REVIEW ARTICLE

Chromatin Changes Associated with Neuronal Maintenance and Their Pharmacological Application

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Abstract: ***Background***: The transcriptional control of neuronal specification and early development has been intensively studied over the past few decades. However, relatively little is known about transcriptional programs associated with the maintenance of terminally differentiated neuronal cells with respect to their functions, structures, and cell type-specific identity features.

Methods: Notably, largely because of the recent advances in related techniques such as next generation sequencing and chromatin immunoprecipitation sequencing, the physiological implications of system-wide regulation of gene expression through changes in chromatin states have begun to be extensively studied in various contexts and systems, including the nervous system.

Results: Here, we attempt to review our current understanding of the link between chromatin changes and neuronal maintenance in the period of life after the completion of neuronal development. Perturbations involving chromatin changes in the system-wide transcriptional control are believed to be closely associated with diverse aspects of neuronal aging and neurodegenerative conditions.

Conclusion: In this review, we focused on heterochromatin and epigenetic dysregulation in neurodegenerative conditions as well as neuronal aging, the most important risk factor leading to neuronal degeneration, in order to highlight the close association between chromatin changes and neuronal maintenance. Lastly, we reviewed the currently available and potential future applications of pharmacological control of the chromatin states associated with neuronal maintenance.

1. INTRODUCTION

Once terminally differentiated, neurons acquire many common properties, such as the ability to actively secrete and re-uptake molecules, undergo rapid changes in membrane potential, and dynamically change their terminal structures for forming synapses with other neurons and excitable cells (*e.g.*, neuromuscular junction). Interestingly, these common properties lie within certain homeostatic ranges, indicative of the presence of certain types of maintenance

mechanisms in neurons (reviewed in [1]). This, in turn, means that any perturbation of these mechanisms during neuronal aging or in neurodegenerative conditions may be a major contributor to the manifested neuronal phenotypes. At this point, it should also be noted that there exist tremendously diverse types of neurons that maintain their own unique identity features (*e.g.*, the cell-type specificity of secreted neurotransmitters) for up to many decades, an ability that should be added to the list of the commonly shared properties described above (reviewed in [1]). These neuron type-specific identity features are thought to be largely dependent on corresponding gene expression profiles, given that all neurons in the body of an animal share the same genomic information (*i.e.*, the same DNA) [2, 3]. With respect to expression, chromatin changes able to confer diversity to neuronal gene expression patterns (reviewed in [4]) appears to be one crucial factor regulating the maintenance of these

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neuronal cell type-specific identity features. Interestingly, a constantly growing literature indicates that chromatin changes may also contribute to the neuronal maintenance of certain properties commonly shared by neurons, such as synapse formation (reviewed in [5]). Thus, chromatin states may be involved in regulating two distinctive features of neuronal maintenance, namely specifying and maintaining unique identity features of each neuronal type, and maintaining the common properties of neurons regardless of their cell type.

Chromatin is found in two forms, transcriptionally active accessible euchromatin and transcriptionally silenced, tightly packaged heterochromatin, with transitions between these two states known to be primarily mediated by epigenetic mechanisms. There are two major types of epigenetic mechanisms, namely DNA CpG methylation and histone modification [6]; these are mediated by the combinatorial actions of many different classes of regulator molecules, such as DNA methyltransferases (DNMTs), histone acetyltransferases (HATs), and histone deacetylases (HDACs) [7]. Chromatin changes can also be mediated by ATP-dependent chromatin remodeling complexes (reviewed in [8]). Notably, and largely because of recent advances in related techniques, the physiological implications of system-wide regulation of gene expression through chromatin changes have begun to be extensively studied in various contexts and systems, including the nervous system (reviewed in [4]). In the following sections, we review the chromatin changes in two closely related neuronal conditions resulting from failures in neuronal maintenance, namely neurodegenerative diseases and neuronal aging, and discuss the pharmacological application of epigenetic drugs to treat these conditions.

