Review

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Histone acetylation in neuronal (dys)function

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Abstract: Cognitive functions require the expression of an appropriate pattern of genes in response to environmental stimuli. Over the last years, many studies have accumulated knowledge towards the understanding of molecular mechanisms that regulate neuronal gene expression. Epigenetic modifications have been shown to play an important role in numerous neuronal functions, from synaptic plasticity to learning and memory. In particular, histone acetylation is a central player in these processes. In this review, we present the molecular mechanisms of histone acetylation and summarize the data underlying the relevance of histone acetylation in cognitive functions in normal and pathological conditions. In the last part, we discuss the different mechanisms underlying the dysregulation of histone acetylation associated with neurological disorders, with a particular focus on environmental causes (stress, drugs, or infectious agents) that are linked to impaired histone acetylation.

Keywords: cognition; epigenetics; histone acetylation; histone acetyltransferase; histone deacetylase; neuron; synaptic plasticity.

Introduction

The brain presents the remarkable property to be adaptable or plastic, a characteristic defined by the term 'neuronal plasticity'. Hence, during an organism's lifetime, highly mobilized connections between neurons will be consolidated, whereas those less solicited will degenerate. This plasticity constitutes the support of cognitive phenomena such as learning and memory. Its dysregulation can lead to neurological, behavioral, or psychiatric pathologies. It is thus essential to better understand the molecular mechanisms underlying neuroplasticity and cognitive functions, both in physiological and pathological contexts. Since the early 2000s, numerous studies have described the importance of epigenetic mechanisms in neuronal plasticity, and more generally, in neuronal physiology. Epigenetics contributes to neuronal development and differentiation and is also associated with the regulation of cognitive and behavioral functions (1). Perturbations of epigenetic mechanisms are shown to be associated with an increasing number of neurological and neuropsychiatric diseases (2). One important support of epigenetics is cellular chromatin, a dynamic structure that can integrate a high number of signals from the environment to generate an appropriate transcriptional response. Among the numerous epigenetic modifications occurring on chromatin, acetylation of histone amino-terminal tails is a crucial mechanism that governs many neuronal functions (3). In this review, we will present the mechanisms of histone acetylation and their regulation and we will address their role in neuronal physiology, both in normal and pathological conditions. We will emphasize the role of environmental factors that are suspected to be major players in histone acetylation-associated pathologies.

Histone acetylation: mechanism, regulation, and control of gene expression

Acetylation is a covalent and reversible post-translational modification that consists of the addition of an acetyl chemical group (CO-CH3) on the lateral chain of a positively charged lysine residue. This process is not restricted to the amino-terminal tail of histones and affects other kinds of cellular proteins (4). It is implicated in nearly all nuclear functions (chromatin dynamics, cell cycle, splicing, etc.) and some cytoplasmic functions (energy metabolism, cytoskeleton dynamics, etc.). Acetylation is

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a dynamic process governed by two types of enzymes with opposing effects: histone acetyltransferases (HATs), which act as 'writers', and histone deacetylases (HDACs), which act as 'erasers' (Figure 1). As acetylation not only concerns histones, the HAT nomenclature has recently been revised to allow homogenization, leading to the novel acronym KAT (for lysine acetyltransferase) (5). Despite this change, the historic nomenclature is often applied and will be used in this review.

There are five different families of nuclear HATs (6):

- The CBP/p300 family, composed of CREB binding protein (CBP) and its homologue p300;
- The Gcn5-related N-acetyltransferases (GNAT) family, composed of general control non-derepressible 5 (Gcn5), p300/CBP-associated factor (PCAF), elongator complex protein 3 (ELP3), HAT1, and activating transcription factor 2 (ATF-2);
- The MOZ, YBF2/Sas3, Sas2, and Tip60 (MYST) family, composed of the four MYSTs and Tat-interactive protein 60 (Tip60);
- The family of transcription factors, composed of human transcription factor IIIC (TCIIIC) and transcription initiation factor TFIID subunit 1 (TAF1);
- The family of nuclear receptor coactivators, composed of steroid receptor coactivator (SRC-1), nuclear receptor coactivator (NCoA-3) and circadian locomotor output cycle kaput (CLOCK).

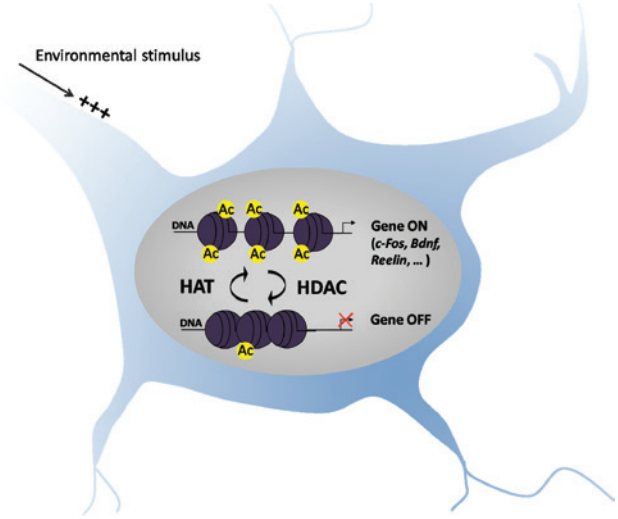

Figure 1: Regulation of histone acetylation in neurons in response to an environmental stimulus.
Following an environmental stimulus, histone acetylation is modified by two families of enzymes with opposite roles: the histone acetyltransferases (HATs) and the histone deacetylases (HDACs). Histone acetylation favors chromatin relaxation, leading to gene expression, whereas histone deacetylation is the first step of a process leading to chromatin compaction and gene repression.

