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REVIEW PAPER

Epigenetic Changes and Its Intervention in Age-Related Neurodegenerative Diseases

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Abstract

Epigenetic mechanisms involving the modulation of gene activity without modifying the DNA bases are reported to have lifelong effects on mature neurons in addition to their impact on synaptic plasticity and cognition. Histone methylation and acetylation are involved in synchronizing gene expression and protein function in neuronal cells. Studies have demonstrated in experimental models of neurodegenerative disorders that manipulations of these two mechanisms influence the susceptibility of neurons to degeneration and apoptosis. In Alzheimer's disease (AD), the expression of presenilin 1 (PSEN1) is markedly increased due to decreased methylation at CpG sites, thus promoting the accumulation of toxic amyloid-β (Aβ) peptide. In Parkinson's disease (PD), dysregulation of α-synuclein (SNCA) expression is presumed to occur via aberrant methylation at CpG sites, which controls the activation or suppression of protein expression. Mutant Huntingtin (mtHTT) alters the activity of histone acetyltransferases (HATs), causing the dysregulation of transcription observed in most Huntington's disease (HD) cases. Folate, vitamin B6, vitamin B12, and *S*-adenosylmethionine (SAM) are vital cofactors involved in DNA methylation modification; 5-azacytidine (AZA) is the most widely studied DNA methyltransferase (DNMT) inhibitor, and dietary polyphenols are DNMT inhibitors in vitro. Drug intervention is believed to reverse the epigenetic mechanisms to serve as a regulator in neuronal diseases. Nevertheless, the biochemical effect of the drugs on brain function and the underlying mechanisms are not well understood. This review focuses on further discussion of therapeutic targets, emphasizing the potential role of epigenetic factors including histone and DNA modifications in the diseases.

Keywords Epigenetics · Alzheimer's disease · Parkinson's disease · Huntington's disease · DNA methylation · Histone deacetylase

Abbreviations

AD	Alzheimer's disease
PSEN1	Presenilin 1
PD	Parkinson's disease
SNCA	α-Synuclein
mtHTT	Mutant Huntingtin
HD	Huntington's disease
HDACs	Histone deacetylases
SAM	*S*-Adenosylmethionine
AZA	5-Azacytidine
DNMT	DNA methyltransferase
HTT	Huntingtin
TF	Transcription factor
CREB	Cyclic adenosine monophosphate response element-binding protein
CBP	CREB binding protein
HATs	Histone acetyltransferases
FDA	Food and Drug Administration
ASD	Autism spectrum disorder
CGIs	CpG islands
HHCys	Hyperhomocysteinemia
NFTs	Neurofibrillary tangles
PP2A	Protein phosphatase 2A
SVs	Synaptic vesicles
LRRK2	Leucine-rich repeat kinase 2
CNV	Copy number variant
ChIP-Seq	Chromatin immunoprecipitation sequencing
HDACi	Histone deacetylase inhibitors
BBB	Blood–brain barrier
VA	Valproic acid

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FA	Folic acid
AzaC	Azacitidine
DNMTi	DNMT inhibitors
MDS	Myelodysplastic syndrome
NMDA	*N*-Methyl-D-aspartate
T6FA	Tacrine-6-ferulic acid
NPI	Neuropsychiatric inventory
ADL	Alzheimer's Disease Cooperative Study-Activities of Daily Living
DRTs	Dopamine replacement therapies
ICDs	Impulse control disorders
5-aza-dC	5-Aza-2′-deoxycytidine
RAR-β_2	Retinoic acid receptor-β_2
ATRA	All-*trans*-retinoic acid
SPB	Sodium phenylbutyrate
SAHA	Suberoylanilide hydroxamic acid
BDNF	Brain-derived neurotrophic factor

Introduction

Many studies over the last decade have strongly implicated epigenetic mechanisms in the regulation of gene expression involved in the regulation of several ageing-related diseases, such as cancer and heart failure, and in promoting the alteration of gene expression responsible for the ageing process of different tissues. Therefore, alteration of the epigenetic mechanisms occurring during ageing renders cells more prone to the transcriptional changes responsible for ageing-related diseases (Lovrečić et al. 2013; Pagiatakis et al. 2019).

Neurodegeneration is a progressive loss of neuronal function that often results in cell death and brain dysfunction (Lu et al. 2013). The phenotypic effects are related to the specific areas encountering cell death (Armstrong and Barker 2001). Aberrant collaboration between proteins that bring about unusual intracellular and extracellular accumulation of self-aggregating misfolded proteins and the development of high-ordered insoluble fibrils are pathological features of many neurodegenerative diseases (Jellinger 2001). Important proteins involved in Alzheimer's disease (AD), Parkinson's disease (PD) and Huntington's disease (HD) are amyloid precursor protein (APP), α-synuclein (SNCA), presenilin, tau, and Huntingtin (HTT) (Winner et al. 2011). SNCA is localized at the presynaptic terminal of neurons in the central nervous system (CNS) (Jakes et al. 1994) and dysfunction of this protein is a common hallmark in PD. The aggregation and deposition of these abnormal SNCA proteins in dopaminergic neurons have been postulated to be responsible for subsequent neurodegeneration (Recchia et al. 2004).

The presenilin 1 (*PSEN1*) gene is a key element in the creation of Aβ (De Strooper et al. 1998) via the proteolytic activity of γ-secretase (Vetrivel et al. 2006). Mutation in this gene alters the activity of the proteolytic enzyme and intensifies the accumulation of Aβ, which is generally found in AD patients. Tau proteins are crucial for maintaining normal cell function by interacting with tubulin in the formation of microtubules (Thomas and Fenech 2007). Hyperphosphorylation of tau protein leads to the formation of tangles, hence leading to the dissociation of the tau-tubulin complex and cell death (Thomas and Fenech 2007). Both Aβ and tangle formation are common in patients diagnosed with AD.

HTT is a multifunctional protein required for transcriptional modulation and intracellular transport and is associated with the endosome–lysosome pathway (Landles and Bates 2004). Mutant huntingtin (mtHTT) results in HD, as it causes bioenergetic failure, HD-linked neural dysfunction and cell death (Bossy-Wetzel et al. 2004).

