Epigenetics and Neurological Disorders

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Abstract

Epigenetics, with its diverse mechanisms such as DNA methylation, histone acetylation, and ncRNAs, holds significant therapeutic potential for a wide range of disorders and diseases. Its intrinsic adaptability prevents DNA from enduring permanent damage while at the same time, regulating gene expression in reversible and plastic ways. It is a natural and dynamic process that needs continuous regulation for our bodies to function properly. However, this essential machinery can be disrupted by various factors. This paper will explore the molecular and cellular changes that occur in the brain due to epigenetic dysregulation, and how these changes are correlated to neurodegenerative diseases such as Alzheimer's and Huntington's disease.

Introduction

Epigenetics

The central dogma of biology states that DNA is transcribed into RNA, then translated into proteins that carry out various functions. To maintain the inheritance of genetic information, DNA needs to be replicated. To replicate, DNA must first be unwound because it is normally compacted into chromatin. Chromatin is composed of DNA wrapped around histone proteins, forming nucleosomes. Chromatin is compacted to make a structure called chromosomes. Histone proteins help compact DNA and regulate gene expression (Figure 1). When chromatin is condensed, it is called heterochromatin. In heterochromatin, gene expression is repressed as RNA polymerase cannot easily transcribe the genetic information. When chromatin is not condensed, it is called euchromatin, which is the state where gene expression occurs. Various types of RNA are transcribed from DNA, such as coding and noncoding RNAs. Coding RNAs are segments translated to produce a protein, while noncoding RNAs (ncRNAs) do not get translated to make a protein but serve other purposes.

Epigenetic mechanisms, such as DNA methylation and histone acetylation, regulate gene expression without altering the DNA sequence itself, by changing the form of chromatin, either to euchromatin or heterochromatin. Epigenetics is a field of study that investigates how individual genes and large gene networks function at the molecular and cellular level [1]. It focuses on understanding the mechanisms that control gene function, including how genes are turned on and off, and how environmental factors influence gene expression. In epigenetics, genes can be regulated by DNA methylation, histone acetylation, non-coding RNAs, and RNA editing.

Discussion

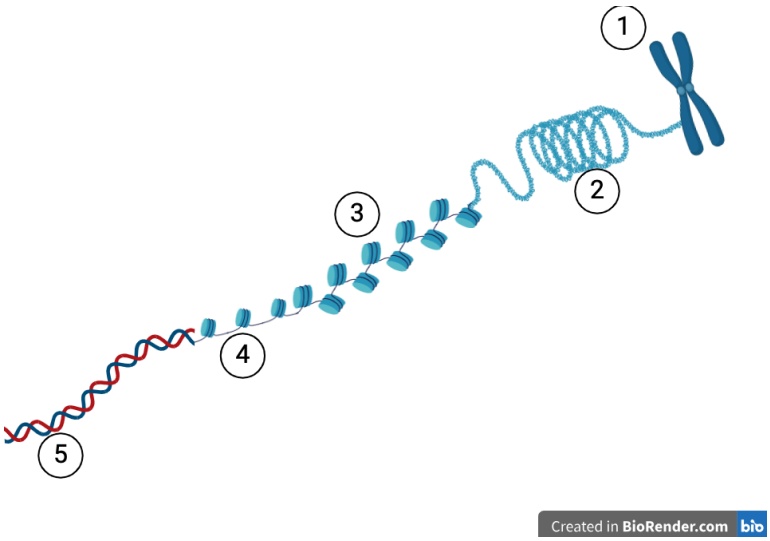

Figure 1. The organization of genetic information. Visual representation of different states that DNA is found in, including 1 (chromosome), 2 (condensed chromatin), 3 (chromatin fiber), 4 (nucleosomes - made up of DNA wrapped around histone proteins), 5 (DNA).

DNA methylation

In DNA methylation, methyl tags are added to the chromatin, causing it to condense. When the chromatin is condensed, enzymes cannot access the DNA to transcribe and translate the information, leading to gene repression. DNA methyltransferase enzymes (DNMTs) are the primary enzymes that catalyze the transfer of a methyl group on the chromatin. DNMTs are expressed throughout neural development and in the mature stem cell generative zones that mediate ongoing neurogenesis. In neurons, DNA methylation prevents premature neural stem cell maturation [1]. DNMTs are regulated by DNA methylation and physiological interactions, promoting neuronal survival, plasticity, and proper neural stem cell maturation [1].