Currently, a lot of questions concerning HAT function and regulation remain, notably: (i) Are KATs and HATs different? (ii) What are the molecular bases of their substrate specificity? (iii) What are the molecular mechanisms governing the regulation of their activity? This last question is particularly relevant because dysregulations of HAT activities are often at the origin of pathologies (7). HAT activity is regulated in at least two ways: by binding to regulatory proteins and through post-translational modifications such as autoacetylation and phosphorylation (8). Many HATs act in the context of protein complexes that modulate their activity and/or substrate specificity. For instance, the substrate preference for free histones or for histone octamers differs when Gcn5 and PCAF act alone or into protein complexes (9, 10). Another example is given by the Sas2 member of the MYST family, whose acetyltransferase activity is dependent on its binding to its partners Sas4 and Sas5 (11, 12). Another way to modulate HAT activity relies on the post-translational modifications harbored by the enzymes. The first one consists of their own autoacetylation, which has been described for PCAF (13), the hMOF MYST protein (14), and CBP/p300 (15). For all of these HATs, autoacetylation has been shown to be required for their activation, although the regulation of this mechanism is not yet understood. Phosphorylation has also been described to regulate HAT activity and is well documented for the CBP/p300 family. Phosphorylation of the CBP serine 301 by calcium/calmodulin-dependent protein kinase IV (CaMKIV) is accompanied by a transcriptional activation after neuronal stimulation (16). CBP phosphorylation on its serine 436 by protein kinase Cζ (PKCζ) has been shown to be necessary for the acetylation of neuronal genes implicated in cellular differentiation (17). Finally, in contrast to the other described phosphorylations, phosphorylation of serine 89 in p300 has been shown to inhibit its own HAT activity (18, 19).

Concerning the HDAC families, 18 different proteins have been inventoried in mammals and they are divided into four classes (I–IV) based on their function and subcellular localization (20), which are summarized as follows:

- Class I: composed exclusively of nuclear HDACs (HDACs 1, 2, 3, and 8);
- Class II: composed of the subclasses IIa (HDACs 4, 5, 7, and 9) and IIb (HDACs 6 and 10), which shuttle between the nucleus and cytoplasm;
- Class III: composed of the sirtuin (SIRT) subfamily, with diverse cellular localizations (cytoplasmic, nuclear, or mitochondrial);
- Class IV: composed only of HDAC 11, exclusively nuclear.

The HDACs from classes I, II, and IV share a zinc-dependent deacetylase activity, whereas the class III HDACs depend on NAD^+ (nicotinamide adenine dinucleotide) for their enzymatic activity. As for the HATs, HDAC activities are tightly regulated and their perturbation has been linked to several pathologies (20). HDACs are regulated by different mechanisms, notably by their interaction with partners to form repressor complexes as with Sin3A/CoREST complexes (21), or by their subcellular localization (22). They can also be modified by numerous post-translational modifications such as acetylation, as exemplified by the acetylation of HDAC 1 by p300, which inhibit its activity (23). Moreover, acetylated HDAC 1 can inhibit HDAC 2 activity upon heterodimerization (24). HDAC phosphorylation is also well described, especially for the class I HDACs HDAC 1 and HDAC 2, for which phosphorylation promotes their enzymatic activity (25, 26) and allows their incorporation into the Sin3 corepressor complex (27). HDAC 3 is a natural substrate for serine/threonine phosphatase 4 and its phosphorylation dramatically impairs its deacetylase activity (28). Phosphorylation of HDAC 5, a class II HDAC, also appears to regulate its nuclear export and its action on gene transcription (29). Interestingly, the regulation of HAT and HDAC activities can also be mediated by reciprocal interactions between the HATs and the HDACs, like acetylation of HDAC 6 by p300 (30), deacetylation of PCAF by HDAC 3 (31), or regulation of Tip60 autoacetylation by SIRT1 and of p300 autoacetylation by SIRT2 (32, 33), mechanisms that suggest the existence of a feedback loop between all activities.

Finally, this last decade has focused on the development of pharmacological HDAC inhibitors (HDACis). Four principal families of HDACis exist: short chain fatty acids (sodium butyrate, phenylbutyrate, valproic acid), hydroxamic acids [trichostatin A, suberoylanilide hydroxamic acid (SAHA)], epoxyketones (trapoxin), and benzamides. Their use favors histone acetylation and they constitute promising molecules for the treatment of some pathologies where acetylation is deficient (7, 34, 35).