Epigenetic processes that modulate gene action without modifying the DNA sequences have been proven to have lifelong effects on mature neurons (Tsankova et al. 2007) and exert their impact on synaptic plasticity and cognition (Abel and Zukin 2008). Histone methylation and acetylation are involved in the regulation of gene expression and protein function in neural stem cells (Mattson 2003). It has been proven in experimental models of neurodegenerative disorders that manipulations of both mechanisms influence the susceptibility of neurons to degeneration and apoptosis (Mattson 2003). In the postmortem AD human brain, higher presenilin 1 (PSEN1) expression during brain development and in disease progression is seen due to the reduced methylation mechanisms both at CpG and non-CpG sites (Monti et al. 2020), and promotes the accumulation of toxic Aβ peptide. In PD, dysregulation of SNCA expression is presumed to be caused by aberrant methylation at CpG sites, which control the activation or suppression of protein expression. The distribution of methylated CpG sites is related to anticipated transcription factor (TF) binding sites, suggesting that a decrease in methylation could stimulate SNCA expression in the PD brain (Jowaed et al. 2010). Cyclic adenosine monophosphate response element-binding protein (CREB) binding protein (CBP) functions as a histone acetyltransferase (HAT) as well as a transcriptional cofactor. CBP acts as a HAT in acetylating histones that contribute to transcription by restoring the chromatin configuration. Significantly, it has been known that sequestration of CBP by mtHTT prompts neuronal transcriptional dysfunction (Lee et al. 2013). MtHTT alters the activity of HATs and causes the transcription regulation anomalies observed in most HD patients (Sadri-Vakili and Cha 2006).

Restraint of histone deacetylase (HDAC) activity controls cellular and molecular capacities, triggering synaptic plasticity and neuronal apoptosis, limiting oxidative stress, activating transcription, and inducing modification of histone acetylation levels, eventually encouraging neuroprotection (Gupta et al. 2020). Folate, vitamin B6, vitamin B12, and *S*-adenosyl methionine (SAM) are vital cofactors involved

in DNA methylation modification (Coppedè 2014); 5-azacytidine (AZA) is the most widely studied DNA methyltransferase (DNMT) inhibitor (Xu et al. 2012b), and dietary polyphenols are DNMT inhibitors in vitro (Fang et al. 2007).

This review is centred on the role of methylation in the pathogenesis of AD, PD, and HD and how methylation is associated with these neurodegenerative diseases. We will also discuss the therapeutic targets available to date highlighting the role of epigenetics in these diseases, including histone and DNA modifications.

Epigenetic Regulation in Neurodegenerative Diseases

Principles of Epigenetics

The mechanisms of epigenetic regulation, which include DNA methylation, chromatin remodelling, histone post-translational modifications, and non-coding RNAs (Pagiatakis et al. 2019), are involved in several aspects of neuronal function and advancement (Berson et al. 2018; Aristizabal et al. 2019). Epigenetic regulation has consequences in human wellbeing, with modifications in chromatin known to be associated with numerous illnesses, in which drugs that hinder DNA methylation and histone deacetylation have been approved for clinical use by the Food and Drug Administration (FDA) (Jones et al. 2016).

With explicit significance in the brain, changes in a few chromatin-related factors lead to neurological disorders, including autism spectrum disorder (ASD), mental retardation, intellectual disability, and epilepsy (Bourgeron 2015), highlighting the vital roles of epigenetic mechanisms for brain development and capacity (Wilson 2008). Methylation of the gene often gives rise to silencing, which will affect the phenotype, and these silenced states are inheritable during cellular division (Miranda and Jones 2007). Hypermethylated DNA retains its methylation and remains transcriptionally silent (McGarvey et al. 2007), hence allowing daughter cells to maintain the same expression pattern as the precursor cells (Miranda and Jones 2007).

DNA methylation is involved in development and normal cell homeostasis by regulating cellular processes such as transcription, chromatin structure, chromosome stability, and genomic imprinting (Robertson 2005). DNA methylation controls transcription by adding a methyl group at the 5′ carbon of the cytosine ring situated in CpG dinucleotides via the action of DNMTs (Lu et al. 2013). CpG islands (CGIs) or unmethylated CpG dinucleotides are localized in tissue-specific genes and vital "housekeeping" genes engaged in routine maintenance and are expressed in most tissues (Rodenhiser and Mann 2006). Unmethylated CpGs promote transcription, and DNA silencing occurs upon methylation of these pairs (Rodenhiser and Mann 2006). Neuronal methylation, which consists of ~ 75% CpG and ~ 25% CpH (H = A/C/T) methylation, is conserved in the human brain, enriched in regions of low CpG density, used up at protein-DNA interaction sites and negatively correlated with gene expression (Guo et al. 2014). Previous reports found that 948 out of 27,578 CpG sites are involved in disease-associated methylation differences in DNA originating from the human prefrontal cortex (Bakulski et al. 2012). Three DNMT isoforms are involved in maintaining the methylation status within the genome: DNMT1, DNMT3a, and DNMT3b, and SAM functions as a methyl donor (Halušková 2010). DNMT1 is fundamental in methylation for appropriate neuronal and CNS functioning during early development (van Groen 2010). Apart from their involvement in synaptic plasticity, learning and memory, DNMT1 and DNMT3 are both required to conserve DNA methylation and to synchronize gene expression in the adult CNS (Tian et al. 2010) (Jin et al. 2011). In addition, the DNA hypomethylation of long interspersed element-1 (LINE-1) and Alu elements (Alu) in circulating blood has potential value for cancer diagnosis (Xu et al. 2012a). However, several studies have shown that there is no significant ageing-associated hypomethylation of LINE-1 and Alu retroelements in cellular DNA from peripheral blood (El-Maarri et al. 2011; Erichsen et al. 2018). Another recent study showed that some locus-specific DNA methylation changes are highly reproducible across aged people, independent of sex and tissue type which point to the existence of a programmed epigenetic reconfiguration during ageing and has given rise to the "epigenetic clock" theory (Ciccarone et al. 2018).

Therefore, further studies should aim to confirm whether DNA methylation also remains stable in older populations (60–80-year-old individuals). It is yet to be proven whether this epigenetic marker is the causative event or a consequence of the progression of these diseases. In addition, the fact that the methylation pattern of DNA varies among individuals and the large amounts of DNA input required to provide sufficient and representative data may limit findings.

Epigenetics and Alzheimer's Disease

AD is a complex multifactorial disorder involving familial and sporadic forms. It is more prevalent in women than men, especially in people aged more than 80 years. Familial forms represent only a minority of the cases, ranging from 5 to 10% of the cases, compared with sporadic forms, which represent most cases and likely occur as a result of complex gene–gene and gene-environmental interplay (Migliore and Coppedè 2009). Familial early-onset AD begins before age 65 years and is mainly caused by point mutations in three genes, *APP*, *PSEN1*, and *PSEN2* (Migliore and Coppedè 2009). These genes are involved in the APP processing pathway, the