Genomic imprinting is another instance of gene methylation and was the initial epigenetic phenomenon discovered in human diseases. In an imprinted gene, one of the two parental alleles is active, and the other is inactive as a result of DNA methylation [2]. It marks DNA in a sex-dependent manner, resulting in the differential expression of a gene depending on its parent of origin [3]. For example, some of the genes on chromosome 15 are paternally or maternally suppressed, and one allele is active over the other. A defect in the active allele of the imprinted gene results in the loss of expression, which is found in neurodevelopmental diseases such as Prader-Willi syndrome (PWS) and Angelman syndrome (AS) [2]. These diseases are similar in the way that both diseases represent the loss of the same gene expression, but PWS occurs when the paternal gene is active but defective, and AS occurs when the maternal gene is active but defective.

Histone acetylation

Histone proteins can have an acetyl group added to them, a process called acetylation. Histones normally have a positive charge because of their lysine and arginine residues. Acetylation usually occurs at lysine residues. Acetyl groups are negatively charged. Thus, when acetyl groups are added to lysine residues, they neutralize the positive charge, causing the histones to move away from the DNA, which has a negative charge. As a result, the chromatin relaxes. The neutralization of histone tails makes them more available for transcription and translation (Figure 2). This process is facilitated by histone acetyltransferase enzymes (HATs). HATs are essential in normal and malignant hematopoiesis.

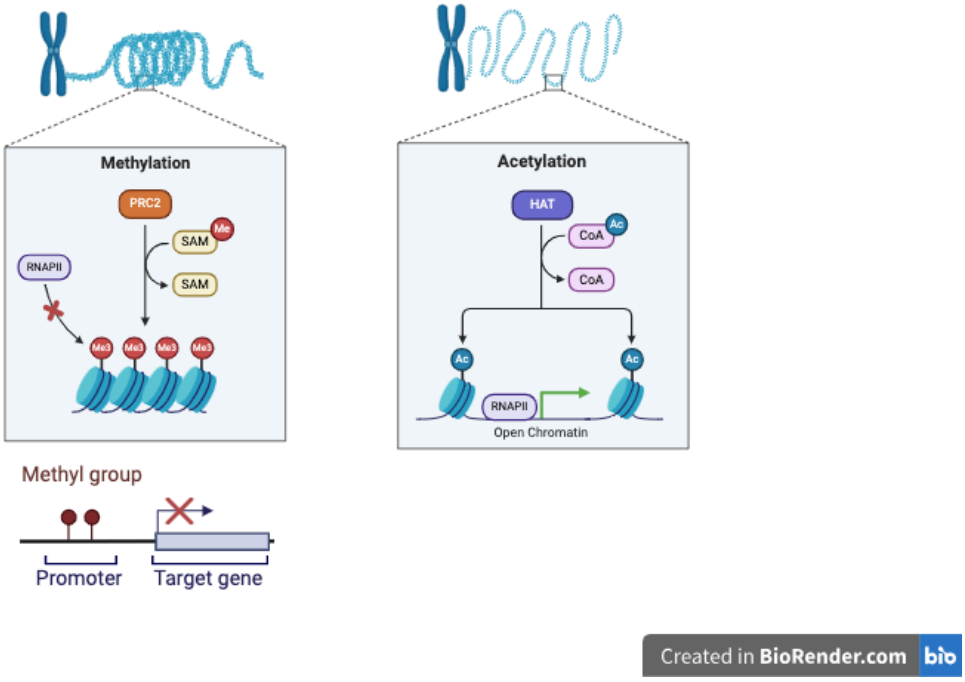

Figure 2. Differences in the effect of DNA methylation (left) and histone acetylation (right) on gene expression. Methyl groups added to the chromatin cause the chromatin to condense. PCR2, a type of DNMT, adds a methyl group. As a result, RNAPII, a type of RNA polymerase that transcribes a target gene is unable to attach to the promoter, and the target gene is not transcribed. When histone proteins are tagged with acetyl groups from coenzyme A, the chromatin is relaxed, enabling RNAPII to attach to the promoter and transcribe the target gene.

Non-coding RNAs

There are several types of non-coding RNAs such as miRNAs, and snoRNAs. Non-coding RNAs can increase or decrease gene expression. Non-coding RNAs (ncRNAs) do not code for proteins. They promote developmental, plasticity, and homeostatic processes [1]. ncRNAs can regulate the activity of other genes by binding to other RNAs to block their expression or mark them for degradation, which decreases gene expression. Additionally, ncRNAs can modify the structure of chromosomes, making genes easier to access for transcription. Chromatin remodeling enzymes can bind to ncRNA to facilitate chromatin remodeling. ncRNAs influence gene expression by targeting common regulatory proteins to DNA regulatory elements such as PREs and TREs, transcribed as ncRNAs themselves [1].

miRNAs are regulatory ncRNAs that inhibit stability or repress translation of target RNAs. They pair up with their targets to repress their expression and can mark them for degradation, leading to less protein production. Brain-specific miRNAs have specialized roles in neural development, adult homeostasis, and plasticity. A single miRNA may differentially repress or activate as many as 1000 target genes with RNA-binding proteins at untranslated regions or additional regulatory sites [1].