The main function of histone acetylation is the regulation of gene transcription by two processes. First, the neutralization of the lysine positive charges that interact with the DNA molecule leads to a mechanical relaxing of chromatin. Second, 'reader' proteins specifically bind to acetylated chromatin and are used as scaffolds for the assembly of the transcription complex. Recognition of acetylated lysine residues is initiated by bromodomains, defined by highly conserved 110 amino acid motifs found on chromatin-interacting proteins including HATs, histone methyltransferases, helicases, transcription factors, or remodeling complexes (36). The first bromodomain was described in *Drosophila* and 61 distinct bromodomains have now been listed and are located on 46 nuclear and cytoplasmic proteins. After their binding to acetylated histones, these bromodomain-containing proteins allow the recruitment of other factors at gene promoters or enhancers that act, depending on the context, as coactivators or corepressors of transcription.

Histone acetylation in neuroplasticity and memory

The central nervous system is able to sense the environment, to integrate information and to create appropriate responses, abilities that rely on neuronal plasticity. Neurons, which are highly specialized post-mitotic cells, are organized in a complex network allowing the transmission of information and are the major actors in this neuroplasticity. They are connected to each other by synapses, functional units with extremely plastic/dynamic structures. Synaptic plasticity is defined as a modulation of synaptic reinforcement, which depends on neuronal electric activity and results in the modification of the neuronal network dynamics (37).

Different types of synaptic plasticity exist and are characteristic of different types of memory: a short-term memory (few hours) and a long-term memory that may persist during the whole life. The two most described forms of long-term synaptic plasticity are long-term potentiation (LTP) and long-term depression (LTD). They are characterized by a durable reinforcement or a weakening of synaptic connections, respectively. LTP induction constitutes an ideal *ex vivo* model to study the synaptic changes that underlie the complexity of learning and memory processes (38). LTP is classically described as a durable reinforcement of synaptic efficiency after repeated and sustained stimulation and is composed by two phases (39): an early and a late phase. The early phase (from 1 to 3 h) principally relies on (i) the phosphorylation of preexisting proteins, such as kinases; (ii) an increase in neurotransmitter release at the presynaptic level; and (iii) the addressing of neurotransmitter-specific receptors at the postsynaptic level. The late phase is a phase of maintenance that requires gene expression and protein neosynthesis to reinforce and durably stabilize synaptic changes initiated at the early phase. These protein syntheses are particularly crucial not only for the production of postsynaptic receptors, but also for cytoskeleton remodeling, and thus requires gene transcription. Activation of gene transcription has principally been shown to be dependent

on the cAMP response element-binding protein (CREB) as well as the NF-κB family of transcription factors (40).

Since the early 2000s, various studies have described the fundamental role of epigenetic mechanisms, notably histone acetylation, in the control of neuronal plasticity, by allowing the rapid establishment of an active transcriptional state (Figure 1). It is well established that LTP is functionally correlated to histone acetylation. LTP causes an increase of H3 and H4 acetylation (41, 42) and can be potentiated by the use of HDACis (34, 35, 42, 43). Moreover, impairment of the HAT CBP in mice decreases the overall acetylation of H2B and disrupts LTP in hippocampal slices (44–46). Increased acetylation levels are often observed at the promoters of genes encoding proteins implicated in synaptic transmission processes, such as the extracellular matrix protein Reelin, the activity-regulated cytoskeleton-associated (Arc) protein, or the neurotrophin brain-derived neurotrophic factor (BDNF) (47).

Resulting from its central implication in neuronal plasticity, histone acetylation has been demonstrated to be a key player in various cognitive processes. Levenson and his collaborators were the first, in 2004, to associate a modulation of H3 and H4 acetylation to cognitive processes like learning and memory (42). Since this study, numerous works confirmed the link between histone hyperacetylation and the different phases of memory (short- or long-term) in mammals (48). Contextual fear conditioning, a well-established behavioral paradigm used to study hippocampus-dependent memory, increases H3 acetylation on lysine residues 9 and 14, H4 acetylation on lysine residues 5, 8 and 12, and H2B acetylation on all lysine residues (lysine 5, 12, 15, and 20) (49–53). Furthermore, the positive effects of the transfer of mice into an enriched environment or of the use of HDACis to modulate learning and long-term memory are associated with an increase of histone acetylation together with an increased number of synapses (54). It has also been shown that alterations of histone acetylation are associated with age-dependent memory impairment in mice (55). Using the chromatin immunoprecipitation method, histone acetylation has been described to occur specifically at the promoter of genes implicated in learning and memory, including *c-fos*, *zif268*, *creb*, and *bdnf*, whose expression increases concomitantly (47). This hyperacetylation could facilitate the recruitment of transcription factors and improve gene expression following learning tasks (52).

Moreover, certain histone marks seem to be dependent of the stage of memory acquisition. For example, in the hippocampus, H3 acetylation on lysine residues 9 and 14 is related to contextual and spatial learning encoding, whereas acetylation of H2B (on lysine residues 5, 12, and 15) and of H4 (on lysine residue 12) are associated with consolidation of memory (49, 50). Such marks could thus be a molecular step towards memory storage. Histone acetylation can also be specific for certain areas of the brain, depending on the task involved. For example, acetylation of H3 is enhanced in the CA1 area of the hippocampus after contextual fear conditioning (42), whereas this increase is observed in the lateral amygdala during auditory fear conditioning (56).

