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Invited review

Epigenetic modifications in the nervous system and their impact upon cognitive impairments

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ABSTRACT

Epigenetic regulation has been long considered to be a critical mechanism in the control of key aspects of cellular functions such as cell division, growth, and cell fate determination. Exciting recent developments have demonstrated that epigenetic mechanisms can also play necessary roles in the nervous system by regulating, for example, neuronal gene expression, DNA damage, and genome stability. Despite the fact that postmitotic neurons are developmentally less active then dividing cells, epigenetic regulation appears to provide means of both long-lasting and very dynamic regulation of neuronal function. Growing evidence indicates that epigenetic mechanisms in the central nervous system (CNS) are important for regulating not only specific aspects of individual neuronal metabolism but also for maintaining function of neuronal circuits and regulating their behavioral outputs. Multiple reports demonstrated that higher-level cognitive behaviors, such as learning and memory, are subject to a sophisticated epigenetic control, which includes interplay between multiple mechanisms of neuronal chromatin modification. Experiments with animal models have demonstrated that various epigenetic manipulations can affect cognition in different ways, from severe dysfunction to substantial improvement. In humans, epigenetic dysregulation has been known to underlie a number of disorders that are accompanied by mental impairment. Here, we review some of the epigenetic mechanisms that regulate cognition and how their disruption may contribute to cognitive dysfunctions. Due to the fact that histone acetylation and DNA methylation are some of the best-studied and critically important epigenomic modifications our research team has particularly strong expertise in, in this review, we are going to concentrate on histone acetylation, as well as DNA methylation/hydroxymethylation, in the mammalian CNS. Additional epigenetic modifications, not surveyed here, are being discussed in depth in the other review articles in this issue of *Neuropharmacology*.

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1. Introduction

Eric Kandel recently recalled that when he and Alden Spencer wrote a perspective on learning and memory for Physiological Reviews in 1968, they pointed out that "there was no frame of reference for studying memory" at that point (Kandel, 2012). During the next 45 years, we witnessed a tremendous progress in learning and memory research, leading to the development of sophisticated conceptual frameworks to explain memory mechanisms (Sweatt, 2009). Even more impressive is the fact that, despite such progress in deciphering memory regulation, completely novel and unexpected levels of investigations keep appearing. In this review, we will survey some of the most recent and exciting developments in the study of learning and memory, which occur in the field of epigenetic regulation of cognitive processes. Although "neuroepigenetics" is a relatively young research area, a considerable amount of data has already been accumulated convincingly demonstrating the critical role of epigenetic mechanisms in memory regulation (Levenson and Sweatt, 2005; Roth and Sweatt, 2009; Lester et al., 2011; Day and Sweatt, 2011). These include mechanisms of chromatin regulation via covalent modifications of DNA and histone proteins, such as DNA methylation and hydroxymethylation, and histone modifications (acetylation, phosphorylation, methylation, ubiquitylation, sumoylation, ADP ribosylation, deamination, proline isomerization). We should also note that the overall epigenetic control of the genome is comprised of highly sophisticated mechanisms involving extensive crosstalk and

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multiple intrinsic and extrinsic feedback circuits involving numerous different epigenetic modifications. Given the complexity of the topic, in the current review, we will concentrate specifically on histone acetylation, DNA methylation, and hydroxymethylation, the former being one of the most-, while the latter one of the least-understood epigenetic marks involved in the regulation of cognition.

2. Histone acetylation as a key mechanism of memory regulation

2.1. Mouse models as powerful tools to study the role of histone acetylation in cognition

The first study examining correlation between learning and histone acetylation in rat brain was published by Schmitt and Matthies in (1979). A renewed interest in histone modification in relation to cognitive processing resulted in a publication by Swank and Sweatt (2001) showing that the exposure of mice to a novel taste can induce long-lasting lysine acetylation and increased histone acetyltransferase activity in the insular cortex. The nonspecific histone deacetylase (HDAC) inhibitor trichostatin A (TSA) caused a similar increase in lysine acetylation. The authors further showed that such acetylation can be regulated by the ERK/MAP pathway, thereby connecting novelty learning and ERK/MAP activation with histone acetyltransferase activity and downstream histone acetylation (Swank and Sweatt, 2001).

Following this work, a plethora of studies tested the effects of various non-specific histone deacetylase inhibitors including trichostatin A (TSA), suberoylanilide hydroxamic acid (SAHA), sodium butyrate (NaBut), phenylbutyrate (PBA), and valproic acid (VPA) on learning and memory in mice (Bourtchouladze et al., 2003; Alarcon et al., 2004; Korzus et al., 2004; Levenson et al., 2004; Wood et al., 2006a,b; Oliveira et al., 2007; Fischer et al., 2007; Bredy et al., 2007; Bredy and Barad, 2008; Stefanko et al., 2009; Peleg et al., 2010; McQuown et al., 2011; Bahari-Javan et al., 2012) and rats (Dash et al., 2009, 2010; Hawk et al., 2011). The general conclusion that could be made from multiple experiments utilizing TSA, NaBut, and VPA is that these treatments could ameliorate cognitive deficits and improve various aspects of learning and memory in different rodent models. Amongst the multiple examples of such improvements are enhancements of spatial learning in mice that either carry a mutant CREB-binding protein (CBP) (Korzus et al., 2004) or experience neurodegeneration due to p25 overexpression (Fischer et al., 2007), as well as in rats following traumatic brain injury (Dash et al., 2009, 2010).