Small nucleolar RNAs (snoRNAs) promote developmental and adult functional complexity by acting on chromosomes, and affecting processes such as genomic imprinting, RNA splicing, transcription, translation, cell cycle progression, and DNA repair [1]. Longer ncRNAs are involved in genomic imprinting, X chromosome inactivation, and serve as sites for miRNAs and snoRNAs. These different classes of ncRNAs help organize the regulation of neural development and local protein synthesis required for synaptic plasticity [1]. These epigenetic mechanisms need to be regulated and function properly for cellular and molecular processes to work effectively.

RNA editing

RNA editing is a process in which RNA modifies and regulates protein-coding genes. It is important in many processes, including neural transmission and presynaptic vesicle release. RNA editing can change the profiles of miRNA targets and can impact every step in the production, processing, and stabilization of mature miRNAs [1]. They can modify miRNAs, target genes, and other non-coding RNAs. By dynamically and reversibly altering bases, RNA editing can adjust the expression profiles and functions of protein-coding genes and non-coding RNAs [1].

RNA editing is mediated by adenosine deaminases acting on RNAs (ADARs). These enzymes swap out one nucleotide for a different one, subsequently changing the sequence's identity. In mammals, there are 3 ADAR enzymes: ADAR1 and ADA2, which are preferentially expressed, and ADAR3, which is restricted to the nervous system [1]. ADARs regulate and manage complex patterns of site-specific editing of individual RNAs, leading to multifaceted and functional consequences. Adenosine deaminases acting on tRNAs (ADAT1-3) modify codon recognition in the process of mRNA decoding, promoting and enabling protein diversity in the developing and adult brain. The gene products that result from RNA editing play various roles in neurodevelopment and adult regulatory functions, including neuronal homeostasis, neural network plasticity, and the epigenetic modulation of learning and memory [1].

Regulation of epigenetic mechanisms by cell and environmental cues

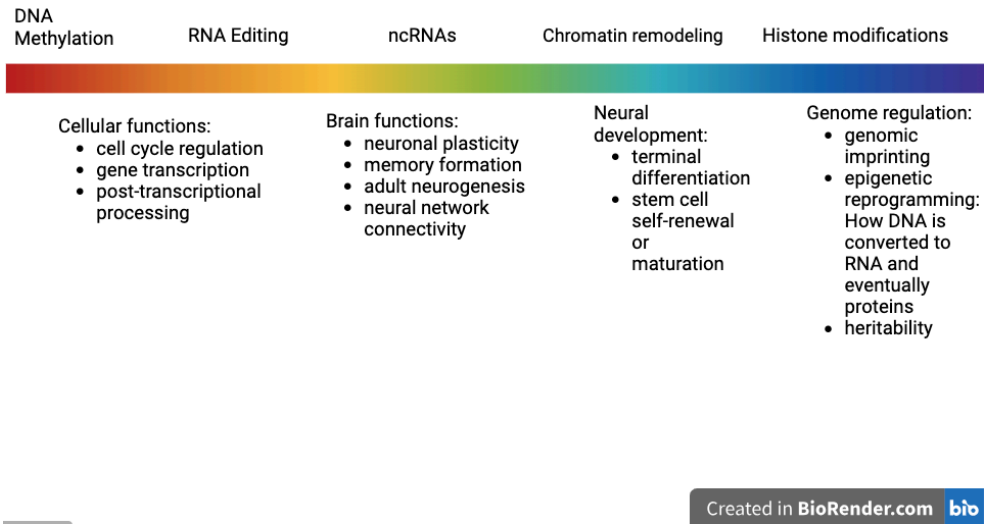

Figure 3. The spectrum of epigenetic mechanisms and some examples of what processes they encompass. Epigenetic mechanisms are all connected, therefore mechanisms are on a spectrum and processes can fall under more than one mechanism. Adapted from [1].

How epigenetic mechanisms get dysregulated

The various epigenetic mechanisms previously described can all be dynamically changed or influenced by environmental factors as well as genetic cues. The dynamics refer to its ability to move between states and changes over time, known as plasticity. The biological definition of plasticity is that organisms have systems and processes that can change their gene expression based on their environment or circumstances. In neurons, plasticity refers to the consistent and necessary regulation of essential mechanisms. Without regulation, these mechanisms would be unable to control the required cellular and molecular processes [1,4].