In conclusion, implication of histone acetylation is now well documented during synaptic plasticity and cognitive processes. However, given the high complexity illustrated by the variety of existing acetylated lysine residues and the variety of the brain's sub-localization of the signal, a lot of work remains towards the elucidation of the precise role of this histone modification.

Histone acetylation in neuronal dysfunctions

Over the past few years, growing evidence suggest that epigenetics, and notably histone acetylation, plays a role in neurodevelopmental, neurodegenerative, and neuropsychiatric diseases (47, 54, 57). Implication of histone acetylation was initially suggested by the observation that the use of HDACis, alone or in combination with antidepressants, ameliorates the behavior associated with severe depression in a rodent model (58). Since this finding, different pathologies associated with impaired cognitive functions have been linked either mainly with histone hypoacetylation (47, 59), or sometimes with histone hyperacetylation (60) in neurons (Figure 2). Salient examples are neurodevelopmental disorders such as Rett syndrome or Rubinstein-Taybi syndrome (RSTS), neurodegenerative disorders such as Alzheimer's disease (AD) or Huntington's disease (HD), or psychiatric disorders such as severe depression or schizophrenia. In some cases, the etiology has been shown to be genetic, with mutations in acetylation-governing actors like HATs or HDACs or in proteins interacting with these enzymes. For others, environment is suspected to play an important role and there is a growing interest in the study of environmental factors that are implicated in the occurrence of such pathologies (61). In the last part of this chapter, we will present examples of different causes of pathologies correlated to deregulation of histone acetylation and we will end with a particular focus on the role of the environment in the etiology of neurological disorders.

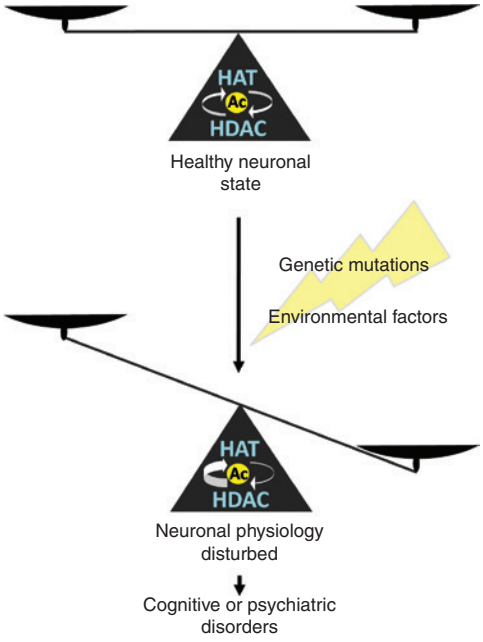

Figure 2: Role of the HAT/HDAC equilibrium in neuronal functions. In steady-state conditions, a proper balance in HAT/HDAC activities allows physiological histone acetylation, ensuring normal neuronal functions. When the HAT/HDAC balance is dysregulated (due to genetic or environmental causes), impaired histone acetylation leads to neuronal dysfunctions, with behavioral and cognitive alterations.

Genetic etiology

The Rubinstein-Taybi syndrome (RSTS)

RSTS is a disease affecting 1 in 100 000 newborns and is characterized by skeletal abnormalities and intellectual disabilities with low levels of intelligence. In 60% of the cases, RSTS is associated with mutations in the gene encoding the HAT CBP, whereas in 3% of cases, mutations are found on the gene encoding the HAT p300 (62). Many mouse models have been developed to confirm the implication of CBP and p300 in RSTS and to characterize the molecular mechanisms associated with the cognitive deficits (59). Hence, *cbp* hemizygous mice, *cbp* conditional knock-out mice, transgenic mice expressing dominant-negative CBP, and mice with focal depletion of CBP all display a phenotype close to that of the RSTS patients, with skeletal malformations and cognitive impairment (45, 46, 63–67). After various behavioral and cognitive challenges, most of the mouse models display specific deficits in long-term memory but not in short-term memory, suggesting a preferential role of CBP in memory consolidation. In contrast, p300-deficient mice exhibited only mild effects (66, 68, 69), in correlation with the phenotype of the RSTS patients bearing a mutation on the p300 gene, who present less intellectual deficits than patients harboring a mutation on the *cbp* gene (70).

Studies done on these different RSTS mouse models have thus demonstrated that impaired histone acetylation, in particular on H2A and H2B, is a critical hallmark of the disease (44, 46). A similar acetylation decrease has also been observed in lymphoblastic cell lines derived from RSTS patients (71). Moreover, administration of HDACi to $cbp^{+/-}$ mice ameliorates their cognitive capacities, underlying the fact that perturbation of histone acetylation may therefore play a direct role in the etiology of the syndrome (44). In parallel, CREB-dependent transcriptions are affected in CBP-deficient mice (46, 72), a defect that may contribute to cognitive deficiencies.

