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Epigenetic mechanisms: a common theme in vertebrate and invertebrate memory formation

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Abstract. In this review we address the idea that conservation of epigenetic mechanisms for information storage represents a unifying model in biology, with epigenetic mechanisms being utilized for cellular memory at levels from behavioral memory to development to cellular differentiation. Epigenetic mechanisms typically involve alterations in chromatin structure, which in turn regulate gene expression. An emerging idea is that the regulation of chromatin structure through histone acetylation and DNA methylation may mediate long-lasting behavioral change in the context of learning and memory. We find this idea fascinating because similar mechanisms are used for triggering and storing long-term 'memory' at the cellular level, for example when cells differentiate. An additional intriguing aspect of the hypothesis of a role for epigenetic mechanisms in information storage is that lifelong behavioral memory storage may involve lasting changes in the physical, three-dimensional structure of DNA itself.

Keywords. Chromatin, learning, memory, transcription, histone, *Aplysia*, LTP, hippocampus.

Introduction

The first modern revolution in the way neuroscientists approached the phenomenon of memory formation came when Eric Kandel proposed that the molecules and mechanisms used to form simple memories in model systems were also used to form complex memories in higher organisms, including humans [1]. Research over the last 3 decades has shown that this hypothesis was correct [2]. Kandel's hypothesis derives a great deal of power from the assertion that if the molecular processes governing memory formation in simple systems are also used in more complex systems, then formation of memory is an ancient and evolutionarily conserved phenomenon. Thus, one corollary of Kandel's original hypothesis could be that formation of long-term memory in general uses many evolutionarily conserved mechanisms.

An emerging theme in modern neuroscience is that many of the signaling pathways and molecules used by the nervous system for processes such as synaptic plasticity, synaptogenesis, formation of memory and even cognition have been co-opted from other, unrelated processes. One example of this is the immune system, where several studies indicate that molecules such as the class I major histocompatibility complex proteins and the NF-κB family of transcription factors are used by the nervous system for induction of synaptic plasticity, synaptic pruning and formation of long-term memory [3–11]. Likewise, several studies indicate that the signaling pathways and molecular mechanisms involved in early development, such as the ras-MEK-ERK MAPK signaling pathway, have also been co-opted to subserve processes involved in plasticity and memory formation [12–18].

Recently, several laboratories have independently discovered that an evolutionarily conserved process thought to be reserved for development, epigenetic tagging of the genome, has been co-opted by the nervous system for use in induction of synaptic plasticity and long-term memory formation. Classically, the term 'epigenetics' refers to a set of heritable and self-perpetuating modifications to DNA and chromatin (for review, see [19]). These modifications take the form of either methylation of DNA or modifications to histones, including acetylation, phosphorylation, methylation and ubiquitylation. Epigenetic

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marking of the genome in metazoans is associated with the developmental processes of determination and differentiation whereby totipotent stem cells are induced to become a terminally differentiated tissue. Epigenetic marking of the genome occurs during this period in development, restricting nonessential genes from being expressed and promoting expression of genes vital for the survival and function of the particular tissue. Thus, epigenetic marking of the genome can be considered a persistent form of cellular memory, whereby terminally differentiated cells remember their phenotype. We propose that the nervous system has co-opted this ancient form of cellular memory to subserve induction of synaptic plasticity, formation of memory and cognition in general.

Epigenetics in the nervous system

In the context of development, epigenetics refers to a set of modifications to chromatin that are static. When a cell differentiates, the genome is marked and these epigenetic tags are carefully preserved. Thus, once an epigenetic cellular memory is formed, it is unchanged. However, the nervous system is dynamic, constantly processing and storing information. If epigenetics is utilized by the nervous system for information processing and storage, then it too must be dynamic. Therefore, in our discussion of epigenetics, we will be specifically referring to modifications of chromatin that are dynamic in nature (see Fig. 1). Moreover, we propose that every form of epigenetic mark, from DNA methylation to histone acetylation, is dynamically regulated in the nervous system.

