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JOINING THE DOTS: FROM CHROMATIN REMODELING TO NEURONAL PLASTICITY

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SUMMARY

In recent years spectacular advances in the field of epigenetics have taken place. Multiple lines of evidence that connect epigenetic regulation to brain functions have been accumulating. Neurons daily convert a variety of external stimuli into rapid or long-lasting changes in gene expression. Control is achieved through several post-translational modifications that occur both on DNA and chromatin. Specific modifications mediate many developmental processes and adult brain functions, such as synaptic plasticity and memory. In this review, we focus on critical chromatin remodeling events that mediate long-lasting neuronal responses. The challenging goal is to reach sufficient understanding of these epigenetic pathways in the brain so that they may be useful for future development of specific pharmacological strategies.

Introduction

'Memory is the diary that we all carry about with us': this quote is not from a neuroscientist, but from Oscar Wilde, who unknowingly highlighted the conceptual role that epigenetics may play in governing the complex mechanisms that underlie memory and neuronal plasticity. A myriad of highly elaborated functions take place in neurons within highly specialized regions of the brain. Since the genome of all neurons in one individual is obviously the same, how to account for the astounding differences of cell types, functions, synaptic connections and plasticity remains unclear. Research in the field of epigenetics appears to provide some answers. Conrad Waddington, a developmental biologist first used the word 'epigenetics' to describe how identical genotypes could generate a wide collection of phenotypes during development [1]. Evolution in the field subsequently imposed additional meanings, so that today epigenetics may indicate "potentially heritable changes in gene expression that do not involve changes in DNA sequence" [2], or even "potentially heritable covalent modifications of chromatin that influence gene expression without changes in DNA sequence" [3]. These loose definitions have acquired additional complexity with the realization that epigenetic control involves a variety of facets, including histone modifications, miRNA pathways, histone variants and DNA methylation [4]. What is the contribution of epigenetic control on neurons? Could the intrinsic plasticity of chromatin remodeling be the molecular foundation for some of the neuronal functions (such as storing information or translating external stimuli) that modulate gene expression? Also, could it be that deregulation of epigenetic processes may have serious pathological consequences, such as neurodegeneration? Importantly, despite the fact that neurons are fully differentiated post-

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mitotic cells, their chromatin shows a surprising level of plasticity [5]. Recently, evidence has started to connect a number of neuronal functions to epigenetic mechanisms of control. In this review we focus on the most recent findings that have established intriguing links between synaptic transmission, memory, drug addiction and the circadian clock to chromatin remodeling.

The alphabet of the epigenetic language: histone modifications

A significant portion of epigenetic control is exerted by dynamic chromatin transitions. Organization of chromatin involves various levels of complexity that are critical to accommodate all nuclear functions, including transcription, silencing, DNA replication and repair. We invite the readers to refer to various review articles that discuss the subject in depth [6–9]. The basic building block of chromatin is the nucleosome which is composed of 147 bp of DNA wrapped around an octamer of histone proteins (two copies each of H2A, H2B, H3 and H4). The N-terminal portion of the histones (commonly referred to as ‘histone tails’), are highly conserved sequences that extrude from the highly compacted nucleosome, and constitute privileged platforms for post-translational modifications (PTMs). A large variety of PTMs can affect the N-terminal histone tails, including acetylation, phosphorylation, methylation, ubiquitination and sumoylation (Figure 1) [6]. While phosphorylation is directed to serine and threonine residues, and arginines can be methylated, lysines are targets for most modifications. Importantly, a large body of evidence supports a scenario in which combinatorial modifications correspond to specific functional chromatin states [10]. Individual PTMs can favor or inhibit consequent modifications on nearby residues of the same tail [11]. Moreover, examples of PTMs that influence modifications on different tails also have been reported [12]. As lysines can be modified in various manners, it is the competition between various PTMs for the same residue that may determine functional outcomes. For example, the lysine 9 residue of the H3 tail can be acetylated or methylated; while acetylation is associated with transcriptional activation, methylation is associated with silencing [10]. In addition, the same modification may be linked to totally opposite functions: histone H3 and H4 lysine or arginine methylation can promote both transcriptional activation or repression [13]. The combinatorial nature of histone PTMs at specific residues is revealing [14]: i. e., H3-K4 methylation facilitates subsequent H3 and H4 acetylation [15], whereas histone deacetylation and methylation of H3-K9 lysine represses transcription [16]. Another example is phosphorylation of Ser-10 on H3, a positive signal for subsequent acetylation at K14 on the same tail [17,18]. These observations have suggested the presence of the so-called ‘histone code’, a thesis based on the concept that distinct combinatorial histone PTMs could correspond to and possibly determine specific biological responses [19]. In another elaboration, the ‘epigenetic indexing code’, we have suggested that progressive histone PTMs may allow the epigenetic transition from an ‘unlocked state’ to a ‘locked state’. In this scenario, the unlocked state still allows plasticity in the response, while the locked state – that could ultimately implicate DNA methylation – would be irreversible [5].