Huntington's disease (HD)

HD is an autosomal-dominant genetic disease with a prevalence of 5–10 cases per 100 000, characterized notably by cognitive disorders and motor impairment with the hallmark feature of chorea (73). Disease is caused by mutations in the Huntingtin (Htt) protein that harbors aberrant expansion of a polyglutamine stretch located in its amino-terminal part. This disease has emerged as a prototypical paradigm of epigenetic dysregulation in a neurodegenerative condition, as it presents aberrant chromatin modifications in neurons at several levels, in histone acetylation, methylation, ubiquitinylation, phosphorylation, and in DNA methylation. The first evidence of deregulated histone acetylation during HD came from the observation that CBP was found in intracellular inclusions in *in vitro* preparations, in brains from animal models and in postmortem tissues from patients (74–76). Concomitantly, a global histone acetylation decrease was observed for histones H3 and H4 in cells expressing mutant Htt (76). Three different mechanisms explain the deficit of CBP activity in neurons: sequestration into Htt aggregates as mentioned above, inhibition by soluble Htt via a direct physical interaction, and degradation of CBP by the ubiquitin/proteasome system (77, 78). Hence, depletion of soluble CBP may affect the transcriptional regulation of neuronal genes, leading to neuron malfunction and cell loss. Importantly, treatments with different HDACis have been described to rescue cellular degeneration and cell death in different models of polyglutamine expansion disorders (79, 80), underlying the fact that histone hypoacetylation may play a central role in HD. Several studies using different animal models also provided convincing evidence that

SIRT1 has a protective role against Htt toxicity, although controversial results were recently reported (81). Interestingly, mutant Htt directly inhibits SIRT1 activity, thereby affecting multiple downstream targets (82).

A multifactorial disease: Alzheimer's disease (AD)

AD is the most prevalent dementia in the world, affecting 35 million people worldwide. AD is characterized by cognitive decline accompanying and even preceding neuronal loss. In AD, several risk factors are intertwined in highly sophisticated ways and include genetic factors such as the expression of different alleles of apolipoprotein E (ApoE), environmental factors and aging. AD is characterized by the accumulation of toxic species of two endogenous proteins: amyloid β, which forms neurotoxic oligomers and plaques, and tau, which forms neurofibrillary tangles (83).

In AD, similar to the aged brain, changes in gene expression that correlate with alterations in chromatin acetylation affect mainly synaptic plasticity-associated genes. Reduced histone acetylation of plasticity-related genes is combined with increased acetylation in the promoter of genes that are involved in the processing of pathogenic species such as presenilin 1 and BACE1 [beta-site amyloid precursor protein (APP)-cleaving enzyme 1], which are critical in the generation of toxic amyloid β (84). In most AD models and in human AD, decreased expression of plasticity-associated genes correlates with reduced histone acetylation, and the role of HDAC 2 in these deficits has strongly been suggested (35). To date, most of the studies have focused on the implication of HDAC rather than HAT in AD, as HDACis offer promising results as cognitive enhancers in many neurodegenerative diseases (35). Indeed, in the brain, HDAC activity targets more specifically the promoters of genes encoding synaptic plasticity-associated factors than general transcription. However, what causes increases of HDAC activity in AD remains to be determined. It has been shown that amyloid β may activate c-Abl, which in turn phosphorylates HDAC 2, thereby preventing its poly-ubiquitinylation and subsequent degradation by the proteasome (85). Another identified mechanism of HDAC increase is stress. Systemic, cellular, and emotional stress activates the steroid receptor GR, which can bind to some elements of the *HDAC 2* promoter and upregulate its expression. Hence, environmental stressors affect histone acetylation in AD. HDAC 1 activity seems also involved as it affects neuronal loss in AD. Although the mechanisms of HDAC 1 impact in AD remain unclear, HDAC 1 inhibitors have neuroprotective effects in AD and other neurodegenerative diseases.

Recent findings also involved changes in HDAC 4 and HDAC 6 nuclear localization that depend on the AD genetic risk factor APOE 4 (86). APOE *ε4* increases by a 2–3 fold chance to develop early onset of AD when it is represented as a single allele and by over 12-fold when two APOE *ε4* alleles are expressed. APOE *ε4* expression in human neurons causes increased nuclear translocation of these two class II HDACs and their increased binding to elements of the *bdnf* promoter, resulting in lower acetylation levels of histones 3 and 4 and lower expression of BDNF. However, the APOE *ε3* allele, which shows neurogenic properties, promotes class II HDAC retention in the cytoplasm by activation of PKCε. Experimentally, activated PKCε was sufficient to prevent APO4-induced HDAC 6 translocation to the nucleus and subsequent decrease in BDNF expression.

Environmental etiologies

There is growing interest to better understand the environmental factors that may modulate epigenetic mechanisms, factors that could *in fine* affect gene expression and cellular phenotype. Many studies have demonstrated that transient or chronic environmental factors can modify the epigenetic code and sometimes modulate the severity of the pathologies. The most famous example is illustrated by monozygotic twins. At birth, they share the same epigenetic heritage, but during their adult lifetime there is a profound accumulation of epigenetic differences, both in DNA methylation and histone acetylation, likely because of different life experiences (87, 88). Thus, epigenetic modifications could allow the prenatal or postnatal environment to influence the organism in the absence of genetic alterations. In the last part of this review, we will focus on the current knowledge concerning the impact of environmental factors on histone acetylation and its consequences on neuronal physiology.

