetic changes contribute to the persisting effects, or "memory", of early-life experiences [40-42, 43••, 44].

Another compelling question concerns how epigenetically driven changes in gene expression are manifest as changes in function at the synapse and elsewhere in the neuron, and on a much broader scale, across neural systems. This is completely unknown at present. However, a central organizing concept of physiological psychology, at least regarding behavioral change, is the principle of Hebbian synaptic plasticity as the central mechanism underlying behavioral modification. Recent work implicating epigenetic mechanisms in memory may necessitate a re-thinking of this fundamental assumption. A single adult neuron can have 10,000 synapses, but has only one nucleus. Within the nucleus there are only one or two copies of a given specific gene. Chemical modification of DNA through DNA methylation implies a state change for the entire neuron. Chemically modifying and completely silencing or activating a given gene must alter the genomic complement of the entire cell. If chemical modification of genes underlies behavioral plasticity, this may necessitate a reevaluation of the fundamental assumption that synaptic plasticity is the locus driving behavioral modification. At a minimum there would be two levels of mechanism in play – one residing at the individual synapse and one residing at the epigenome and operating cell- or system-wide (Figure 2). This iconoclastic concept might require a fundamental re-assessment of the role of synapse specificity in behavioral change.

An additional thought is that epigenetics has emerged largely out of developmental biology and one of its central tenets has been that DNA methylation is immutable once laid down during cell fate determination. Recent studies have proposed DNA chemical modification is in fact plastic in non-dividing, terminally differentiated neurons. This idea being true will require a redefinition of several of the fundamental tenets of epigenetics, introducing both the idea of plasticity of DNA methylation and that epigenetic mechanisms are functionally active in terminally differentiated, non-dividing cells.

Most studies to date investigating epigenetic mechanisms in memory have utilized a target-gene approach to assessing changes at specific candidate gene loci. As an expansion beyond the target-gene approach, in the future the principal alternative is likely to be to utilize whole-epigenome approaches. These are still in development, but are likely to come online during the next few years. The capacity to use whole-epigenome high-throughput sequencing, or to use methods such as ChIPseq [45, 46] that allow comprehensive assessment of chromatin

modifications across the genome, will allow investigators to identify the fraction of the genome subject to experience-driven epigenetic plasticity in the adult CNS.

Finally, we feel that there are several important missing pieces concerning the idea of a histone code in memory. While histone acetylation and phosphorylation have been more extensively examined in memory, one important missing piece is the role of *histone methylation* in memory. For many years the prevailing model was histone methylation was irreversible [for a review see [47]]. However, histone methylation changes clearly are associated with changes in gene transcription and cognitive dysfunction [[48, 49]]. Furthermore, histone demethylases have been recently discovered and active regulation of histone demethylation is known to occur [[48, 50]]. The idea of changes in histone methylation, and sumoylation for that matter, involved in memory formation as part of a "histone code" is an open question, and evaluating this idea will test one of the critical predictions of the histone code hypothesis. On a related note, it will be important to resolve whether histone-modifying enzymes have any nonhistone functions.

In conclusion, the idea that there could be an *epigenetic code* operating to subserve behavioral change in the context of memory formation is beginning to gain traction. Indeed, the most recent discoveries indicate that chemical modification of DNA is also a component of the epigenetic molecular mechanisms supporting *behavioral change broadly defined*. While it is certainly not possible to test this epigenetic code concept thoroughly in the course of one or a few single experiments, this intriguing theory is motivating the interest of an increasing number of investigators.