In the present review, we will focus solely on evidence for involvement of dynamic changes in the epigenetic state of chromatin in the nervous system in response to induction of plasticity and formation of memory. We have recently published a review of epigenetics in the nervous system that provides a thorough introduction to topic, and suggest it to readers unfamiliar with epigenetics as it relates to the nervous system (see [19]).

Epigenetics in memory formation

Formation of long-term memory requires an intricate regulatory network of signal transduction, transcription and translation. A great deal is known about the processes of induction and expression of memory, but little is known about how memories can persist in the face of constant molecular turnover. How does a childhood memory survive in a nervous system that is ‘renewed’ about every 2 months? One constant in every neuron is the genome. While minor changes occur to DNA strands in a neuron as a consequence of DNA repair, the genome itself does not undergo continuous breakdown and resynthesis. Therefore, chromatin represents a relatively

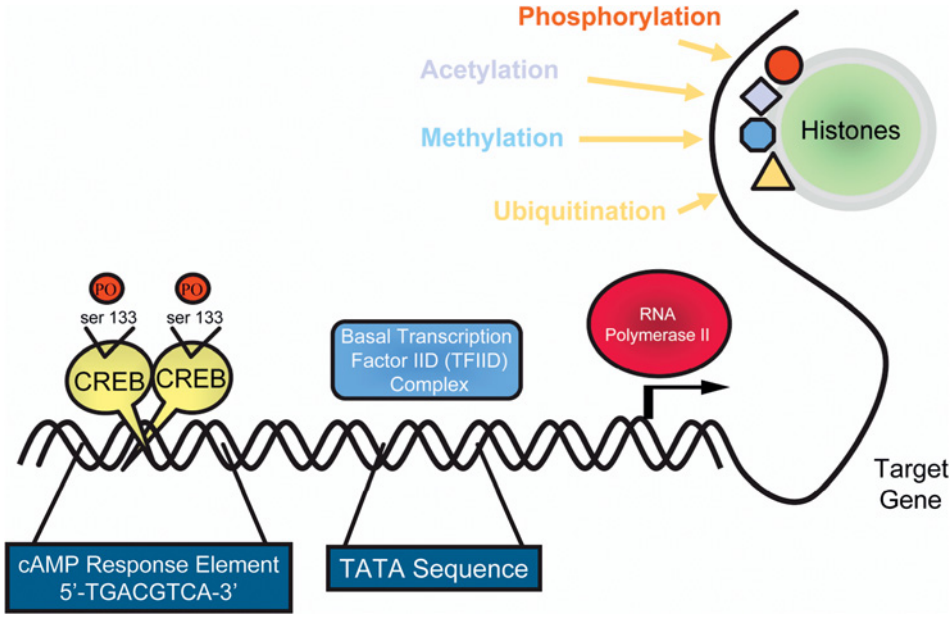

Figure 1. Multiple mechanism of transcriptional regulation in neurons. In contrast to the prototypical mechanism for altering gene expression, regulation of transcription factor activation, new studies in the area of epigenetics have highlighted the importance of post-translational modifications of histones as an important mechanism for controlling gene expression. These mechanisms of chromatin modification, including histone acetylation, methylation, ubiquitination and phosphorylation, constitute an additional robust site of regulating transcription. Thus, an emerging new view is that regulation of gene expression is a multi-level process involving both transcription factors and chromatin structure.

stable substrate upon which to encode persistent changes in cellular state.