2. HETEROCHROMATIN DYSREGULATION IN NEURODEGENERATIVE DISEASES

Maintenance of the heterochromatin and euchromatin states is crucial for gene regulation and genome stability. Histone hypoacetylation, methylation of histone H3 on lysine 9 (H3K9me), presence of HP1 (heterochromatin protein 1), and cytosine methylation are the epigenetic markers of heterochromatin [9]. In addition, a series of protein components, such as histone H3K9 methyltransferases and the HP-1-binding protein, ATRX (alpha thalassemia/mental retardation X linked), have been implicated in heterochromatin formation [10, 11]. Given the essential roles of heterochromatin in gene regulation and genome stability, it comes as no surprise that a number of human diseases are connected to dysregulation of heterochromatin [12]. Notably, both abnormal condensation and relaxation of heterochromatin have been linked to neurodegenerative diseases (Fig. **1**).

In patients with Huntington's disease (HD) and transgenic HD mice, the expression of the ERG-associated protein with SET domain (ESET; also known as SETDB1), a histone H3K9 methyltransferase, and the abundance of histone H3 trimethylated on lysine 9 (H3K9me3) are markedly increased [13]. In the same study, suppression of the increased H3K9me3 level by down-regulating ESET expression rescues the neurological phenotypes of the HD-model mice [13]. Another study showed that mutant Huntingtin (mtHtt), which contains an expanded polyglutamine (polyQ) repeat sequence, induces expression of ATRX [14], a DNA-dependent ATPase/helicase with chromatin remodeling activity that belongs to the SNF2 family [15, 16]. ATRX overexpression induces condensation of pericentromeric heterochromatin in mammalian cells, while knockdown of *Drosophila* ATRX reduces the toxicity of mtHtt in a *Drosophila* HD model [14]. Thus, it seems likely that ATRX contributes to the pathogenesis of HD by regulating heterochromatin condensation. As a whole, these studies suggest that abnormal heterochromatin condensation induced by mtHtt may be an important event in the pathogenesis of HD.

Aberrant heterochromatin changes have also been implicated in Parkinson's disease (PD). In a PD mouse model generated by injecting 6-hydroxydopamine (6-OHDA) into the brain, the induced neuronal loss was accompanied by disruption of heterochromatin marks, such as lower H3K9me3 and H3K27me3 levels and reduced size of 4′,6-diamidino-2-phenylindole-dense spots in the dopaminergic neurons [17], whereas a second brain injection with the Engrailed homeoprotein, which has been associated with PD [18, 19], suppressed the 6-OHDA-induced heterochromatin loss [17]. Moreover, the same study identified several chromatin remodeling-associated genes, including *suv39h2* and *phf1*, as differentially expressed genes in *Engrailed1* heterozygous mouse. However, the molecular mechanisms through which Engrailed contributes to heterochromatin maintenance are yet to be uncovered.

In Alzheimer's disease (AD), the microtubule-associated tau protein, which is the major component of neurofibrillary tangles, acts as a downstream effector of amyloid β to induce neurotoxicity *via* various mechanisms [20]. One of these is its role in heterochromatin formation [21, 22]. Besides its microtubule-associated functions, nuclear tau protein binds to pericentromeric DNA [23] and regulates the integrity of neuronal pericentromeric heterochromatin [22]. In addition, global heterochromatin loss has been observed in the brains of AD patients, as well as in those of tau transgenic flies and mice [21]. Moreover, the tau-induced heterochromatin relaxation results in the aberrant expression of heterochromatic genes that have been suggested to induce apoptosis of neurons *via* promoting erroneous cell cycle reentry, such as piwi like RNA-mediated gene silencing 1 (*PIWIL1*) [21, 24]. More recently, it was reported that lamin dysfunction induced by tau is responsible for heterochromatin relaxation and cell cycle reentry in neurons [25]. As a whole, these data suggest that tau, a major player in AD, may perform important functions in maintaining heterochromatin structure; disruption of heterochromatin by aberrant tau regulation seems to be a critical step in AD pathogenesis.