proteins of which are encoded on chromosome 21, chromosome 14, and chromosome 1. More than 150 mutations in *PSEN1* and a few in *PSEN2* have been reported, for a total of approximately 160 mutations in the PSEN genes alone (Migliore and Coppedè 2009). Mutation of *PSEN1* fosters the deposition of Aβ by increasing extracellular cleavage, known as the amyloidogenic pathway, through the action of γ-secretase and β-secretase, releasing Aβ1-42 peptides, whereas the non-amyloidogenic pathway releases Aβ1-40 by the cleavage of α-secretase and γ-secretase. Research has shown an elevated ratio of Aβ1-42/Aβ1-40 in the brains of young transgenic animals co-expressing APP and mutant PS1 compared to the brains of transgenic mice co-expressing APP alone and transgenic mice co-expressing wild-type human PS1 and APP (Borchelt et al. 1996). Another study proved that PS1 mutants caused AD by modulating APP processing and favouring the production of Aβ1-42/43, while the loss of normal PS1 function did not lead to AD (Davis et al. 1998). Full-length Aβ1-42 and the modified pyroglutamate peptides Aβp3-42 and Aβp11-42 are found abundantly in the AD brain, but less study has been devoted to the truncated proteins than to the full-length proteins (Sanders et al. 2009). Recent findings proved that the truncated, modified peptides can inhibit the aggregation of full-length Aβ1-42 (Sanders et al. 2009). The latest studies proposed that cerebrospinal fluid biomarker profiles characterized by decreased Aβ peptide levels and increased total and phosphorylated tau levels at threonine 181 (pT181) can be used to discriminate between AD and other neurodegenerative diseases. However, these changes are not entirely specific to AD, and it is noteworthy that other phosphorylated isoforms of tau, possibly more specific for the disease process, have been described in the brain parenchyma of patients (NICE. and NICE 2018; Barthélemy et al. 2020).

DNA methylation plays a pivotal role in running the biochemical process in the higher organisms for normal development. These processes involve the accumulation of methyl group in the 5′ of the cytosine within the CpG dinucleotides. This accumulation is enhanced by DNA methyltransferases (DNMTs), which is heritable (Yi and Kim 2015).

In AD, DNA methylation has already been proven to be involved in modulating Aβ production by regulating the expression of *PSEN1* and *BACE1*. Hypomethylation of both genes boosts their expression and gives rise to the mass build-up of Aβ peptides (Fuso et al. 2005). Fuso et al. (2011) reported a hypomethylated *PSEN1* gene promoter in cell lines and transgenic mouse models of AD carrying *APP* gene mutations (Fuso et al. 2011). BACE1 contributes to synaptic functions by regulating the cAMP/PKA/CREB pathway, and alteration of its expression has been proven to have a significant effect on memory functions and cognitive deficits in transgenic mice (Chen et al. 2012). In late 2019, a case–control study was conducted in Colombia involving 50 individuals with late-onset Alzheimer disease (LOAD) and 50 age- and sex-matched controls to evaluate DNA methylation patterns in the *BIN1* (bridging integrator 1) 3′ intergenic region. The findings of this study showed that loss of DNA methylation at CpGs in *BIN1* might play an important role in the expression of *BIN1* and may be a biomarker for identifying individuals at high risk of developing LOAD in the future (Salcedo-Tacuma et al. 2019).

In view of histone modifications in epigenetics, there is a significant increase in the levels of histone deacetylase 6, a modulator for tau phosphorylation and accumulation has been seen in the brain regions such as hippocampus tissues and cerebral cortical in Alzheimer's disease patients when compared with the control subjects (Ding et al. 2008). Another trait of AD that is most likely connected to memory impairment and cognitive decline is synaptic failure. APOE isoforms differentially manage synaptic plasticity and repair. It is intriguing to note that studies of one-month-old mice uncovered comparable outcomes, suggesting that APOE4-driven changes in neuronal circuitry occur early (Safieh et al. 2019). Approximately 20% of the individuals in a typical control population carry at least one APOE4 allele (Zhong and Weisgraber 2009). In addition to this major risk genetic factor, hyperhomocysteinemia (HHCys) has been correlated with AD and PD, especially in the late stages of the illnesses or after long-term levodopa treatment. A longitudinal study, lasting ≥ 8 years, which involved 1092 individuals with dementia (mean age = 76 years), disclosed that the risk of developing AD was doubled in patients with levels of HHCys > 14 µmol/l (Feligioni et al. 2019). In addition, low concentrations of dietary and circulating folate during gestation increased the risks of premature delivery, underweight infants, and foetal growth retardation (Hernández-Díaz et al. 2000), resulting in elevation of homocysteine levels and an increased risk of AD. This condition was found to stimulate neuronal degeneration of APP-mutant transgenic mice and increased Aβ-induced death in cultured hippocampal neurons (Kruman et al. 2002). In 2014, Lunnon et al. (2014) and De Jager et al. (2014) reported the results of the first two large-scale, epigenome-wide association studies (EWAS) in AD. These two-independent epigenome-wide association studies of AD cohorts have identified overlapping methylation signals in four loci, ANK1, RPL13, RHBDF2, and CDH23.

Likewise, Aβ-induced phosphorylation of tau protein and its resultant inability to bind microtubules will lead to the formation of intracellular tangles known as neurofibrillary tangles (NFTs), the presence of which has been reported to correlate with protein phosphatase 2A (PP2A), which modulates tau phosphorylation by reverting it (Cleveland et al. 1977), (Xu et al. 2006). Increased demethylation of PP2A at the L309 site is mediated by Aβ overexpression, giving rise to compromised dephosphorylation of abnormally

hyperphosphorylated tau (Zhou et al. 2008). The aforementioned study also conveys a subunit-specific reduction in PP2A catalytic and regulatory mRNA, resulting in diminished protein expression and phosphatase activity, hyperphosphorylation of tau, the formation of NFTs and neuronal degeneration (Vogelsberg-Ragaglia et al. 2001). There have likewise been reports of overexpression of endogenous inhibitors of PP2A, such as inhibitor 2, along with their cleavage and redistribution, and when overexpressed in an in vivo model, these inhibitors resulted in key features of AD, including amyloid-β deposition, tau hyperphosphorylation, neurodegeneration and cognitive deficits (Voronkov et al. 2011). In some postmortem brains or neuronal cells of AD individuals, a lot of work has been done to find more specific evidence. Wang et al. (2008) had demonstrated that patients with LOAD have a larger epigenetic distance from the normal in brain tissue. It has been compared with controls and that the epigenetic distance increases with age. Hence, these findings supporting the role of epigenetic effects in the development of the disease. Some genes that play central roles in amyloid-β processing are PSEN1 and APOE, and methylation homeostasis such as MTHFR and DNMT1 also show a significant interindividual epigenetic variability, which may contribute to AD predisposition. In cortical neurons of a postmortem AD brain, immunoreactivity for 5-methylcytosine (5-mC) was decreased compared to the control (Mastroeni et al. 2010).

Epigenetics and Parkinson's Disease

Mutations in *SNCA, PARK2, LRRK2, PINK1, UCHL1,* or *DF1* have been reported to be the causative genes and found occasionally in most of the sporadic cases of PD, although there is no evidence in the majority of the cases (Matsumoto et al. 2010). Less than 1% of PD patients in the general population have gene mutations in *SNCA*, while the majority have abnormal aggregation of SNCA protein (Maraganore et al. 2006).