Chwang et al. (2006) demonstrated that Pavlovian fear conditioning induces a rapid increase in the phosphorylation of histone H3 in hippocampal CA1 that is regulated by the ERK/MAPK pathway. A further examination of the role of ERK/MAPK cascade in cognition showed that mice null for mitogen- and stress-activated protein kinase 1 (MSK1), a downstream kinase of the ERK/MAPK pathway, demonstrated deficits in fear memory as well as decreased histone H3 acetylation and phosphorylation (Chwang et al., 2007). These two studies demonstrate connections between fear memory, histone acetylation, and phosphorylation in the hippocampus, and show that this pathway of epigenetic regulation is mediated by the ERK/MAPK cascade.

The connection between histone H3 phosphorylation/acetylation and fear memory regulation was further strengthened by the findings of Lubin and Sweatt (2007), who showed that the inhibition of a component of the NFκB complex, IKKα, led to an impairment of fear memory reconsolidation. They showed that a subset of genes, whose expression is induced in hippocampal area CA1 by fear conditioning, have NFκB regulatory elements in their promoter regions. An analysis of the well-studied memory-related gene *Zif268* indicated that fear memory recall induced increases in histone H3 phosphoacetylation and acetylation and that administration of the NFκB inhibitor, diethyldithiocarbamate (DDTC), significantly attenuated both phosphoacetylation and acetylation of histone H3 (Lubin and Sweatt, 2007).

Another interesting example of chromatin modification as a mechanism of cognitive regulation came from findings by Genoux et al. (2002) and Koshibu et al. (2009). Genoux et al. (2002) showed that the Ser/Thr Protein Phosphatase type 1 (PP1), an enzyme involved in the dephosphorylation of a wide variety of cellular targets, serves as a molecular suppressor of learning and memory. Genoux et al. (2002) showed that PP1 inhibition following learning was able to prolong object memory. A follow-up study by Koshibu et al. (2009) demonstrated that nuclear PP1 inhibition in the hippocampus and cortex resulted in an increased object recognition memory and led to multiple alterations in histone modifications at the promoter of the major memory gene CREB (cAMP response element-binding protein). These modifications included increases in H3 serine (S)10 phosphorylation, H3 lysine (K)36 trimethylation, as well as H3K15 acetylation (Koshibu et al., 2009). These studies show that a protein phosphatase can regulate learning and memory via mechanisms involving not only locus-specific (de)phosphorylation, but also histone acetylation, suggesting a complex relationship between different modes of epigenetic control.

When considering the growing evidence that administration of various HDAC inhibitors can lead to improved learning and memory, it is hardly surprising that a number of recent studies have concentrated on the role of specific HDACs in cognition. Bahari-Javan et al. (2012) implicated a founding member of the class I HDACs, HDAC1, in specific aspects of cognitive regulation. Overexpression of HDAC1 in the mouse hippocampus led to an increase of fear memory extinction, while the pharmacological inhibition of HDAC1 impaired fear extinction (Bahari-Javan et al., 2012). Mechanistically, the authors showed that memory extinction training leads to recruitment of HDAC1 to the promoter of the neuronal activity-regulated gene, c-*Fos*, as well as histone H3K9 deacetylation (Bahari-Javan et al., 2012).

McQuown et al. (2011) examined a potential role for another Class I HDAC, HDAC3, in learning and memory. Ablation of HDAC3 in the dorsal hippocampus led to an enhancement of long-term object memory accompanied by the increased acetylation of histone H4K8 and upregulation of the immediate early genes c-*Fos* and *Nr4a2*. Surprisingly, while the memory for the location of the object was augmented, there was no increase in memory for the object itself. Such specificity could potentially be explained by the finding that the expression of another class II HDAC, HDAC4, was significantly reduced in the area of HDAC3 deletion. This discovery may suggest that these two HDACs share a role in the regulation of object memory, perhaps as components of the NCoR co-repressor complex (Fischle et al., 2002). Another piece of evidence supporting HDAC3's role in cognition came from a recent study by Malvaez et al. (2013). The authors showed that administration of the HDAC3-specific inhibitor RGF966 led to an enhancement of long-term object memory as well as the facilitated extinction of cocaine-seeking behavior. Mechanistically, RGF966 causes increased acetylation of histones H4K8 in the infralimbic cortex as well as H3K14 in infralimbic cortex, hippocampus, and nucleus accumbens one hour following the first extinction session; however, acetylation of H2BK12 was unchanged, demonstrating the specificity of the HDAC3 effect of histone acetylation during learning (Malvaez et al., 2013).

In 2012, Kim et al., revealed an essential role for HDAC4 in synaptic plasticity and memory formation. They showed that the selective loss of HDAC4 in forebrain neurons leads to impairments