3. EPIGENETIC CHANGES UNDERLYING DEFECTIVE SYNAPSE FUNCTION CAUSED BY NEURONAL AGING AND NEURODEGENERATIVE DISEASES

In addition to heterochromatin dysregulation, neuronal aging and neurodegenerative diseases are accompanied by shifts in the epigenetic signatures [26]. For example, in aging rodent cerebral cortex and hippocampus, the open chromatin-associated H4 acetylation decreases, while methylated H3K9, a repressive chromatin marker, is up-regulated [27]. Another study reported that the brains of senescence-
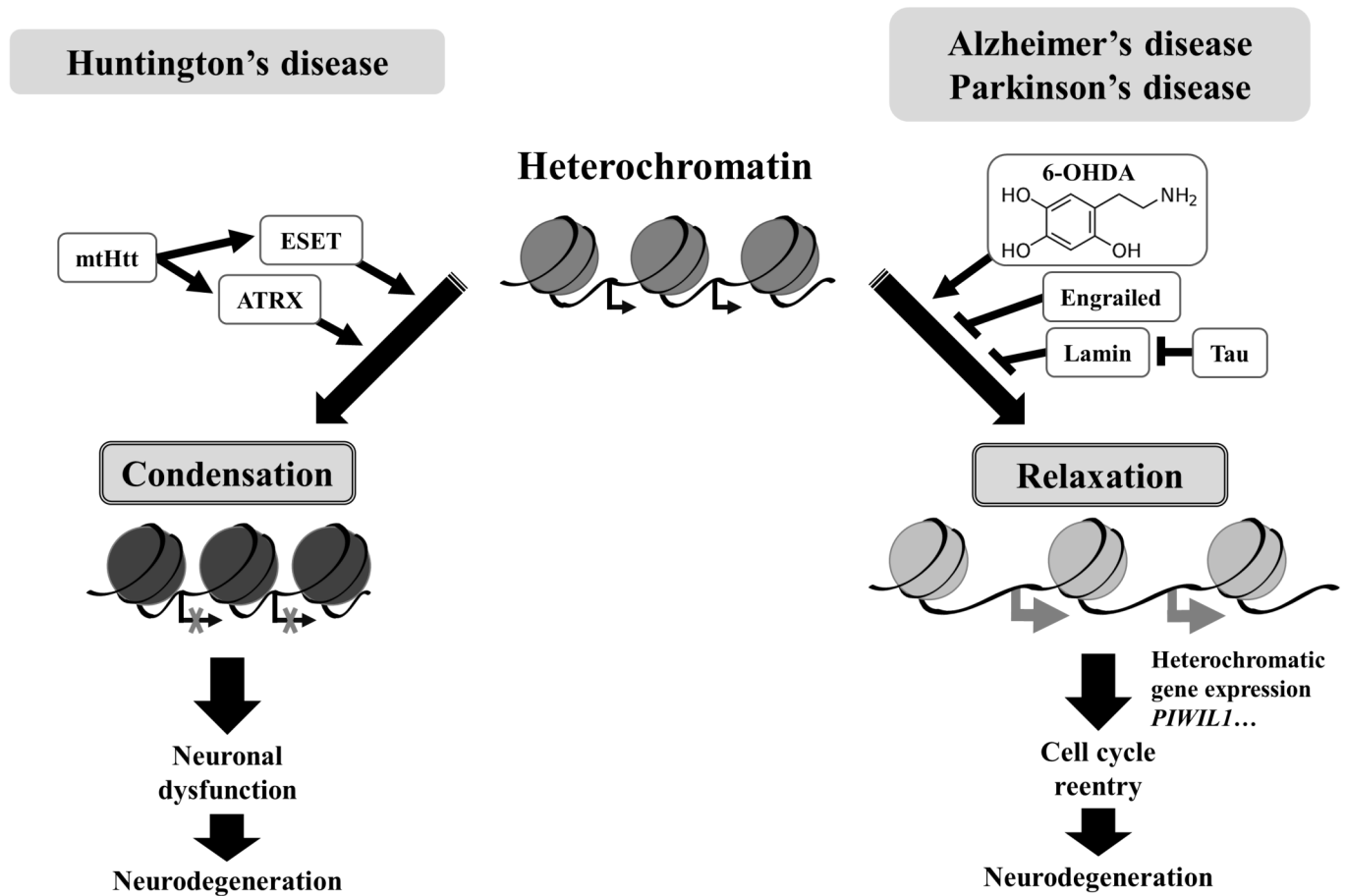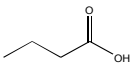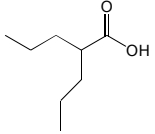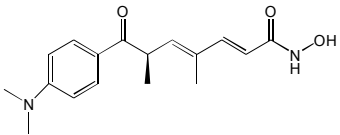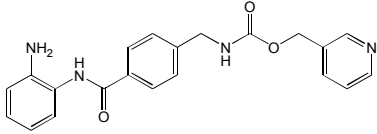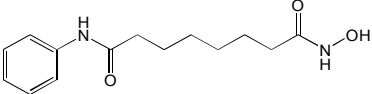
Fig. (1). Heterochromatin dysregulation in neurodegenerative diseases. Mutant Huntingtin (mtHtt) with expanded polyglutamine repeats induces the formation of heterochromatin by activating the expression of heterochromatin-related genes, such as ESET and