The brain contains an abundance of synuclein protein, consisting of three members: α-synuclein, β-synuclein, and γ-synuclein (Goedert 2001). Among these, α-synuclein (SNCA), which is the main component of Lewy bodies and Lewy neuritis and makes up the filamentous inclusions of system atrophy, is the cardinal neuropathological marker in PD and other neurodegenerative disorders (Spillantini et al. 1998). SNCA also plays a critical role in PD pathogenesis. Both duplication or triplication and point mutations (e.g. A30P, E46K, and A53T) in SNCA1 are associated with autosomal dominant familial PD (Huang et al. 2019). Extracellular aggregated SNCA induced microglial activation and later enhanced dopaminergic neurodegeneration in a mesencephalic neuron-glia culture system (Zhang et al. 2005). Lewy bodies, which are related to nerve loss are more abundant in patients with mild and moderate neuronal loss than in those with severe neuronal loss (Schulz-Schaeffer 2010).

Current studies have reported that there is a decrease in DNA methylation in the regulatory regions of specific genes in PD brains. Decreased levels of nuclear *DNMT1* are mediated by SNCA, leading to global DNA hypomethylation, which was observed in postmortem human brain samples and the brains of SNCA transgenic mouse models (Desplats et al. 2011). Findings in other studies indicated that mRNA expression of SNCA is decreased but the protein levels are maintained at high levels due to the regulation of post-translational stabilization of the proteins (Li et al. 2004). Hypomethylation in the DNA from the substantia nigra, putamen, and cortex region of sporadic PD patients has been reported (Jowaed et al. 2010). A study on methylation of SNCA and leucine-rich repeat kinase 2 (*LRRK2*) showed significant hypomethylation in certain CpG sites in leukocyte DNA from PD patients compared to controls (Tan et al. 2014). In contrast, analysis of the *SNCA* methylation level on CpG islands located in intron 1 of PD patients showed no significant differences between PD patients and controls (Song et al. 2014b).

Oxidative stress by free radicals is one of the significant causes of PD. It is currently well established that free radicals play a vital role in ageing (Hamilton et al. 2001), and PD has been regarded as one of the greatest risk factors in ageing. Initially, the proof for the presence of oxidative stress in PD originated from reports dependent on postmortem examinations of brain samples from patients with PD that exhibited elevated degrees of oxidized proteins, lipids, and nucleic acids (Kumar et al. 2012).

Genome-wide methylation analysis of sporadic PD patients discovered a single hypomethylated gene, *CYP2E1,* in both putamen and cortex regions (Kaut et al. 2012), indicating that epigenetic variants in this gene contribute to PD susceptibility.

Epigenetics and Huntington's Disease

Although the loss of neurons in many brain areas has been accounted for in HD, the selective neurodegeneration of the γ-aminobutyric acid-releasing spiny-projection neurons of the striatum is predominant (Landles and Bates 2004). Damage of brain striatal neurons is a consequence of the extension of CAG repeats in the HTT protein, which lead to HD characteristics (Steffan et al. 2000). HD pathogenesis includes cytoplasmic cleavage of HTT, which releases an amino-terminal fragment capable of nuclear localization (Steffan et al. 2000). Individuals with normal amounts of CAG repeats have 7–34 repeats, whereas mutations in exon 1 of this gene extend the cytosine-adenine-guanine

trinucleotide repeats, which code for the polyglutamine (polyQ) moiety in the HTT protein (Sadri-Vakili and Cha 2006).

However, the age of onset of symptoms depends on whether the gene is passed through the paternal or maternal germline. The gene itself becomes modified differently, and paternal transmission has been shown to involve DNA methylation that can lead to higher or earlier expression of the gene (Reik 1988). There is proof for a relationship between male exposure to various drugs/toxins and increased mutations, including numerical and basic chromosomal abnormalities, point mutations, copy number variations (CNVs), and duplications/deletion of microsatellite regions (Curley et al. 2011).

Transcriptional impairment has been proven to be involved in HD (Ferrante et al. 2003). Genome-wide chromatin immunoprecipitation sequencing (ChIP-Seq) confirmed that AP-1 and SOX2 are transcriptional regulators associated with methylation changes in regions of low CpG content due to the presence of mtHTT in cell lines derived from mouse striatal neurons (Ng et al. 2013). Specific and significant losses of acetylated essential histone (AcH2A, AcH2B, AcH3, and AcH4) expression in cells in the caudate nucleus and Purkinje cells of the cerebellum were observed in HD compared with patients with frontotemporal lobar degeneration and control subjects, while the level of HDAC5 was elevated in these cells (Yeh et al. 2013). The epigenetic changes that occur in AD, PD and HD is summarized in Table 1.

Therapeutic Interventions for Neurodegenerative Diseases

Epigenetics and Therapeutic Approaches

Mounting evidence of the involvement and importance of epigenetic alterations in neurodegenerative disorders has presented new therapeutic interventions for these disorders. Experiments in animal models of neurodegenerative disorders have confirmed the possible role of epigenetic drugs, together with inhibitors of histone deacetylases and methyl donor compounds (Adwan and Zawia 2013). Small drugs such as histone deacetylase inhibitors (HDACi) can cross the blood–brain barrier (BBB), thus slowing the initiation and development of symptoms in animal models of neurodegenerative diseases (Coppedè 2014).

HDACs are separated into four different classes; HDACIs, HDACIIs, HDACIIIs, and HDACIV (Dokmanovic et al. 2007). HDACs are potential therapeutic targets in various chronic diseases, including cancer and fibrotic disorders (Pang and Zhuang 2010). HDAC-induced histone hypoacetylation is associated with gene silencing; thus, altered expression and mutations in genes encoding HDACs have been correlated with tumour development (Ropero and Esteller 2007). HDAC3 deficiency increases collagen deposition in atherosclerotic lesions and induces the stable plaque phenotype observed in transplanted atherosclerosis-susceptible mice upon HDAC3 deletion (Hoeksema and de Winther 2016). HDACi stimulates growth arrest, inhibits differentiation, induces apoptosis of tumour cells, and affects the acetylation status and function of non-histone proteins, with minimal effects on normal tissue (Kim et al. 2006; Lane and Chabner 2009). Although the mechanisms of HDACi are not completely elucidated, they are believed to be able to cause a build-up of acetylated histones and many non-histone proteins that are implicated in the regulation of gene expression, cell proliferation, cell migration, and cell death, and a wide diversity of altered cells are sensitive to inhibitor-induced cell death (Dokmanovic et al. 2007). Several structural classes of HDACi are under clinical trial for various diseases, including hydroxamic acids (vorinostat), cyclic peptides (depsipeptide or romidepsin), benzamides, and aliphatic acids (valproic acid (VA)) (Adwan and Zawia 2013).