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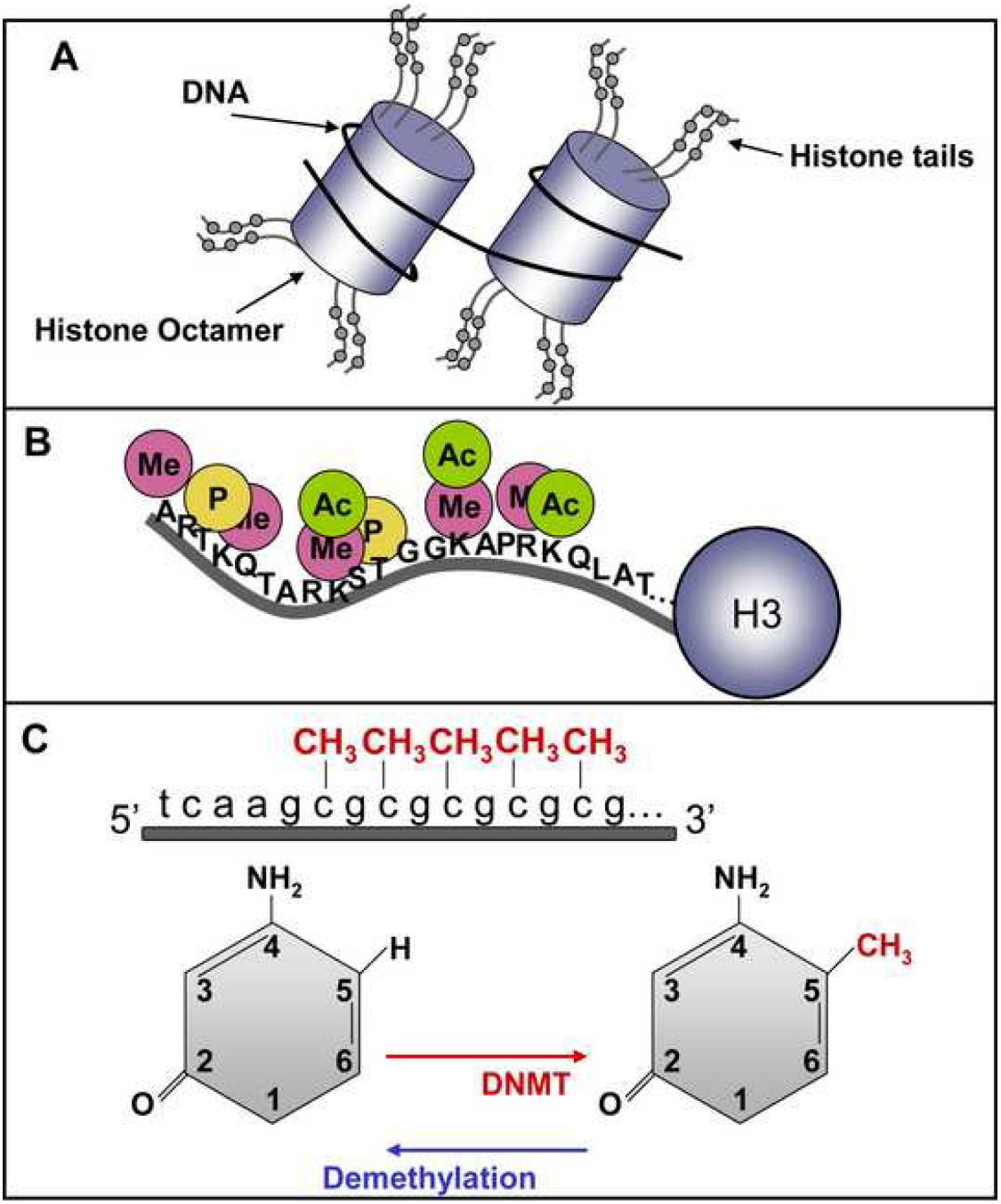

Figure 1.

Schematic of epigenetic marks. **A)** In the nucleus, DNA is compressed through interactions with histones, and this DNA-protein complex is referred to as chromatin. Two copies each of histones H2A, H2B, H3 and H4 assemble, forming a histone octamer, around which DNA wraps and condenses. The DNA-histone interaction occurs at the N-terminal tail of a histone **(B)**, where for example on the H3 N-terminal tail there are many sites for epigenetic marking via acetylation (Ac), methylation (Me), and phosphorylation (P). **(C)** Top - Overview of DNA methylation, where methyl groups are added to cytosine-guanine dinucleotides in an around gene regulatory regions. Bottom - DNA methylation is catalyzed by a class of enzymes known as DNA methyltransferases (DNMTs), which transfer methyl groups to the 5-position of the

pyrimidine ring. DNA methylation is also a reversible process, and recent work suggests that one mechanism for active demethylation is through a DNA repair-like process.