Epigenetics is an example of plasticity, as it can alter gene expression without changing the DNA sequence. Epigenetics is continuously happening in normal human cells, while irreversible gene regulation systems like CRISPR Cas-9 do not occur naturally in human cells, but can be used in a therapeutic approach. Plasticity is important to acknowledge from a therapeutic perspective. CRISPR is used for therapeutics involving permanent changes, which are not always aligned with biology's needs. Targeting epigenetics because of its plasticity may be a better strategy.

Two of the ways that epigenetic mechanisms can get dysregulated are through DNA methylation inhibitors and environmental cues.

Presence of inhibitors of DNA methylation

Examples of inhibitors of DNA methylation are cytidine analogs 5-azacytidine and zebularine, as well as nucleoside analogs that sequester DNMT enzymes after being incorporated into DNA. When administered into the brain tissues of mice and rats, inhibitors that do not allow DNMT enzymes to transfer methyl groups onto the chromatin disrupt synaptic plasticity and hippocampal learning and memory [4]. DNA methylation inhibitors can reactivate genes that should be silenced, leading to unintentional and overexpression expression of certain genes.

Environment and lifestyle

There is increasing evidence that several lifestyle factors can influence epigenetic patterns. These factors include diet, obesity, level of physical activity, tobacco, smoking, alcohol consumption, environmental pollutants, and stress. Most studies have focused on the effects of these factors on DNA methylation, and only a few studies examine their effects on histone modifications and ncRNAs (Figure 4). Since genetic factors control energy balance and body weight, dietary components like macronutrients that affect DNA methylation could play a role in the development of obesity. Previous research has suggested that DNA methylation is sensitive to environmental stress during early development and later in life. There are epigenetic biomarkers for obesity, such as methylation patterns of obesity-related genes like *FGF2*, *PTEN*, *CDKN1A*, and *ESR*, suggesting a correlation between obesity and changing levels of methylation [5].

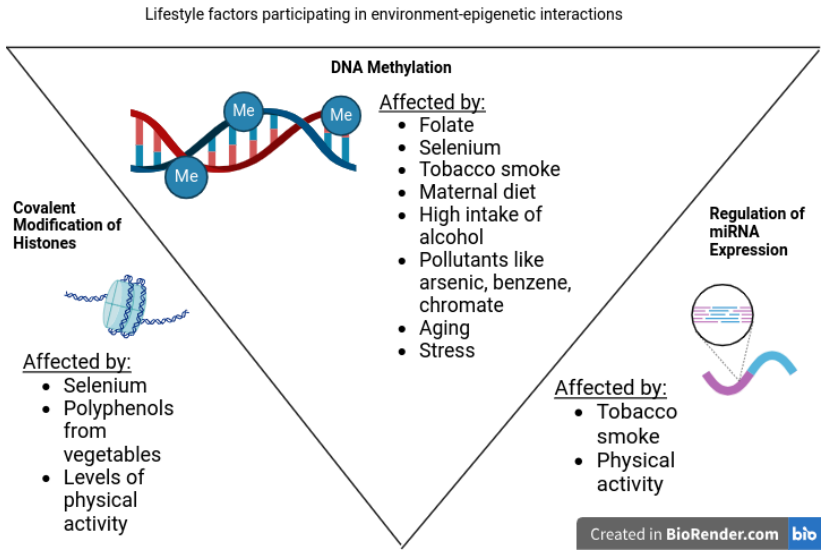

Figure 4. Lifestyle factors that participate in environment-epigenetic interactions. DNA methylation, histone modifications, and the regulation of miRNA expression can be affected by various lifestyle factors. Adapted from [5].

How dysregulation of epigenetic mechanisms contributes to factors linked to Alzheimer's and Huntington's

Alzheimer's disease

Recent studies have suggested a link between dysfunctional epigenetics and the death of neurons, contributing to Alzheimer's disease (AD). AD is the most common form of dementia and affects the elderly population. It is characterized by ongoing and progressive neurodegeneration in specific regions of the brain, including the hippocampus, temporal lobe, frontal lobes, and frontal cortex [6]. This degeneration leads to memory impairment and progressive cognitive dysfunction. This disease is associated with the development and accumulation of amyloid β (Aβ) peptide in the brain, which is caused by hyperphosphorylated tau proteins within the neurons [6]. Individuals with AD may experience symptoms such as mood disorders, unpredictable mood swings, reduced self-care, linguistic difficulties, social isolation, and depression.