Nutrition and dietary compounds, for instance, vitamin B, folate, and methionine, are known to affect epigenetic regulation and mechanisms, especially DNA methylation and one-carbon metabolism. In addition, dietary compounds can modulate the activity of protein-related methylation; for example, they can inhibit DNMTs. Thus, both nutriepigenetic or nutriepigenomic molecules, which influence basic human wellbeing, have been developed as another promising field in current research. Polyphenols, as an example, highlight the unique cooperation between the genome and the environment, particularly at physiological concentrations (Remely et al. 2015). They induce a significant effect only if consumed in large amounts or if the levels of methyl donors are limited; however, but possible toxicity resulting from oxidation of polyphenols might occur, and precautions need to be taken upon consuming these compounds (Fang et al. 2007).

Folate supplementation, for instance, can inhibit the adverse effects of ageing, for example, uracil misincorporation, DNA methylation, protein methylation, mitochondrial deletion, and critical gene expression, and was observed to protect against colon cancer (Jang et al. 2005; Kim 2005). However, severe folate insufficiency generated hypomethylation (by 40%) within a mutation hot spot (exons 6–7), but not in exon 8, of the p53 tumour suppressor gene, despite a 56% increase in genomic DNA methylation in the rat liver. This finding increases the likelihood that the impact of folate insufficiency on DNA methylation might be site- and gene-specific and proposes that the progression of genomic and site-specific DNA methylation because of folate deficiency may vary (Mierzecki et al. 2015).

Table 1 Epigenetic changes in neurodegenerative diseases

	Author (year)	Type of study	Result	Findings
Alzheimer's disease	Borchelt, Thinakaran et al. (1996)	Experimental study: in vitro and in vivo	Elevated extracellular concentrations of amyloidogenic Aβ1–42(43) peptides precipitate disease in PS1-linked FAD	Mutation of *PSEN1* fosters the deposition of Aβ by increasing extracellular cleavage, known as the amyloidogenic pathway
	Davis, Naruse et al. (1998)	Experimental study: in vivo	The levels of Aβ1–42/ 43 and Aβ1–40 in the brains of young $PS1^{+/+}$ mice expressing APPswe were not significantly different than the Aβ levels in $PS1^{+/+}$ mice expressing APPswe	PS1 mutants caused AD by modulating APP processing and favouring the production of Aβ1-42/43
	Fuso, Seminara et al. (2005)	Experimental study: in vitro	SAM level was lower in differentiation medium (DM) than in growth medium (GM); folate and vitamin B12 deprivation induced a significant SAM decrease	Hypomethylation of *PSEN1* and *BACE1* gives rise to the mass build-up of Aβ peptides
	Migliore and Coppedè (2009)	Observational study		Familial early-onset AD caused by point mutations in three genes, *APP*, *PSEN1*, and *PSEN2*. 150 mutations in *PSEN1* and a few in *PSEN2* have been reported
	Sanders, Lust et al. (2009)	Experimental study: in vitro	Full-length Aβ1-42 aggregates were similar to Aβp11-42, yet much faster than Aβp3-42	Full-length Aβ1-42 and the modified pyroglutamate peptides Aβp3-42 and Aβp11-42 were found abundantly in the AD brain
	Fuso, Nicolia et al. (2011)	Experimental study: in vitro and in vivo	PSEN1 was overexpressed in vitamin B deficient and SAM was able to revert the effect by preventing the site-specific DNA methylation both in neuroblastoma cell line and mice brain	PSEN1 was overexpressed in vitamin B deficient and SAM was able to revert the effect by preventing the site-specific DNA methylation both in neuroblastoma cell line and mice brain
	Chen, Huang et al. (2012)	Experimental study: in vitro and in vivo	Overexpression of human BACE1 in mouse neuroblastoma N2a cells. The levels of phosphorylated CREB were significantly reduced in the brains of both BACE1 transgenic and BACE1 knock-out mice	BACE1 contributes to synaptic functions by regulating the cAMP/PKA/CREB pathway, and alteration of its expression has been proven to have a significant effect on memory functions and cognitive deficits in transgenic mice
	Salcedo-Tacuma, Melgarejo et al. (2019)	Case–control study	Participants with LOAD had significantly lower methylation levels on CpG26. Adjusted regression models showed that decreased methylation levels of these CpGs remained as risk factors for LOAD	Loss of DNA methylation at CpGs in *BIN1* play a role in the expression of *BIN1* and may be a biomarker for identifying individuals at high risk of developing LOAD

Table 1 (continued)

	Author (year)	Type of study	Result	Findings
Parkinson's disease	Matsumoto et al. (2010)	Experimental study: in vitro	Postmortem brain analysis revealed regional non-specific methylation differences in the CpG region in the anterior cingulate and putamen among controls and PD; however, in the substantia nigra of PD, methylation was significantly decreased	Mutations in *SNCA, PARK2, LRRK2, PINK1, UCHL1,* or *DF1* caused most of the sporadic cases of PD
	Jowaed, Schmitt et al. (2010)	Human study	The study found that $SNCA_{(-1524/-189)}$ in intron 1 as a methylation-dependent, transcriptionally active region of the human *SNCA* gene and found that $SNCA_{(-926/-483)}$ is hypomethylated in sporadic PD patients' brains	Hypomethylation in the DNA from the substantia nigra, putamen, and cortex region of sporadic PD patients
	Desplats, Spencer et al. (2011)	Experimental study: in vitro and in vivo	A pronounced decrease in DNMT1 protein in total homogenates from the cortex of both PD and DLB cases when compared with controls was observed. Western blot analysis showed a reduction of almost 50% in nuclear DNMT1 in PD and DLB brains	Decreased levels of nuclear *DNMT1* were mediated by *SNCA*, leading to global DNA hypomethylation
	Kaut, Schmitt et al. (2012)	Experimental study: in vitro	In putamen the catalase gene (CAT, geneID 847) was identified with a 2.5-fold threshold of differential methylation, but $\Delta\beta$ was <0.17 (0.14). Only CYP2E1, which displayed a >2.5-fold differential methylation, was identified hypomethylated in both cortex and putamen of PD patients. CYP2E1 remained significantly hypomethylated when men and women were analysed separately. Significantly hypermethylated genes in PD patients compared to controls were detected only in putamen but not in cortex DNA	Genome-wide methylation analysis of sporadic PD patients discovered a single hypomethylated gene, *CYP2E1,* in both putamen and cortex regions
	Huang, Wang et al. (2019)	Observational study		*SNCA* also plays a critical role in PD pathogenesis. Both duplication or triplication and point mutations (e.g. A30P, E46K, and A53T) in *SNCA1* were associated with autosomal dominant familial P

Table 1 (continued)