A critical hallmark of histone modifications is that these are modulated by activation of intracellular transduction pathways [20]. Specific signaling pathways target the enzymatic machinery devoted to modify chromatin, by either inducing phosphorylation of specific regulators, or by modulating their interactions [21,22]. Indeed, all PTMs are brought by specific enzymes whose nature and function has been at the heart of epigenetic research in the past decade. We have conceptually divided these proteins in ‘writers’, ‘readers’ and ‘erasers’ [5]. Writers include kinases, HATs (histone acetyltransferases) and HMTs (histone methyltransferases), while erasers are composed of phosphatases, HDACs (histone deacetylases) and DMTs (histone demethylases). The group of proteins ‘readers’ is composed of a large number of regulators characterized by specific domains that are critical

in the recognition of specific PTMs [5]. Recently, a detailed nomenclature has been proposed for the major chromatin-modifying enzymes [23].

Epigenetic ‘tags’ in neurons

The dynamic changes in gene expression associated with neuronal plasticity involve events of chromatin remodeling [3,24]. Here we review some recent findings that implicate critical histone modifications in the modulation of neuronal function.

Phosphorylation

Histone phosphorylation at specific residues has been associated with a large number of neuronal responses [25]. Early observations demonstrated that hippocampal neurons show a powerful and transient phosphorylation at the Ser-10 residue of the histone H3 (H3-S10) in response to agonists activating dopaminergic receptors, muscarinic acetylcholine receptors and kainate glutamate receptors [26]. Further studies indicate that even psychological stress, such as the one induced by a forced swimming test in rodents, lead to the same modification [27].

Whether histone phosphorylation is causally linked to neuronal plasticity still awaits solid proof, but a number of studies have been providing significant evidence. Most studies have centered on H3-S10 phosphorylation. In proliferating cells, H3-S10 phosphorylation is brought about by the Aurora-B kinase and has been associated with condensation of chromatin at mitosis [28,29]. In mature neurons the same modification seems to play an important role in gene expression mediated by synaptic activity. An important direction has been to identify the kinases (the ‘writers’) for histone phosphorylation. H3-S10 phosphorylation has been connected to learning and memory, in part through the activity of two kinases: the mitogen- and stress-activated protein kinase 1 (MSK1) [Table 1] and the extracellular signal-regulated-kinases (ERKs)/mitogen-activated protein kinases (MAPKs). ERKs regulate the activity of Elk-1, a transcription factor involved in the activation of memory-associated genes [25]. MSK1 mediates the mitogen- and stress induced phosphorylation of H3-S10, of cAMP response element-binding protein (CREB) and of other transcription factors [30]. An intriguing case is the one of the Rsk-2 kinase. Mutations in the gene that encodes Rsk-2 contribute to the Coffin-Lowry syndrome, an X-linked disease characterized by mental retardation [31]. Rsk-2 was found to phosphorylate CREB and H3-S10 (Figure 2) [32,33]. The relative contribution of these kinases to induced H3-S10 phosphorylation in neurons of various brain regions and in response to a variety of stimuli is still unclear. Future studies using cell-specific ablation by homologous recombination for the genes encoding the kinases will help to elucidate this issue.