Stress

Severe stress is known to affect lifelong cerebral functions and mental health, in particular, traumatic events that took place during infancy. Moreover, cerebral dysfunctions resulting from severe stress have been shown to persist across generations (89). The Bilang-Bleuel

experiment was one of the earliest to examine the effects of stress on epigenetic modifications in the brain. Her work demonstrated that rats exposed to several acute stresses (forced swim, predator, and social defeat stress), showed a significant increase of H3 phosphorylation and acetylation, at serine 10 and lysine 14, respectively, in the dentate gyrus area of the hippocampus (90). Other studies have confirmed the implication of H3 acetylation on lysine 14, particularly after the chronic social defeat model of depression (91). Chronic social defeat stress in mice causes a transient decrease, followed by a persistent increase in H3 acetylation in the nucleus accumbens of the limbic system (92). This acetylation increase is correlated with disruptions of HDAC expression, notably a reduction in HDAC 2 and HDAC 5 levels (92, 93). Interestingly, chronic treatment with the antidepressant imipramine increases *HDAC 5* mRNA levels in the nucleus accumbens, consistent with the observation that HDAC 5 knockout mice show a more severe response after chronic social defeat than wild type (WT) control mice (93). In contrast to the antidepressant-like function of HDAC 5 in the nucleus accumbens, the role of HDAC 5 in the hippocampus seems to be more pro-depressive (91, 94). Indeed, socially defeated mice treated with imipramine are characterized by a decrease of HDAC 5 expression in the hippocampus (91). Moreover, a persistent decrease of H3 acetylation is observed in the hippocampus of both chronic social defeat stressed mice (95) and high responders in a rat model of individual differences in response to stress (96). Therefore, the two brain structures, nucleus accumbens and hippocampus, seem to play a different role in depression-related behavior, probably via HDAC 5 functions that need to be further investigated. Otherwise, recent studies suggest a role for SIRT2 in depression in different models, by regulating hippocampal neurogenesis in a rat chronic unpredictable stress model (97), and by an upregulation in conjunction with HDAC 5 in the prefrontal cortex upon the chronic social defeat stress model (98).

Maternal care has also long been recognized as a key factor to psychological development and well-being of the offspring (99). Several studies subjecting rodents to neonatal stress have shown that consequences of stressful experiments are heritable via epigenetic modifications. They are characterized by various forms, from anxious state with an increased response to stress, to cognitive perturbations (100). For example, mice which received low licking and grooming from their mother showed higher anxiety and impaired learning when adults. High maternal care has been correlated with epigenetic modifications in the offspring, notably with an enrichment of CBP binding on the promoter region of the glucocorticoid receptor gene in the hippocampus, associated with an increased level of H3 acetylation on lysine 9, leading to increased glucocorticoid receptor expression (101, 102).

In humans, many studies describe that exposure to adverse environmental conditions (famine, war, childhood abuse, maternal neglect, etc.) is an important risk factor to further develop psychiatric disorders, particularly depression and post-traumatic stress disorder (89). Numerous studies currently try to understand what could be the consequences on the offspring of the exposure of gestating mothers to psychologically and/or physically threatening situations. Prenatal stress has been associated with several behavioral alterations and is often associated with disturbances in DNA or histone methylation. In view of the difficulties to perform human studies, the role of histone acetylation in response to exposition to traumatic experiences has not been investigated yet, but its concomitant role together with methylation seems obvious (100, 103).

Drugs

Drug abuse is characterized by perturbations of neuronal plasticity and function, resulting in stable and persistent changes at the cellular level and consequently at the behavioral level. Recently, epigenetic mechanisms and especially histone acetylation have been implicated in drug-induced neuronal disruptions, development of addiction, as well as its heritability to subsequent generations (104, 105).

Alcohol, considered as a central nervous system depressant for its slowdown of vital functions, is one of the most available and commonly consumed drugs. Indeed, there is a clear association between chronic ethanol exposure and altered histone acetylation (106). Ethanol increases global levels of H3 and H4 acetylation in the prefrontal cortex, nucleus accumbens, and amygdala of ethanol-exposed rats (107, 108). Moreover, chronic exposure to ethanol leads to inhibition of HDAC activity in the amygdala and to a rapid tolerance to the anxiolytic effects of ethanol (108, 109). Furthermore, treatment of rats with a potent HDAC inhibitor (trichostatin A) decreases anxiety-like symptoms observed during ethanol withdrawal after chronic exposure (108). Taken together, these results support the fact that histone acetylation plays a crucial role in the rapid tolerance to the anxiolytic effects of ethanol that may promote drinking.