	Author (year)	Type of study	Result	Findings
Huntington's disease	Steffan et al. (2000)	Experimental study: in vitro and in vivo	p53 colocalizes with expanded httex1p in inclusions in mammalian cell culture and interacts with httex1p in vitro and in cell culture	Extension of CAG repeats in the HTT protein causing damage of brain striatal neurons, which lead to HD characteristics
	Ng et al. (2013)	Experimental study: in vitro	Expression of mutant HTT and/or loss of wild-type HTT were associated with DNA methylation changes in a striatal cell line raises the possibility that HTT might also be associated with physiological changes in DNA methylation in neurons. By impairing the normal regulation of DNA methylation, HTT could cause neuronal dysfunction long before any signs of neuronal death	AP-1 and SOX2 were transcriptional regulators associated with methylation changes in regions of low CpG content due to the presence of mtHTT in cell lines derived from mouse striatal neurons
	Yeh et al. (2013)	Human study	There were significant losses of AcH2A, AcH2B, AcH3 and AcH4 expression from cells in the caudate nucleus and Purkinje cells of the cerebellum in HD compared to patients with FTLD and control subjects, while the level of HDAC 5 was increased in these cells	Specific and significant losses of acetylated essential histone (AcH2A, AcH2B, AcH3, and AcH4) expression in cells in the caudate nucleus and Purkinje cells of the cerebellum were observed in HD compared with patients with frontotemporal lobar degeneration (FTLD)

5-Azacytidine or azacitidine (AzaC) is one of the most widely studied DNMT inhibitors (DNMTi) and is mainly used in managing myelodysplastic syndrome (MDS), in which it functions as a methyl donor remover in vitro to weaken the gene silencing effect upon methylation. A 67-year-old man with high-risk MDS exhibited haematological improvement three months after the first cycle of AzaC therapy (Takaoka et al. 2014).

AD and Epigenetic Therapy

The current drugs agreed upon by the FDA for the treatment of AD are acetylcholinesterase inhibitors such as donepezil, rivastigmine, galantamine, and tacrine along with the N-methyl-D-aspartate (NMDA) receptor antagonist memantine, but they do not impede the progression of AD and instead merely target symptoms. It has been demonstrated on AD models that some epigenetic drugs might be beneficial in protecting against neurodegeneration and improving cognitive function (Adwan and Zawia 2013; Cacabelos and Teijido 2018). Moreover, the donepezil-treated group revealed a considerably lower incidence of cardiac rupture during the acute phase of myocardial infarction than the untreated group, an effect that occurred via the inhibition of metalloproteinase-9-related acute inflammatory tissue injury (Arikawa et al. 2011). Combined administration of donepezil and memantine deters the diminution of cerebral blood flow in the prefrontal area and improves clinical symptoms of overall cognitive function and behavioural and psychological symptoms of dementia in AD patients (Araki et al. 2014). Nasal administration enables the potential absorption of the drug into the CNS by bypassing the BBB and ensures targeting of therapeutics to the CNS with rapid achievement of sufficient drug levels in the target tissue and low systemic exposure (Sharma et al. 2015). Recently, a nanoemulsion (NE) loaded with memantine was studied. The finalized NE showed a particle size of ~ 11 nm and a percentage transmittance of ~ 99%. The in vitro release studies showed 80% drug release in simulated nasal fluid. The developed NE loaded with memantine could be used for intranasal administration to enhance the effect on AD (Kaur et al. 2020).

Galantamine had an apparent effect on the preservation of memory in patients with mild-to-moderate AD during 26 weeks (Song et al. 2014a). The one and only drug that actively promoted for the treatment of AD with proven activity as an allosteric modulator of nicotinic acetylcholine receptors (nAChRs), a competitive inhibitor of acetylcholinesterase (AChE) and reversible is galantamine. With galantamine, it helps to decrease in activity and expression of nAChRs promote a huge reduction in central cholinergic neurotransmission in patients with AD (Lilienfeld 2002). Tacrine-6-ferulic acid (T6FA) significantly inhibits autoaggregation and acetylcholinesterase-induced aggregation of $A\beta_{1–40}$ in vitro, blocks cell death induced by $A\beta_{1–40}$ in PC12 cells, and improves cognitive ability in an AD mouse model (Pi et al. 2012). Hybrid tacrine-8-hydroxyquinoline (IQM-622) decreases the deposition of Aβ in APP/PS1 mice, promotes the degradation of intracellular Aβ in astrocytes and protects against Aβ toxicity in cultured astrocytes and neurons (Antequera et al. 2012). Patients that treated with tacrine required multiple-dosage regimen to maintain the therapeutic level in given of its short half-life and adverse effect. These patients also need to undergo regular blood monitoring due to the hepatotoxicity of the drugs (Watkins et al. 1994). Up to date, tacrine was discontinued due to the liver toxicity and many side effects (Sharma 2019). Significant improvements with the rivastigmine patch and capsule were observed in patients with advanced dementia stage, yet no significant improvements were noted in patients with mild-to-moderate AD (Farlow et al. 2011).

Cognitive capacities in the neurodegenerating brain are not lost but merely impaired due to epigenetic blockade mediated by HDAC2, which can potentially be reversed (Gräff et al. 2012). Treatments with sodium valproate, sodium butyrate, or vorinostat completely restored contextual memory in APPswe/PS1dE9 mice and inhibited HDACI isoforms, indicating that HDACI inhibition is plausible for treating cognitive deficits associated with early-stage AD (Kilgore et al. 2010). Valproic acid (VPA) decreased Aβ production by halting the GSK-3β-mediated γ-secretase cleavage of APP, reduced neuritic plaque formation, and alleviated memory deficits in APP23 mice carrying the human Swedish mutant APP751 (Qing et al. 2008). VPA alleviated p65 NF-κB phosphorylation and boosted the levels of acetyl-H3, Bcl-2, and GSK-3β in the hippocampus of APPswe/PS1dE9 (APP/PS1) transgenic mice (Xuan et al. 2015).

In addition, ageing-related memory impairments can also be affected by sodium butyrate via its influence on the early consolidation phase of memory formation. However, sodium butyrate showed no effect in younger rats with normal memory retention (Reolon et al. 2011). Sodium butyrate improves associative memory by elevating hippocampal histone acetylation and increasing the expression of genes implicated in associative learning in APPPS1-21 mice even when administered at an advanced stage of pathology (Govindarajan et al. 2011).

Another study reported that high consumption of vitamins C, E, B6, and B12, folate, unsaturated fatty acids, and fish can decrease AD risk (Luchsinger and Mayeux 2004). Another study showed that SAM, exerts a neuroprotective function on both methylation and oxidation metabolism by preventing oxidative stress and lipid peroxidation and modulating glutathione metabolism through superoxide dismutase and glutathione *S*-transferase activity (Cavallaro et al. 2010). Patients receiving vitamin or nutraceutical formulations (folate, vitamin B6, alpha-tocopherol, SAM,

N-acetyl cysteine, and acetyl-L-carnitine) had improved the domains of the Neuropsychiatric Inventory (NPI) and maintenance of performance in the Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADL) when compared with patients receiving naproxen, rofecoxib, or placebo. These studies also showed equivalent or more profound effects than previous studies using donepezil and galantamine (Chan et al. 2009). Rofecoxib (Vioxx), however, was removed from the market due to the increased risk of cardiovascular events.