Knowledge about the phosphatases (the “erasers”) that dephosphorylate histones in neurons is very limited. Recently, the Ser/Thr phosphatase 1 (PP1) has been shown to play a role in chromatin remodeling in neurons [34]. PP1 associates with the histone deacetylase 1 (HDAC1) and the histone demethylase JMJD2A (jumonji domain-containing protein 2A) in the brain. Moreover, inhibition of PP1 activity in the forebrain of transgenic mice affects not only the levels of H3-S10 phosphorylation, but also H3-K36 tri-methylation and H3-K14, H4-K5 acetylation levels at the CREB promoter [Table 1] [34].

Methylation

Among all histone modifications, methylation is considered to be more stable due to its slow turnover. Lysine residues can be mono-, di-, or tri-methylated, while arginine residues can be mono or di-methylated with the di-methylation occurring in a symmetric or asymmetric fashion [35]. There are more HMTs (the ‘writers’) than all other enzymes in the classes of histone modifying proteins, suggesting that the role of methylation in chromatin remodeling

involves a high degree of specificity and complexity. In addition, the identification of lysine demethylases (DMTs, the ‘erasers’) for almost all of the well-known sites for lysine methylation in histones raises the possibility that all three degrees of methylation are reversible [36]. While histone methylation is almost always associated with transcriptional silencing, methylation at the H3-K4 residue is considered to be a hallmark of gene activation [37]. A number of findings indicate that some of the enzymes involved in histone methylation have unique functions in neurons. For example, misregulation of the H3-K4 tri-demethylase SMCX, that acts as a transcriptional repressor on sodium channel type 2A (SCN2A) and synapsin1 promoters, results in X-linked mental retardation (Figure 2) [38]. Methylation at H3-K9 also appears to be critical: it was recently shown that postnatal neuron-specific deficiency of the complex composed by the H3-K9 dimethyltransferases G9a/GLP results in derepression of nonneuronal (e.g. *Serpinb1b*, *Serpinb5*) and early neuron progenitor (e.g. *Dach2*) genes [39*]. This event reflects on complex behavioral abnormalities, such as defects in learning, motivation and environmental adaptation [Table 1] [39*].

In addition to histones, DNA also becomes methylated [40,41], an epigenetic process that has been associated with the postulated establishment of a ‘locked’, irreversible state [5]. Interestingly, DNA methylation has been also associated with synaptic activity and memory formation [42]. Methylation of CpG islands is an important regulatory mechanism for chromatin remodeling in the mammalian nervous system [43]. The activity of brain-derived neurotrophic factor (BDNF) during memory formation is regulated through DNA methylation [44]. Moreover, *BDNF* gene expression has been linked to reduced DNA methylation and the release of a repressor complex comprising the methyl-CpG-binding protein 2 (MeCP2) [45,46]. Mutations in the *MeCP2* gene, that recruits histone deacetylases to methylated DNA, cause the neurodevelopmental X-linked disorder known as Rett syndrome (Figure 2) [47,48]. In a recent study, early life stress (ELS) was linked to DNA methylation [49*]. Adult ELS-exposed mice show memory deficits and upregulation of arginine vasopressin (AVP) expression in neurons of the hypothalamic paraventricular nucleus. Moreover, altered AVP expression is associated with DNA hypomethylation of CpG residues that are DNA-binding sites for the protein MeCP2 [49*]. The impaired learning is thought to result from the effects of prenatal stress on hippocampal function [50]. In addition, a recent study links Gadd45b (growth arrest and DNA-damage-inducible protein 45b) to DNA methylation. This protein promotes DNA demethylation at key regulatory regions of the genes encoding brain derived neurotrophic factor (BDNF) and fibroblast growth factor 1, both crucial genes for adult neurogenesis [51*].