ATRX. T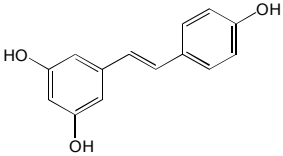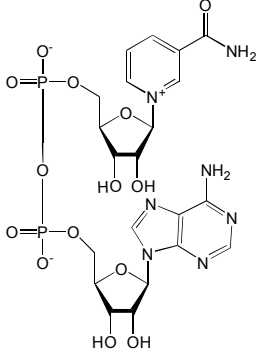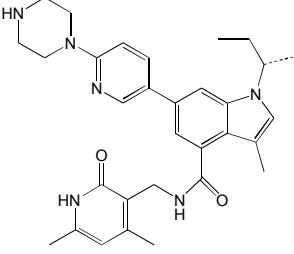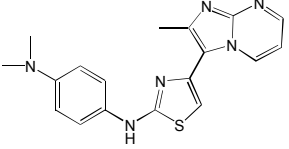his aberrant hypercondensation of chromatin contributes to the pathology of Huntington's disease by inducing neuronal dysfunction and apoptosis. On the contrary, the pathologies of Parkinson's disease and Alzheimer's disease are associated with the relaxation of heterochromatin that is induced by 6-OHDA and dysregulated tau protein, respectively. The Engrailed protein suppresses the 6-OHDA-induced heterochromatin relaxation and neurotoxicity. The dysfunction of lamin caused by pathological tau is responsible for the tau-induced heterochromatin relaxation. This chromatin change promotes erroneous cell cycle reentry by inducing aberrant expression of heterochromatic genes, such as *PIWIL1.* ATRX, alpha thalassemia/mental retardation X linked; ESET, ERG-associated protein with SET domain; mtHtt, mutant Huntingtin; PIWIL1, piwi like RNA-mediated gene silencing 1; 6-OHDA, 6-hydroxydopamine.