PD and Epigenetic Therapy

Dopamine replacement therapies (DRTs) have improved PD management, yet these treatments cause weakening when used in the long term and do not protect deteriorating neurons against death (Harrison and Dexter 2013). Impulse control disorders (ICDs) are prevalent among patients with PD receiving dopaminergic medications and begin after initiation of dopamine (DA) agonist therapy and cease upon its discontinuation (Ambermoon et al. 2011). A correlation analysis in a cohort study uncovered that increasing doses of DA were related with decreasing performance on a pattern recognition task in treated patients with PD, showing that DRT improves frontal lobe function (strategizing) yet degrades temporal lobe function (visual memory) (Miah et al. 2012).

There is increasing evidence that there is a pathological disparity in PD among the deacetylation and acetylation of histone proteins, and therefore, the utilization of histone deacetylase-inhibiting agents has been proposed to improve this pathological imbalance (Harrison and Dexter 2013). In a study of novel recognition tests, the time spent discovering new objects by mice was markedly improved and there was a SIRT2-induced decrease in cell proliferation and neuroblast differentiation in the dentate gyrus after treatment with sodium butyrate (Yoo et al. 2015). Trichostatin A (TSA) increases astrocytic glutamate uptake when neurotoxicity occurs, thus enhancing glutamate uptake to decrease the MPP-induced elevation of glutamate in the medium, which might partially prevent the downregulation of GluTs. This finding might be a new mechanism implicated in the neuroprotection of HDACIs (Wu et al. 2008). Nevertheless, TSA treatment influences PD pathogenesis by decreasing cell survival and increasing apoptosis in dopaminergic neuronal cells (Wang et al. 2009).

Apart from the anticonvulsant drug sodium valproate, also known as Epilim, valproate also likely acts as a brain-penetrant and has been well tested and used clinically (Nalivaeva et al. 2009). It is noteworthy that in the action of mood stabilizers, epigenetics may propose a crucial role. As one of the histone deacetylase (HDAC) inhibitor, sodium valproate probably has a downstream epigenetics action (Lee et al. 2015). It is widely known that HDAC inhibitors are one of the epigenetic regulators with numerous beneficial effects at both systemic and cellular levels (Hull et al. 2016). Nonetheless, accumulating reports suggest that valproate leads to adverse effects such as organ failure, birth defects if consumed during gestation, and a decline in IQ in children. Administration of valproate to eight patients with PD with defects in GABA metabolism did not markedly alter any of the disease features; instead, it increased dyskinesia in the patients (Nutt et al. 1979). However, a recent study reported that a combination of valproate and lithium carbonate ameliorated the loss of dihydroxyphenyl acetic acid and rescued dopaminergic neurons following MPTP treatment in male C57BL/6 mice with PD (Li et al. 2012). Apart from that, given the progressive degeneration of dopaminergic neurons and aggregation of a-synuclein that correlated with PD pathophysiology, it is reported that HDAC6 help to relieve polyglutamine-mediated neurodegeneration via autophagy (Shukla and Tekwani 2020).

The DNMT inhibitor 5-aza-2′-deoxycytidine (5-aza-dC) induced transcriptional upregulation of tyrosine hydroxylase and SNCA, thus increasing the vulnerability of dopaminergic neurons to neurotoxic damage (Wang et al. 2013). 5-Aza-dC restored retinoic acid receptor-β_2 (RAR-β_2) inducibility by all-*trans*-retinoic acid (ATRA) in some cell lines with a hypermethylated RAR-β_2 promoter (Youssef et al. 2004).

HD and Epigenetic Therapy

Drugs aimed at correcting epigenetic alterations, including histone modifications and DNA modifications, have shown promise in treating HD (Wang et al. 2014). Potential disease-modifying therapeutics for HD include histone deacetylase inhibitors, such as sodium phenylbutyrate (SPB) or sodium butyrate (Hu et al. 2011). Sodium butyrate amplified histone and specificity protein-1 acetylation, protected against 3-nitropropionic acid neurotoxicity, and limited neuropathological sequelae in the R6/2 transgenic mouse model of HD (Ferrante et al. 2003). Administration of phenylbutyrate increased brain histone acetylation, decreased histone methylation levels, and exerted neuroprotective effects in the N171-82Q transgenic mouse model of HD (Gardian et al. 2005).

The HDACi 4b and 136 presented a strong ability to inhibit HDAC3 and were most effective in limiting the expression of genes relevant to HD, including *Ppp1r1b*, in R6/2 transgenic mice (Jia et al. 2012). SIRT2 enhances motor function, extends survival, and reduces brain atrophy and is associated with a decrease in aggregated mtHTT in two genetic mouse models of HD (Chopra et al. 2012). SIRT2-specific inhibitor AK-1 treatment-induced proteasomal degradation of the Snail transcription factor resulted in the upregulation of p21, a cyclin-dependent kinase inhibitor,

Table 2 Epigenetic intervention in neurodegenerative diseases

	Author (year)	Methodology	Findings
Alzheimer's disease	Luchsinger and Mayeux (2004)	Observational study	High consumption of vitamins C, E, B6, and B12, folate, unsaturated fatty acids, and fish can decrease AD risk
	Kilgore et al. (2010)	In vivo study using APPswe/PS1dE9 double- transgenic mice (APP/PS1)	Treatments with sodium valproate, sodium butyrate, or vorinostat completely restored contextual memory and inhibited HDACI isoforms, indicating that HDACI inhibition is plausible for treating cognitive deficits associated with early-stage AD
	Farlow et al. (2011)	AD patients treated with 9.5 mg/24 h rivastigmine patch, 17.4 mg/24 h rivastigmine patch, rivastigmine capsule (12 mg/day), or placebo were stratified according to baseline Mini-Mental State Examination (MMSE) scores	Significant improvements with the rivastigmine patch and capsule were observed in patients with advanced dementia stage, yet no significant improvements were noted in patients with mild-to-moderate AD
	Adwan and Zawia (2013); Cacabelos and Teijido (2018)	Observational study	Epigenetic drugs might be beneficial in protecting against neurodegeneration and improving cognitive function
	Araki et al. (2014)	The effect of memantine administration was evaluated from baseline on Clinical Global Impression-Improvement scale, Mini-Mental State Examination (MMSE), Clock Drawing Test (CDT), Neuropsychiatric Inventory (NPI), Japanese version of the Zarit Burden Interview (J-ZBI) and NIRS in two groups. Donepezil administration memantine combination group (combination group, $n=19$), donepezil administration memantine non-administration group (control group, $n=18$) were assessed at weeks 0, 4, 12, and 24	Combined administration of donepezil and memantine deters the diminution of cerebral blood flow in the prefrontal area and improves clinical symptoms of overall cognitive function and behavioural and psychological symptoms of dementia in AD patients
	Song et al. (2014a, b)	Patients were recruited from the Clinical Trials Program of the Samsung Medical Center Geropsychiatry Clinic	Galantamine had an apparent effect on the preservation of memory in patients with mild-to-moderate AD during 26 weeks treatment
	Kaur et al. (2020)	The nanoemulsion was prepared using homogenization and ultrasonication methods. The developed nanoemulsion was characterized, in vitro release and antioxidant potential was analysed The in vivo studies were carried out by radiolabelling the memantine with technetium pertechnetate	The developed nanoemulsion loaded with memantine could be used for intranasal administration to enhance the effect on AD