Acetylation

HATs-mediated addition of acetyl groups to histone H3 and H4 is thought to decrease the affinity between DNA and histone proteins, allowing genes to be transcribed. This covalent modification is considered to be highly dynamic and reversible by the removal of the acetyl group mediated by HDACs [52]. The CREB-binding protein (CBP), a transcriptional coactivator with HAT activity, [53] appears to play an important role in synaptic plasticity and long term memory (Figure 1) [54]. Phosphorylation of CREB induces its association with CBP and transcriptional activation on the promoter of the target genes [55]. Mutations within the HAT domain of CBP cause the Rubinstein-Taybi syndrome (RSTS), that is characterized by mental retardation (Figure 2) [56]. Moreover, haploinsufficient mice for CBP display altered neuronal plasticity and aberrant histone acetylation at target promoters [57]. On the other hand, histone deacetylation is not permissive for long term memory storage, since inhibition of HDACs by non selective HDACs inhibitors is reported to enhance synaptic plasticity [58,59]. However, HDAC2 has been recently implicated in negative regulation of memory formation and synaptic plasticity [Table 1] [60**]. HDAC2 is

recruited at the promoter of critical genes implicated in synaptic remodelling and plasticity (*Bdnf* promoter I/II, *Fos*, *Nrn1*, *Creb1*, *Crebbp*). Interestingly, the treatment with suberoylanilide hydroxamic acid (SAHA), a pharmacological inhibitor of class I and II HDACs, improves memory and synaptic activity. In keeping with these results, HDAC2 overexpression results in decreased spine density and synapse number, while HDAC2 inhibition causes the same response as SAHA treatment [60^{**}]. Finally, it has been shown that inhibition of HDAC1 and HDAC2 during early synaptogenesis has remarkable and specific consequences [61^{*}]. Using mice with conditional mutations in the genes encoding these two HDACs, it was shown that a decreased activity of both HDAC1 and HDAC2 in immature hippocampal neurons triggers excitatory synapse maturation. Conversely, only HDAC2 inhibition, but not HDAC1, reduces excitatory synaptic activity in mature neurons [61^{*}].

Chromatin remodeling in drug-induced plasticity

Drugs of abuse cause addiction by producing long-lasting changes in synaptic plasticity in the brain [62]. The mesolimbic dopamine system has been proposed as a key component in mediating the rewarding action of drugs [63]. This area comprises the dopaminergic neurons in the ventral tegmental area (VTA) of the midbrain and several forebrain structures innervating from these neurons. One such structure is the nucleus accumbens (also called the ventral striatum). The nucleus accumbens (NAc) has been identified as a key site for drug-induced changes in gene expression, largely mediated by the dopaminergic system [64].

Intuitively, it seems conceivable that acute or chronic treatment of drugs can activate or repress different sets of genes, depending on the type of drug used. Some studies implicate the action of different HATs and HDACs in this process. For example, acute treatment with cocaine increases H4 acetylation at the level of the promoter of specific genes (*cFos* and *FosB*), whereas chronic treatment upregulates H3 acetylation at the promoter of *FosB*, *Cdk5* and *BDNF* genes [65]. CBP, through its HAT activity, elicits H4 acetylation and increases *FosB* expression [66]. The loss of *cFos* induction after chronic cocaine treatment has been linked to the Δ FosB-mediated recruitment of HDAC1 on its promoter [67]. Δ FosB is a truncated splice variant of *fosB* that is induced by chronic, but not acute, drug treatment [68]. Moreover chronic, not acute, cocaine treatment induces chromatin remodeling in the nucleus accumbens through the activity of a class II histone deacetylase, HDAC5. After chronic injection of cocaine, HDAC5 phosphorylation is triggered. This event results in the nuclear export of HDAC5 and consequently in increased histone acetylation at the promoter of HDAC5 target genes [69].