Epigenetic marking of the genome during development represents the ultimate example of long-term memory storage in metazoans. Once differentiated, cells do not forget their phenotype. Therefore, if neurons in general and formation of memory specifically utilize evolutionarily conserved pathways, then it is possible that epigenetic marking of the genome has been co-opted by the nervous system to subserve long-term memory formation. Initial studies of the role of epigenetics in memory formation used the marine mollusk *Aplysia* [20]. Exposing animals to a treatment known to induce long-term sensitization, a simple form of nonassociative memory resulting in enhancement of defensive reflexes, increased histone acetylation associated with the ApC/EBP gene [20]. In a mammalian system using contextual fear conditioning, a learning paradigm whereby an animal learns to associate a novel context with an aversive stimulus [21, 22], Levenson et al. [23] observed significant increases in acetylation of histone H3, but not H4, after training. Formation of long-term contextual fear memory, like most long-term memories in general, requires N-methyl-D-aspartate receptor (NMDA-R)-dependent synaptic transmission and the MEK-ERK MAPK signaling cascade in the hippocampus [15, 24, 25]. Likewise, inhibition of either NMDA-Rs or MEK blocks the fear conditioning-dependent increase in acetylation of H3 [23]. These observations were the first to indicate that epigenetic marking of the genome in the form of histone acetylation occurs during consolidation of long-term memory in the hippocampus.

Acetylation of histones is an enzymatic process that is governed by histone acetyltransferases (HATs) and histone deacetylases (HDACs). At least some forms of long-term memory are associated with changes in histone acetylation. Therefore, manipulations of the enzymes governing histone acetylation could influence formation of long-term memory. Early studies focused on the role that one HAT, CREB-binding protein (CBP), played in formation of long-term memory. CBP is a transcriptional coactivator [26]. Mice heterozygous for a dominant negative form of truncated CBP ($CBP^{+/-}_{DN}$) [27] have significant deficits in step-through passive avoidance, novel object recognition and cued fear conditioning [27, 28]. Unfortunately, CREB and CBP play major roles in development [29, 30]. Not surprisingly, $CBP^{+/-}_{DN}$ mice have several developmental abnormalities, making straightforward interpretation of memory formation in these animals difficult [27].

To avoid the effects of CBP on development, three laboratories independently developed CBP-deficient mice that lack the problems of the classic $CBP^{+/-}_{DN}$ animals. The laboratory of Mark Mayford [31] coupled expression of a CBP_{DN} allele to an inducible promoter ($CBP^{+/-}_{I\text{-}DN}$). The laboratory of Eric Kandel [32] generated mice where one allele of CBP was knocked out ($CBP^{+/-}$). Finally, Ted Abel's laboratory [33] constructed a transgene where expression of a truncated form of CBP was coupled to the CaMKIIα promoter (CBPΔ1), restricting expression of the dominant negative form of CBP to forebrain neurons. All of the newly developed CBP mouse models exhibit significant deficits in the spatial watermaze task and contextual fear conditioning [31–33]. Both $CBP^{+/-}_{I\text{-}DN}$ and $CBP^{+/-}$ mice also exhibited deficits in novel object recognition [31, 32]. Considered together, all of these results suggest that impairment of CBP function has serious consequences for formation of long-term memory in the hippocampus, and further support the hypothesis that regulation of the epigenome is an important component to memory formation in mammals.

All of the studies discussed thus far have investigated the role of epigenetic marking of the genome in an early and acute phase of memory formation. A recent study published from the Meaney laboratory [34] suggests that DNA methylation patterns of specific genes in the brain are used to remember early childhood experiences. Mother rats exhibit strong nurturing behaviors toward their pups, most notably in the form of licking and grooming their offspring. Patterns of DNA methylation in the glucocorticoid receptor gene are directly correlated with the quality of maternal care, and these patterns of DNA methylation persist into adulthood [34]. Moreover, these changes in DNA methylation patterns result in decreased anxiety and a strong maternal nurturing instinct in the adult offspring [34]. Therefore, alterations in DNA methylation result in 'learned' and persistent change in adult behavior. Moreover, persistence of neonatally acquired patterns of DNA methylation in the mature central nervous system (CNS) is consistent with our hypothesis that epigenetic mechanisms contribute to persistent changes in neural function. Interestingly, this study suggests a unique mechanism whereby the status of at least one component of the epigenome is transmitted across generations using the basic mechanisms in place for information storage in the nervous system.