accelerated prone mice show reduced levels of certain transcriptional markers, such as the monomethylated histone H4K20 and trimethylated H3K36, and a concomitant increase in the level of the repressive marker, H3K27me3 [28]. Moreover, memory disturbances in a mouse model of aging brain were shown to be associated with altered hippocampal chromatin plasticity attributed to deregulated H4K12 acetylation [29]. Similar to these results in aged mice, an APP-PS1 transgenic mouse model for AD showed impaired induction of H4 acetylation following fear-dependent learning [30], and AD-related cognitive deficits in aged AD mice were ameliorated by reducing HDAC6 [31]. In addition, a recent study analyzing postmortem human brain and mouse brain samples reported the accumulation of a variant histone H3.3 with age along with a concomitant decrease in canonical histones (H3.1 and H3.2) [32]. However, the exact causal relationship between neuronal aging or neurodegenerative diseases and epigenetic changes remains elusive.

Notably, two of the most prominent phenotypes of aging animals, namely cognitive decline and loss of motor function, involve degradation of proper neuronal functions (reviewed in [5]) similar to what can occur in neurodegenerative diseases. Among many neuronal features, defects in synapse function and structure have been well described in aging animals, and are suspected as a crucial contributor to the age-related decline in cognitive and memory functions (reviewed in [5, 33]). Indeed, aging and neurodegenerative diseases have been shown to cause obvious dendrite aberration in the neurons of model animals [34-36]. Given that proper synapse formation requires the meticulous transcriptional orchestration of many genes [37], system-wide transcriptional dysregulation involving chromatin changes is thought to be a crucial contributor to age-associated changes in synapse formation. In support of this idea, Guan *et al.* reported that genetic modulation of the HDAC2 level leads to obvious changes in the synaptic structure in mouse hippocampus

Table 1. **Selected disease targets and their modulator candidates.**

Target	Disease	Mechanism	Compound	Structure
HDACs	AD HD Ataxia Telangiectasia	Inhibitor	Butyrate	
			Valproic acid	
			Trichostatin A	
			Entinostat	
			Vorinostat	
SIRT1	AD	Activator	Resveratrol	
			NAD$^+$	
EZH2	Ataxia Telangiectasia	Inhibitor	GSK126	
REST	HD	Inhibitor	C91 [58]	Not disclosed
			Compound 19 [59]	

[38]. In the same study, overexpression of HDAC2 (but not HDAC1) in neurons was shown to decrease dendritic spine density, synapse number, and synaptic plasticity, while HDAC2 deficiency leads to an increase in synapse number. A recent study showed that binding of HDAC2 was higher and the levels of H3K9 and H3K14 acetylation were lower at the promoter of hippocampal plasticity genes in old mice compared to young mice [39]. In the same study, HDAC2 inhibition suppressed the reduction of the plasticity gene expression during aging. Additionally, several other studies reported that decreased acetylation of H4K12 and histone turnover in aged animals or some neuronal diseases are correlated with a decline in activity-dependent synaptic plasticity [32, 40-42]. Thus, collectively, epigenetic changes may account, to a certain extent, for certain neuronal phenotypes, such as the changes in synapse formation, caused by neuronal aging or neurodegenerative diseases.

4. PHARMACOLOGICAL CONTROL OF CHROMATIN STATES FOR NEURONAL MAINTENANCE

Given that pharmacological manipulation of epigenetic factors and processes can significantly affect neuronal maintenance, the discovery and validation of therapeutic targets are of most importance. Among HDACs, HDAC4 may be a promising therapeutic target, as its nuclear accumulation directly contributes to neurodegeneration in ataxia telangiectasia [43], while HDAC4 downregulation reduces cytoplasmic mtHtt aggregate formation and ameliorates the neurodegenerative phenotype in a HD mouse model [44]. Furthermore, deficiency of SIRT1 (it belongs to another class of HDACs) in mice microglia, seems to be responsible for age-related cognitive decline and neurodegeneration [45]. In accordance with the above results, a variety of HDAC inhibitors, such as sodium butyrate, suberoylanilide hydroxamic acid (SAHA, also known as vorinostat), entinostat, trichostatin A (TSA), and valproate (VPA), have been demonstrated to reverse memory defects as well as reduce neuroinflammation and amyloid plaque accumulation in various AD models [30, 46, 47]. In addition, a couple of studies have shown that HDAC inhibitors may also be effective in HD models [48]. One of the main concerns for the clinical use of HDAC inhibitors is, however, their promiscuous inhibitory activity, *i.e.*, their ability to inhibit multiple HDAC proteins. Therefore, for HD, the discovery of a specific HDAC4 inhibitor may hold great potential to mitigate symptoms and avoid potential toxicity. For SIRT1, there are many reports suggesting that sirtuin-activating compounds (STACs), including resveratrol and NAD^+, improve organ function, ameliorate metabolic disorders, and prolong life [49]. Several lines of evidence demonstrate that enzymes of the NAD^+ metabolic pathway have a key role in peripheral neuropathies [50]; however, it has not been yet investigated whether administration of STACs to animal models of neurodegenerative diseases has any therapeutic effect.