A highly interesting group of HDACs constitutes the class III. These proteins take the general name of sirtuins, from the original yeast Sir2 protein [70]. There are seven SIRT proteins in mammals, located in various cellular compartments. Sirtuins are unique because of their dependence on NAD⁺ as a coenzyme, thereby establishing a direct link between chromatin remodeling and cellular metabolism [71]. Sirtuins have been implicated in regulating metabolism, aging and neurodegeneration [72–74]. Both mRNA levels and the catalytic activity of SIRT1 and SIRT2 are up-regulated after chronic cocaine treatment. Biochemical analyses reveal an increase in Δ FosB binding on the *sirt2* promoter in the nucleus accumbens (NAc), indicating a potential role in drug addiction. Finally, treatment with the natural sirtuin activator resveratrol appears to increase neuronal electrical excitability and potentiates the rewarding effects of cocaine in NAc medium spiny neurons (Figure 1) [75^{**}].

A recent study links histone methylation to cocaine-induced plasticity [76^{**}]. For example repeated cocaine treatments were shown to reduce global H3-K9 di-methylation levels in the

nucleus accumbens, a result of Δ FosB-mediated repression of the histone methyltransferase G9a transcript (Figure 1). Notably, G9a down-regulation results in increased dendritic spine density in the NAc after cocaine treatment [76**]. Recent findings also correlate the NAc-VTA pathway to mood regulation and depression [77]. Finally, chronic social stress is reflected by changes in H3 acetylation in the NAc, and administration of HDACs inhibitors produces antidepressant effects [78*]. Altogether, these studies underscore the importance of chromatin remodeling complexes in fine-tuning multiple brain activities.

Epigenetics and time: the circadian clock connection

Circadian cycles take place approximately every 24 h and dominate a large array of physiological and metabolic functions in most life forms. In mammals, the master pacemaker, a group of about 15,000 neurons, is located within the hypothalamic suprachiasmatic nucleus (SCN) and it is capable of synchronizing peripheral oscillators [79]. The mammalian clock machinery is composed of three period proteins (PER1, PER2 and PER3), two cryptochromes (CRY1 and CRY2), CLOCK and two BMAL1 proteins. After translation, PER and CRY proteins form a complex and translocate into the nucleus to inhibit CLOCK:BMAL1-mediated transcription, thereby closing the negative loop. Notably, it has been described that at least 10% of all mammalian transcripts oscillate in a circadian manner [80], revealing an interesting connection between the circadian clock, metabolism, cell cycle and chromatin remodeling [81]. Moreover, CLOCK, a master clock regulator, has intrinsic HAT function and can acetylate histones (H3-Lys 14 and to a lesser extent H3-Lys9 and H4) [82]. Importantly, CLOCK also acetylates non-histone proteins, such as its transcriptional partner BMAL1, and possibly others [83]. CLOCK interacts with SIRT1, establishing a revealing link between the circadian clock, cellular metabolism and aging/neurodegeneration [84,85]. Interestingly, the levels of NAD⁺, a SIRT1 activator, that oscillate in a circadian fashion. This oscillation is achieved through the activity of CLOCK and BMAL1 on the *Nampt* gene promoter, a rate limiting enzyme in the NAD⁺ salvage pathway [86,87]. SIRT1 is recruited to the *Nampt* promoter in a circadian fashion contributing to the circadian chromatin remodeling on the promoter of this gene. Importantly, SIRT1 is linked to aging-related neurodegenerative diseases [88].