Cocaine is another substance known to affect the epigenome. It has notably been shown that cocaine causes a selective acetylation of H3 and H4 on the promoter of

genes involved in neuronal and behavioral adaptations to cocaine (104). Rat models of addiction revealed that cocaine provokes important perturbations of chromatin remodeling in some brain areas that are transmitted to inheritance. For instance, Vassoler and his collaborators showed that self-administration of cocaine causes an enrichment in both *bdnf* mRNA and protein in the prefontal cortical region in male but not female rats, which is the consequence of an increase of H3 acetylation on *bdnf* promoter. In addition, the H3 acetylation on the *bdnf* promoter is also observed in sperm and subsequently transmitted to the male offspring, resulting in reduced cocaine reinforcement (110). A study using chromatin immunoprecipitation coupled with promoter microarray analysis characterized genome-wide chromatin changes in the mouse nucleus accumbens after repeated cocaine treatment (111). It demonstrated that a high number of genes exhibited increased levels of H3 and H4 acetylation (i.e. *cfos*, *fosb*, *bdnf II*, and *cdk5)* after cocaine injections. Furthermore, it described a new role for HDAC SIRT1 and 2, whose expressions were induced by cocaine in the mouse brain and associated with an increase of the behavioral effects of the drug. Role of SIRT1 in cocaine action was further investigated in a genome-wide study that revealed two modes of SIRT1 action: first, a depletion of SIRT1 from gene promoters associated with an enrichment of H4K16 acetylation; and second, the deacetylation and activation of the FOXO3a transcription factor which enhances cocaine effect on place conditioning (112). HDACs 4 and 5 are also known to play an important role in mediating cocaine-induced acetylation and subsequent effects on drug-seeking behavior (104). Thus, HDACi treatment may constitute a novel, promising therapeutic approach to facilitate extinction of cocaine-seeking behavior. A recent study reported that the protein reader bromodomain-containing protein 4 (Brd4) was enriched in the nucleus accumbens and recruited to promoter regions of addiction-related genes, following repeated cocaine administration. In addition, inhibition of Brd4 attenuates transcriptional and behavioral responses to cocaine, thus revealing that bromodomain and extra-terminal motif (BET) inhibitors may also have therapeutic utility in the treatment of cocaine addiction (113).

While drug-induced alterations in histone acetylation have, to date, been implicated in the behavioral responses in simple models such as conditioned place preference and locomotor assays, future research is needed to translate these findings to more sophisticated models of human addiction, such as self-administration and relapse paradigms. These preclinical behavioral models could directly assess the role of histone acetylation in the pathogenesis and maintenance of the addicted state by studying how animals acquire drug self-administration and how they relapse after periods of drug withdrawal (111).

Infectious agents

Recently, several studies suggested that modifications of the *in utero* environment due to maternal exposure to infections (influenzavirus, *Toxoplasma gondii*, herpes simplex virus type 2) could disturb brain development and play a role in the etiology of behavioral disorders, such as autism or schizophrenia (114, 115). However, the molecular mechanisms involved in perturbations of brain structure and function remain poorly understood, even if epigenetics is highly suspected. A recent study using a mouse model of maternal immune activation mimicked by polyriboinosinic polyribocytidilic acid (polyI:C) injection revealed that *in utero* exposure to polyI:C causes an increase in global acetylation levels of histones H3 and H4 in the cortex of offspring. These changes were associated with deficits in the expression of genes associated with neuronal development, synaptic transmission, and immune signaling in the offspring cortex, and correlated with behavioral abnormalities (116).

Human immunodeficiency virus type 1 (HIV-1) infection of the central nervous system is also described to be responsible for severe neurological disorders, designated as HIV-associated neurocognitive disorders (HAND) (117). The viral trans-activating protein (Tat) has been shown to play a central role in these effects, notably by hijacking epigenetic signaling of the host cell. Indeed, HIV-1 Tat protein upregulates HDAC 2 expression in neuronal cells, leading to transcriptional repression of genes involved in synaptic plasticity and neuronal function (118). Another study showed that interaction between HIV-1 Tat and the HAT PCAF inhibits histone H3 and H4 acetylation and CREB-dependent trans-activation in response to neurotrophins, resulting in neuronal apoptosis (119). Moreover, Tat-PCAF nuclear complexes were visualized in postmortem brain tissues from HIV-1-infected patients with neurological disease, suggesting that HIV-1 Tat may contribute to HAND by impairment of the neuronal epigenetic signaling.

Viruses that persist in the central nervous system are also serious candidates for environmental factors involved in the etiology of neurological disorders. The Bornavirus (Borna disease Virus, BDV) constitutes an interesting model to assess the impact of viral infection on neuronal epigenetics and its consequences on behavior. This non-cytolytic negative-stranded RNA virus persistently infects neurons of the limbic system and causes various cognitive disorders in mammals, from subtle behavioral alterations

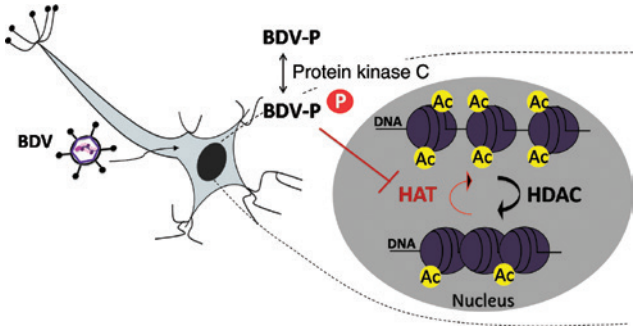

Figure 3: Model of Bornavirus interference with histone acetylation in infected neurons.
During neuronal infection by the Bornavirus (BDV), the viral phosphoprotein (BDV-P) interferes with cellular HAT activities in a protein kinase C-dependent manner, leading to histone hypoacetylation.