Epigenetics in synaptic plasticity

Synaptic plasticity refers to a process whereby synapses can undergo activity-dependent changes in their strength. Interestingly, the mechanisms responsible for induction of synaptic plasticity are very similar to those involved in the formation of long-term memory [35–37]. Thus, long-term forms of synaptic plasticity, such as long-term memory, require transcription and translation. Moreover, there is growing evidence *in vivo* that synaptic plasticity occurs during acquisition of memory [38–40]. Therefore, induction of synaptic plasticity might in-

volve epigenetic mechanisms such as those involved in long-term memory.

Initial studies of the role epigenetics might play in synaptic plasticity utilized the sensorimotor synapse of the marine mollusk *Aplysia californica*. The sensorimotor synapse displays at least two forms of plasticity. Application of serotonin (5-HT) to the sensorimotor synapse results in induction of long-term facilitation (LTF), a persistent form of plasticity that results in enhancement of synaptic transmission [41]. Conversely, exposure to the neuropeptide FMRFamide results in long-term depression (LTD), which is a lasting decrease in synaptic transmission [42]. Using these neuromodulatory substances, Guan et al. discovered that acetylation of histone H4 around the promoter of the immediate early gene ApC/EBP [43] was transiently increased by 5-HT, and transiently decreased after exposure to FMRFamide [20]. Thus, two opposing forms of plasticity in *Aplysia*, LTF and LTD, induced opposing changes in the epigenome, suggesting that the epigenome of *Aplysia* could be used as a molecular read-out of the functional state of neurons.

Several studies indicate that regulation of the epigenome occurs during induction of synaptic plasticity in mammalian systems. Long-term potentiation (LTP) is a form of synaptic plasticity whereby synaptic strength is enhanced in response to high-frequency synaptic activity. First discovered by Bliss and colleagues [44], induction of LTP requires the activation of NMDA-Rs and engagement of the MEK-ERK MAPK signaling cascade [13, 45, 46]. Direct activation of NMDA-Rs in the hippocampus resulted in an ERK-dependent increase in acetylation of histone H3 [23]. Additionally, phosphorylation of histone H3 is increased in response to activation of various neurotransmitter pathways in the hippocampus, including dopaminergic, cholinergic and glutamatergic [47]. Thus, induction of synaptic plasticity in the mammalian hippocampus leads to ERK-dependent increases in histone acetylation and phosphorylation (see Fig. 2).

Regulation of the epigenome occurs in response to induction of synaptic plasticity in the hippocampus. Several recent studies have investigated whether changes in the epigenome could affect the induction of synaptic plasticity. In *Aplysia*, elevation of basal levels of histone acetylation with the HDAC inhibitor trichostatin A transforms short-term facilitation, which does not require transcription for its induction, into LTF [20]. Induction of late-phase LTP, which requires transcription, was significantly impaired in $CBP^{+/-}$ animals [32]. Treatment of hippocampal slices from $CBP^{+/-}$ animals with the HDAC inhibitor suberoylanilide hydroxamic acid significantly improved L-LTP induction [32]. In other studies using hippocampal slices, induction of LTP using high-frequency stimulation was significantly enhanced by two HDAC inhibitors, trichostatin A and sodium butyrate [23]. In addition, LTP in the amygdala that was induced by forskolin was also enhanced by the HDAC inhibitor trichostatin A [48]. These studies indicate that the epigenetic state of the genome, from invertebrates to mammals, affects the induction of long-term forms of mammalian synaptic plasticity.