Table 2 (continued)

	Author (year)	Methodology	Findings
Parkinson's disease	Wang et al. (2009)	In vitro: A Trichostatin A (TSA) was tested in dopaminergic neuronal cell lines: rat N27, mouse MN9D, and human SH-SY5Y cells	Trichostatin A (TSA) treatment affected PD pathogenesis by decreasing cell survival and increasing apoptosis in dopaminergic neuronal cells
	Wang et al. (2013)	In vitro: The DNMT inhibitor 5-aza-2′-deoxycytidine (5-aza-dC) was tested in cultured dopaminergic cells. Cell viability and apoptosis were assayed with 5-aza-dC alone. Neurotoxicity of 1-methyl-4-phenylpyridinium (MPP +), 6-hydroxydopamine or rotenone was assayed with 5-aza-dC pretreatment. mRNA levels of several key PD-related genes, and CpG methylation of *α-synuclein* promoter was determined	The DNMT inhibitor 5-aza-2′-deoxycytidine (5-aza-dC) induced transcriptional upregulation of tyrosine hydroxylase and SNCA, thus increasing the vulnerability of dopaminergic neurons to neurotoxic damage
	Yoo et al. (2015)	Mice were divided into three groups: vehicle (PEP-1), SIRT2, and SIRT2 with sodium butyrate (an HDAC inhibitor). PEP-1 or PEP-1-SIRT2 fusion protein was administered intraperitoneally to 7-week-old mice once a day for 3 weeks, and the mice were killed 2 h after the last administration. Sodium butyrate, an HDAC inhibitor, was subcutaneously administered in parallel with PEP-1-SIRT2 once a day for 3 weeks	Sodium butyrate helped in SIRT2-induced reduction in cell proliferation and neuroblast differentiation in the dentate gyrus
	Lee, Pirooznia et al. (2015)	In vivo: Li ($N=12$), VPA ($N=12$), and normal chow ($N=12$) were administered to Brown Norway rats for 30 days. Genomic DNA and mRNA were extracted from the hippocampus	Sodium valproate is one of the histone deacetylase (HDAC) inhibitor and it has a downstream epigenetics action

Table 2 (continued)

	Author (year)	Methodology	Findings
Huntington's disease	Ferrante et al. (2003)	A dose–response study of sodium butyrate was performed on R6/2 transgenic model of HD, Control groups were treated with PBS injection or untreated. Approximately 240 mice were used for behavioural and survival analyses	Sodium butyrate has significant efficacy in improving the neurological and neuropathological phenotype observed in the R6/2 transgenic model of HD. It is suggested that HDAC inhibitors may provide clinical benefit to HD patients, most likely by preventing the deleterious effects of mutant huntingtin on transcription
	Gardian et al. (2005)	Transgenic N171-82Q mice received intraperitoneal injections of 4-phenylbutyric acid sodium salt (100 mg/kg/day, volume 3.33 ml/kg; or vehicle (PBS, 3.33 ml/kg), 6 days per week from 75 days of age	Administration of phenylbutyrate increased brain histone acetylation, decreased histone methylation levels, and exerted neuroprotective effects
	Dompierre et al. (2007)	In vitro: Mouse striatal cells derived from WT htt (WT striatal cells, +/+) mice and from Hdh^{Q109} knock-in (109Q/109Q) mice, HEK293 cells, Cos7 cells, and primary cortical neurons were prepared	HDAC inhibitors, including trichostatin A (TSA), increased vesicular transport of brain-derived neurotrophic factor (BDNF) by inhibiting HDAC6 thus increased acetylation at lysine 40 of α-tubulin in HD brains
	Hu et al. (2011)	119 human blood samples were interrogated for transcripts associated with HD. The association precedes the onset of clinical symptoms was confirmed in two mouse models, and was independently replicated in cross-sectional and longitudinal clinical studies comprising 142 participants	Potential disease-modifying therapeutics for HD include histone deacetylase inhibitors, such as sodium phenylbutyrate (SPB) or sodium butyrate
	Mielcarek et al. (2011)	In vivo: WT and R6/2 mice were administered vehicle or suberoylanilide hydroxamic acid (SAHA) in the drinking water (0.67 mg/ml) from five to nine weeks of age. HDAC4 protein levels were measured in three different brain regions: cortex, hippocampus and brain stem	Prolonged SAHA treatment causes degradation of HDAC4 in the cortex and brain stem but not in the hippocampus and decreases HDAC2 levels without affecting their transcript levels in vivo
	Chopra et al. (2012)	In vivo: Female R6/2 mice used in the study were generated by back-crossing male R6/2 with C57BL/6 X CBA F1 females. 140CAG knock-in mice were also maintained on B6CBA background	SIRT2 enhances motor function, extends survival, and reduces brain atrophy and is associated with a decrease in aggregated mtHTT in two genetic mouse models of HD
	Wang, et al. (2014)	Observational study	Drugs aimed at correcting epigenetic alterations, including histone modifications and DNA modifications, have shown promise in treating HD

leading to G1 arrest, slow proliferation, and slow wound-healing activity in HCT116 human colon cancer cells (Cheon et al. 2015).

Vorinostat or suberoylanilide hydroxamic acid (SAHA), an inhibitor of HDACIs and HDACIIs, can cross the BBB and increase histone acetylation in the brain and can be administered orally by drinking water when complexed with cyclodextrins (Hockly et al. 2003). Prolonged SAHA treatment causes degradation of HDAC4 in the cortex and brain stem but not in the hippocampus and decreases HDAC2 levels without affecting their transcript levels in vivo (Mielcarek et al. 2011). SAHA, on the other hand, increases vesicular transport of BDNF by inhibiting HDAC6, thereby increasing acetylation at lysine 40 of α-tubulin in HD brains (Dompierre et al. 2007). The Epigenetic intervention in AD, PD and HD is summarized in Table 2.

Conclusion

Epigenetic changes play an important role in the progression of AD, PD and HD. Thus, it is important to develop and improve techniques to examine chromatin structure and function to understand epigenetic regulation in normal ageing and neurodegenerative diseases. More studies should be conducted aiming at restoring chromatin dynamics and therefore proper gene expression, which may provide novel therapeutic strategies if applied early and in combination with other therapies addressing all aspects of these diseases.

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Compliance with Ethical Standards

Conflict of interest All authors declare that they have no conflict of interest.

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