Polycomb repressive complex 2 (PRC2) has been demonstrated to facilitate neural development by repressing non-neuronal gene expression; this is achieved through the increase of H3K27me3, which is catalyzed by two enzymes of the complex, namely EZH1 and EZH2 [51]. Moreover, it has

been reported that EZH2-mediated increase in H3K27me3 levels directly contributes to neurodegeneration in ataxia telangiectasia [52], suggesting that several potent EZH2 inhibitors initially developed as anti-cancer reagents, such as GSK126, may be promising therapeutic candidates. Conversely, increased expression of proteins belonging to the Polycomb group, including EZH2, results in global transcriptional repression and exert a protective effect during ischemia and brain seizures [53, 54]. Furthermore, a recent study clearly showed that deficiency of EZH1 and EZH2 in the adult forebrain leads to the de-repression of genes that are detrimental to neurons, resulting in progressive neurodegeneration [55].

Another important transcriptional repressor, the RE1-silencing transcription factor (REST), is known to be involved in neurodegeneration and neuronal aging. REST is an important transcriptional and epigenetic factor for neuronal development, acting as a scaffold for HDACs, the histone demethylase LSD1, as well as two co-repressors, namely mSIN3a/b and coREST. REST and its partners have been implicated in the modulation of large numbers of neural genes and in cross-talk with the aforementioned Polycomb complex [56, 57]. In diseases such as AD, frontotemporal dementia, and dementia with Lewy bodies, REST is excluded from the nucleus of neurons in the hippocampus and localizes at autophagosomes, whereas it accumulates in the nuclei of the neurons in healthy-aging humans [58]. By contrast, mtHtt in HD is not able to sequester REST in the cytoplasm, resulting in its translocation to the nucleus and transcriptional dysregulation, which is one of the hallmarks of the molecular pathophysiology of HD [59, 60]. These findings suggest that modulating REST and its complex could be therapeutically promising; several small-molecule inhibitors are now being investigated to target the activity of the REST complex [61, 62].

The major concern regarding the use of epigenetic modulator compounds is that the inhibition or augmentation of epigenetic factors may affect the global transcriptional profile in various tissues in different ways, even if a certain compound modulates a specific protein. To evaluate and increase the benefit-risk ratio, careful dosing and long-term studies are required before human application.

CONCLUSION

Here, we reviewed current knowledge on the chromatin changes associated with neuronal maintenance, and discussed potential pharmacological applications for neurodegenerative diseases (Table **1**). Accumulating evidence suggests that the alteration of heterochromatin structure and the subsequent dysregulation of gene expression profiles may be responsible for failures in neuronal maintenance, leading to either neuronal aging or neurodegenerative conditions. Notably, recent technical advances begin to open up the way for us to better analyze the relationship between chromatin changes and neuronal maintenance. For example, single-cell sequencing of the transcriptome and methylome allows us to integrate an epigenetic signature with the transcriptional output specifically in a neuron of interest in terms of neuronal aging, as was recently shown in studies using an *Aplysia*

model [63, 64]. Also, the Hi-C technique for "capturing" the conformation of genomes, which was presented in 2012 [65] is expected to prove very useful for monitoring the dynamic changes of chromatin states in terms of neuronal maintenance with high accuracy.

Lastly, we propose that emphasis should be placed on restoring proper transcriptional programming in the various neurodegenerative diseases by means of therapeutic intervention including epigenetic medicine, regardless of disease etiology. Indeed, the pharmacological modulators for epigenetic protein complexes are currently being very actively explored for the treatment of a variety of neurological diseases. However, it should also be noted that the field of epigenetic medicine is still at its dawn, and controversial data exist regarding the role of each epigenetic component. For this reason, a large number of additional studies are required for the practical application of epigenetic medicine in neurodegenerative disease treatment.

LIST OF ABBREVIATIONS

AD	=	Alzheimer's disease
ATRX	=	Alpha thalassemia/mental retardation X linked
H3K9me3	=	Histone H3 trimethylated on lysine 9
HD	=	Huntington's disease
HDAC	=	Histone deacetylase
mtHtt	=	Mutant huntingtin

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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