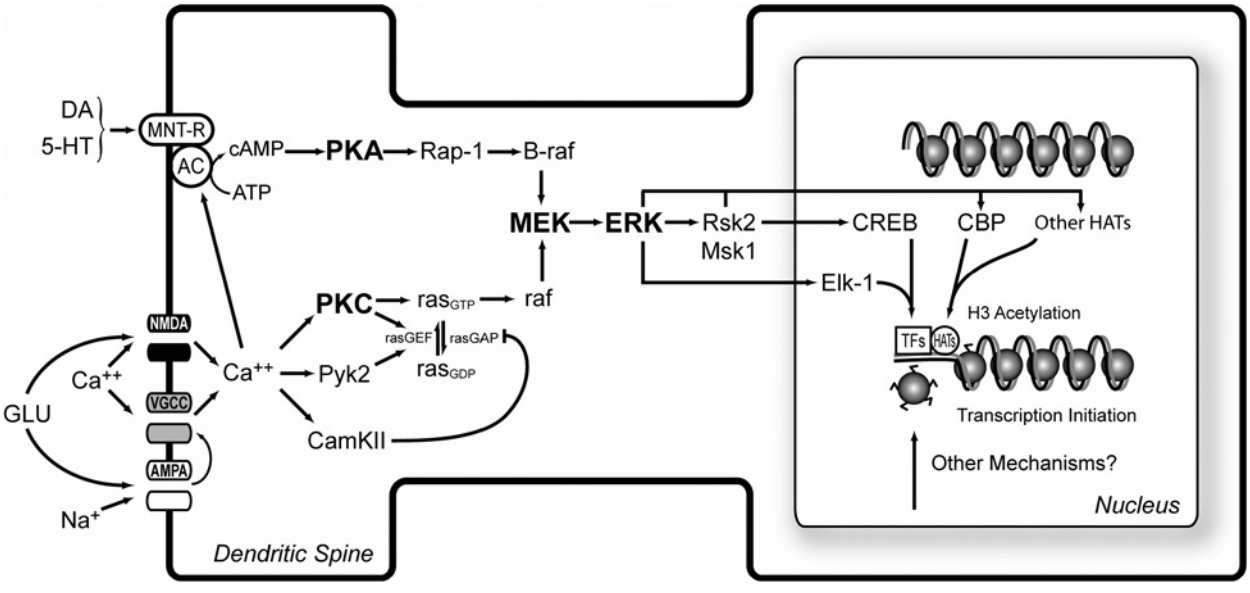

Figure 2. Signal transduction mechanism operating to regulate chromatin structure in the hippocampus. A wide variety of cell surface receptors are coupled to complex intracellular signal transduction processes in hippocampal neurons, ultimately leading to alterations in both transcription factors and chromatin structure. One hypothetical set of pathways leading to epigenetic regulation in hippocampal pyramidal neurons is illustrated in this figure. Please see the text for additional details and relevant references.

Epigenetics in cognition

As reviewed thus far, the state of the epigenome is regulated in response to memory formation and induction of synaptic plasticity. Moreover, this regulation occurs in simple invertebrates and complex mammalian species, suggesting that the evolution of the epigenome as a substrate for dynamically encoding neuronal states occurred early in the progression of metazoans. Therefore, the role of epigenetics in nervous system function might extend beyond merely plasticity and memory formation, and affect complex processes such as cognition itself.

In the beginning of this review, we noted that early development relies heavily on epigenetics for programming cellular phenotype. Thus, when discussing the role that epigenetics might play in higher cognitive function, it is important to distinguish epigenetic mechanisms of neurodevelopment from the dynamic epigenetic processes that occur in fully developed postmitotic neurons. In the following examples of how epigenetics might influence cognitive function, we will emphasize the role that epigenetics plays in the adult nervous system.

Several disorders of human cognition can be at least partly attributed to dysfunction in the mechanisms that underlie epigenetic marking of the genome. Rubinstein-Taybi syndrome (RTS), an inherited autosomal dominant disease, is due to mutation of CBP [49, 50]. Several studies using animal models to investigate the molecular basis of RTS indicate that deficiency in CBP has severe consequences for long-term memory formation [27, 28, 31–33]. Interestingly, in at least some animals models of this disease, treatment with HDAC inhibitors can ameliorate the memory impairments, suggesting a possible treatment for RTS [31, 32].

An increase in soluble β-amyloid peptides in the brain is the leading candidate mechanism for the pathogenesis of Alzheimer's disease, the most prevalent form of senile dementia [51]. β-amyloid peptides are created by endoproteolytic cleavage of the transmembrane amyloid precursor protein (APP) by β- and γ-secretases [52]. While countless studies have focused on the extracellular β-amyloid peptides, especially in their involvement in the production of amyloid plaques, cleavage of APP also results in production of an intracellular fragment, the APP intracellular domain (AICD). AICD is a transcription factor that actively recruits the adapter protein Fe65 and the HAT Tip60 to chromatin [53–56]. Thus, AICD-mediated derangement of histone acetylation could underlie some of the pathology of Alzheimer's disease.