to fatal encephalomyelitis (120). Despite many controversies about the potential link between BDV infection and human neuropsychiatric disorders, neonatal BDV-infected rats display neurodevelopmental and behavioral abnormalities reminiscent of several human mental diseases (121). At the molecular level, BDV has the remarkable property for a RNA virus to replicate into the nucleus, in close association with cellular chromatin (122). Moreover, a recent study from our team demonstrated that BDV infection resulted in a decrease of H2B and H4 acetylation on selected lysine residues in primary cultures of cortical neurons (123) (Figure 3). We also showed that the viral phosphoprotein, a cofactor of the viral polymerase, was responsible for this decrease in histone acetylation, by inhibiting cellular HAT activity. Moreover, a mutant of the protein, that has lost the ability to be phosphorylated by protein kinase C, was no longer able to reduce histone acetylation. Interestingly, when we expressed the BDV phosphoprotein alone in the dentate gyrus area of the hippocampus of mice, we observed many behavioral and cognitive impairments, including elevated basal anxiety or a defect in short-term memory (unpublished observations). These defects were no longer observed with the expression of the non-phosphorylatable mutant of the protein, indicating that its action on neuronal histone acetylation is merely the cause of behavioral disorders. These data would then constitute the first demonstration that a viral protein can perturb cognitive functions of animals by manipulating epigenetic signaling in neurons.

Conclusions

Histone acetylation is a chromatin modification that plays a central role in many neuronal functions. It is required for proper cognitive functions and its dysregulation is found in numerous neurological disorders. In addition, there are an increasing number of studies showing that HDACi treatments increase cognitive capacities and reduce cognition impairment in various neuronal diseases. Histone acetylation may also be altered by environmental factors, which could constitute a new non-genetic etiology for neuronal disorders. Hence, many aspects of the research in neurosciences in the coming years will focus on deciphering the epigenetic control that governs brain functions such as synaptic plasticity and memory, both in normal conditions and in the pathological brain.

Expert opinion

The implication of histone acetylation as a key mechanism involved in cognitive processes is currently the subject of numerous debates (124), supported by different arguments. However, these arguments are to be nuanced until further investigation of the exact role of histone acetylation in transcription mechanisms or in cognitive processes. Firstly, histone acetylation is a transcription permissive mark but its action is not direct and requires the presence of other histone post-translational modifications and of 'reader' proteins to allow gene transcription activation. Secondly, transcription activation may be associated with a local increase of histone hyperacetylation aiming at relaxing the chromatin structure. Hence, the hyperacetylation observed during a mnesic task would be the consequence of the induction of transcription rather than the cause. Lastly, as hundreds of proteins are susceptible to acetylation, pharmacological or genetic modulation of the HAT/HDAC balance that leads to changes of histone acetylation levels may also modify the acetylation of non-histone substrates, notably transcription factors. Hence, transcriptional changes observed under HDACi treatments may be independent from their effects on histone acetylation. Moreover, the use of such strategies to treat neurological disorders is highly hazardous given the fact that they will certainly have pleiotropic and cytotoxic effects.

Outlook

We have to keep in mind that histone acetylation does not act alone in neuroplasticity and cognitive processes; indeed, other epigenetic marks have been shown to be crucial, including histone methylation (125, 126) and DNA

methylation (127, 128). Moreover, new types of epigenetic modifications on DNA and histone variants are still being identified in the brain (129, 130). In particular, evidence indicate a critical interplay between the different epigenetic modifications for the control of learning and memory processes, defining an epigenetic code for learning and memory, underlying the difficulty to study isolated modifications and their consequences. Currently, the development of whole genome approaches is likely to unravel the full complexity of the cognitive epigenetic landscape and will be the challenge in the coming years.

Highlights

- In neurons, histone acetylation is a key process that allows the rapid conversion of an environmental stimulus to an appropriate cellular response.
- Histone acetylation levels control the accessibility of chromatin to transcription factor, favoring gene expression.
- Histone acetylation is a dynamic process controlled by two families of enzymes: the histone acetyltransferases (HATs) and the histone deacetylases (HDACs).
- There are many HAT and HDAC families whose activity is tightly regulated by post-translational modifications and protein-protein interactions.
- Histone acetylation is a central mechanism governing neuronal functions, such as synaptic plasticity and learning and memory.
- When the HAT/HDAC balance is perturbed, it leads to neuronal dysfunctions, manifested by cognitive impairment or neurological disorders.
- There are different mechanisms leading to perturbation of acetylation and cognitive impairments: mutations of genes governing the HAT/HDAC balance or environmental factors including stress, drugs, or infectious agents.
- Future research in neurosciences will aim to decipher epigenetic mechanisms that govern brain functions in normal and pathological conditions.

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List of abbreviations

HAT	histone acetyl-transferase
HDAC	histone de-acetylase
SIRT	sirtuin
HDACi	HDAC inhibitors
CBP	CREB binding protein
LTP	long-term potentiation
RSTS	Rubinstein-Taybi syndrome
HD	Huntington's disease
Htt	Huntingtin
AD	Alzheimer's disease
BDV	Borna disease virus

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