Circadian rhythms are critical for many brain functions, being intimately associated with the sleep-wake cycle and mood [89,90]. It has been postulated that circadian functions may be modulated by neuronal responses, and specifically dopaminergic signaling, which is highly active in clock structures [91]. Thus, an intriguing molecular link thereby may exist that could connect the circadian clock machinery to dopamine neurotransmission. This may occur mainly through D2 receptors [92]. Interestingly, dopamine is the major catecholamine in the vertebrate retina playing a central role in adaptation to light [93]. From a transcriptional viewpoint, activation of dopamine D2 receptors potentiates the transcriptional activity of CLOCK:BMAL1, through the MAPK signaling pathway [94]. As CLOCK has a HAT activity, it is tempting to speculate that dopamine could exert its role by targeting the HAT function of CLOCK. While this is yet unclear, it appears that D2R-mediated signaling plays a central role in the control of light masking of circadian locomotor activity [95]. Finally, the photic pathway of the circadian system involves DARP-32, a phosphatase that operates as an important molecular target of the dopamine signaling pathway [96]. D2 receptors are also capable to modulate Akt/GSK-3 β pathway *in vivo* [97]. The kinase GSK-3 β is regulated by the antidepressant lithium [98] and phosphorylates different clock proteins, such as PER2, CRY2, Rev-Erba, but also CLOCK and BMAL1 [99–103]. Moreover, new lines of evidence emphasize the influence of the circadian clock in memory [104]. The activity of the cAMP and MAPK signaling pathways, which play a pivotal role in the consolidation of hippocampus-dependent memory, oscillate in a circadian

fashion [105*]. In conclusion, multiple links between the circadian clock machinery, chromatin remodeling and neuronal responses exist.

Conclusions and future directions

In recent years accumulating data highlight a critical role for the epigenetic code in neurons. As mentioned above, histone deacetylation appears to prevent long-term memory storage, a finding that suggests the intriguing possibility that the use of HDACs inhibitors as a therapeutic agents for the treatment of cognitive impairments might be possible [60**]. As exciting are findings linking histone deacetylation to cocaine-induced chromatin remodeling. Sirtuin activators, such as resveratrol, increase neuronal electrical excitability and potentiate the rewarding effects of cocaine [75**]. These results suggest that the use of sirtuin inhibitors may be valuable therapeutic agents for cocaine addiction. In conclusion, chromatin remodeling events seem to constitute privileged checkpoints for the induction and establishment of neuronal responses. The challenge for the future will be to dissect highly specific epigenetic pathways implicated in the modulation of unique functions in the brain such as synaptic plasticity, memory, addiction and the stress responses. These would represent highly promising avenues of pharmacological exploration.

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Fig. 1.

Partial view of the histone H3 N-terminal tail and some of the key post-translational modifications, including phosphorylation, acetylation and methylation at specific residues. A larger number of modifications occur on the H3 tail as well as on the tails of the other histones (6,10,14, 19). Some regulators indicated here are implicated in chromatin remodeling and have been shown to link specific neuronal functions to distinct histone modifications. Thus, signaling elicited by neuronal responses may be translated in epigenetic changes leading to either activation or silencing of gene expression. The 'epigenetic indexing code' scenario [5] indicates that modifications may become more stable and less reversible upon sustained and/or repetitive signaling events.

Fig. 2.

A number of neurodegenerative disorders and mental retardation disorders have an epigenetic basis. This is a partial view of the epigenetic regulators which have been demonstrated to have direct links with specific events of chromatin remodeling and their effect on gene expression.

Table 1

Protein	Activity	Neuronal function
MSK1	CREB phosphorylation H3-S10 phosphorylation	Long term memory formation
Rsk-2	CREB phosphorylation H3-S10 phosphorylation	Long term memory formation
PP1	H3-S10 dephosphorylation	Long term memory formation
G9a/GLP	H3-K9 di-methylation	Cognition and adaptative behaviour
SMCX	H3-K4 tri-demethylase	Cognitive functions
MeCP2	Methyl CpG binding protein	Memory and synaptic plasticity
CBP	Histone acetyltransferase	Long term memory consolidation
HDAC2	Histone deacetylase	Negative regulator of synaptogenesis and memory formation