Rett syndrome (RS) is an inherited, X-linked disease due, at least in part, to a mutation of the methyl CpG-binding protein 2 (MeCP2) [57–59]. MeCP2 belongs to a family of methyl CpG-binding proteins whose function is to bind methylated cytosines and recruit chromatin-remodeling enzymes that suppress transcription. Surprisingly, overexpression of MeCP2 actually enhanced long-term memory formation and the induction of hippocampal LTP, two processes that require transcription [60]. These results were the first to suggest that components of the molecular machinery involved in DNA (cytosine-5) methylation, a process believed to be static in nonproliferating cells, might play a role in higher cognitive function.

The most commonly inherited form of mental retardation is Fragile X syndrome. Fragile X is caused by an expansion of trinucleotide repeats within one of the Fragile X genes: FMR1 and FMR2 [61, 62]. Both FMR1 and FMR2 contain a polymorphic trinucleotide repeat, CGG and CCG, respectively, in their 5′ untranslated regions responsible for the loss of gene expression [63, 64]. Expansion of these repeats results in hypermethylation of these regions and flanking CpG islands, leading to transcriptional silencing of the FMR and surrounding genes. Thus, Fragile X represents another example of how dysregulation of DNA methylation can adversely affect cognition.

Finally, schizophrenia is a serious disorder of cognition, rendering sufferers unable to function normally in social situations and in performing everyday cognitive tasks. An emerging body of evidence suggests that deficiencies in the extracellular matrix protein reelin are responsible for the etiology of schizophrenia [65]. Post-mortem brains of patients with schizophrenia have a significant increase in expression of DNA (cytosine-5) methyltransferase and decrease in reelin expression in cortical gamma-aminobutyric acid (GABA)-ergic neurons [66]. The reelin promoter contains several sites for DNA methylation, suggesting that epigenetic mechanisms may regulate expression of reelin in the adult nervous system [67]. Artificially enhancing DNA methylation by exposure to excess methionine increases methylation of the reelin promoter and decreases expression of reelin [68, 69]. Inhibitors of HDAC and DNMT activity decrease methylation of the reelin promoter and increase expression of reelin [67]. All of these studies indicate that the status of the epigenome can influence expression of reelin, a molecule implicated in the pathogenesis of schizophrenia.

Conclusions

Biological systems have a fascinating capacity to remember stimuli in their environment. The capacity for memory formation is an evolutionarily ancient phenomenon, present even in protozoans [70, 71]. It is not surprising then, that the mechanisms used by simple invertebrates for the formation of long-term memory are very similar to those used by more complex animals such as mammals. In the last 5 years, it has become increasingly clear that an evolutionarily conserved and ancient form of cellular memory, epigenetic marking of chromatin, has been

co-opted by the nervous system to subserve long-term memory formation.

One question that has eluded neuroscientists is, How can the brain store information over the lifetime of an organism in the face of molecular turnover? This question is especially relevant for understanding a complex process such as cognition, which relies heavily on the ability to store and recall information for periods longer than the half-lives of most of the molecules utilized in these processes. Chromatin is the one structure that remains relatively constant in almost every cell of a metazoan. It is not surprising that many recent studies in the nervous system indicate that from invertebrates to mammals, chromatin is a dynamic structure that integrates potentially hundreds of signals from the cell surface and effects a coordinated and appropriate transcriptional response. More important, chromatin is perhaps the only structure in a neuron capable of such higher-level signal integration and information storage that is not continually turned over. Bolstering the assertion that chromatin is a key player in cognition are the many cognitive disorders that appear to be due, at least in part, to disruptions in the mechanisms responsible for modulating chromatin. We are at an exciting juncture in the field of neuroscience, and we suspect that understanding the epigenetic regulation of neural function will be vital for fully understanding the molecular processes that govern memory formation and human cognition.

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