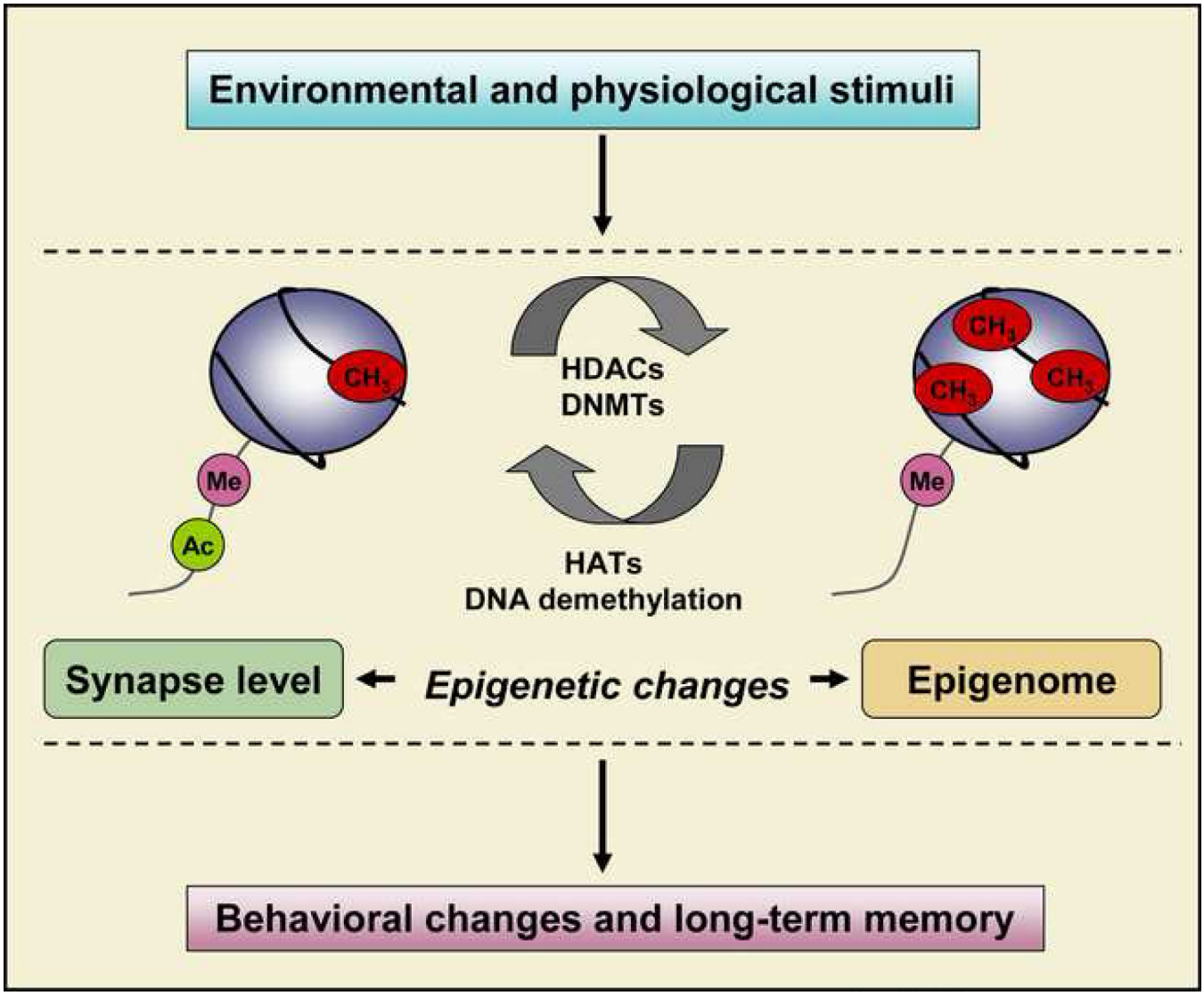

Figure 2.

Epigenetic mechanisms provide a substrate for the long-term changes in gene patterns underlying behavior. Physiological cues and environmentally-relevant stimuli modulate the activity of chromatin modifying enzymes, such as histone acetyltransferases (HATs), histone deacetylases (HDACs), and DNA methyltransferases (DNMTs) that in turn modify the histone tails and methylation of CpG dinucleotides. Such changes then affect neuronal gene transcription at the synapse level to that of the epigenome and neural systems levels.

Table 1

Classical HDAC isoforms and their targeted HDAC inhibitors.

Classes	HDAC Isoforms	Inhibitors
Class I	HDACs 1, 2, 3, 8	Trichostatin A, Sodium Butyrate, Valproic Acid, SAHA
Class II	HDACs 4, 5, 6, 7, 9, 10	Trichostatin A, Sodium Butyrate, SAHA
Class IV	HDAC 11	SAHA