The role of genetic factors in the development of AD has been established in around 70% of the cases and involves multiple genes. Mutations in genes that regulate the production of Aβ peptide (*PSEN1*, *APP*, *PSEN2* genes) have been identified as the cause of early onset AD, accounting for 1% of cases [6]. The cause of the remaining cases is not fully understood. Researchers have found that mutations in the gene *APOE* are a major risk factor for the development and progression of late-onset AD (LOAD), but mutations in *APOE* alone cannot explain the development and progression of LOAD [6]. At LOAD loci, the genes encode proteins that are involved in inflammatory pathways, cholesterol metabolism pathways, and endosomal vesicle recycling pathways. However, individually, none of these pathways are considered a major risk factor for the development and progression of AD. While the pathogenesis and symptoms of AD have been established, the pathways that lead to these symptoms and the pathogenesis of AD are still not well understood, and there is currently no cure for AD. AD is a result of a complex interplay between genetic and environmental factors, therefore, the pathogenesis of AD could be explained by dysregulated epigenetic mechanisms.

Dysregulated epigenetic mechanisms in AD include DNA hypermethylation, deacylation of histones, and a general repressed chromatin state. It is important to remember that the chromatin structure becomes tightened (into heterochromatin) due to various epigenetic factors like methylation, which ultimately leads to the repression of gene expression. In AD, the methylation levels of the amyloid precursor protein (APP) promoter region in the temporal lobe are significantly lower compared to those in healthy individuals [6]. This lower amount of methylation results in higher expression, leading to increased protein production and worsening of the condition due to protein aggregation. Studies have shown that AD brains exhibit a large number of differentially methylated (DMRs) or hydroxymethylated (DhMRs) regions compared with control brains. This suggests that the dysregulation of epigenetic mechanisms can potentially serve as a biomarker for downstream correlated factors in AD. Other research findings indicate that enhanced acetylation of histone H4 occurs at the lysine 12 (H4K12ac) residue during the early stages of amyloid protein aggregation in the brain [6]. Given the shared symptoms of cognitive impairment seen in amnesia, change observed during amnesia may be relevant to AD. For example, acetylation of histone H4 at the lysine 12 (H4K12ac) has been observed during amnestic mild cognitive impairment, indicating its potential as an early-stage

biomarker for AD. The protein BACE1 is responsible for the generation of Aβ peptide in the brain and is characterized by regulated miRNAs in the brain and blood of AD patients, It is important to note that the role of epigenetics in AD is considered as downstream and correlated to AD, rather than being a cause.

Huntington's disease

Huntington's disease (HD) is a genetic disorder that primarily affects medium spiny neurons in the striatum. This condition causes the brain cells to gradually lose function and die, impacting the areas of the brain responsible for controlling voluntary movement and memory. Symptoms of HD include uncontrollable movements and changes in thinking, behavior, and personality, which worsen over time [7].

Huntington's disease is caused by a genetic change in the gene *HTT*, resulting in unstable expanded CAG repeats (>35-39 repeats) and producing a mutant protein (mHtt) with a toxic polyglutamine (ployQ) tract. The *HTT* gene is responsible for making a protein called huntingtin, which is essential for the proper functioning of neurons. Individuals with HD lack the necessary genetic information to produce the huntingtin protein. Consequently, the abnormal shape of these proteins leads to the destruction of neurons, causing them to die. The mutation responsible for Huntington's disease can be inherited in an autosomal dominant pattern. If one parent has HD, there is a 50% chance their child will also develop the disease.

Studies have shown significant changes in gene transcription in the brains of individuals with HD [8]. This demonstrates how disruptions in RNA editing and ncRNAs can contribute to neurological diseases. It is important to note that research investigating the correlation between dysfunctional epigenetic mechanisms and the disease indicates that these mechanisms are more of a downstream effect, rather than the root cause of the mutation of the *HTT* gene. In the brains of individuals with Huntington's disease, there is a re-expression of Hox genes and other homeobox genes. This causes the transcription mechanisms in Huntington's disease neurons to resemble those of immature neurons [9], suggesting impaired transcriptional mechanisms. In cellular systems with overexpressed mutant HTT, extensive changes in histone acetylation levels have been observed. Increased H2A ubiquitylation (H2Aub) was found at down-regulated genes in HD R6/2 mice. Changes in DNA methylation in response to mutant HTT were found at both proximal and distal regulatory regions of genes. A large proportion of the genes that displayed altered expression due to the expression of mutant HTT also exhibited changes in DNA methylation, indicating a potential causal relationship.

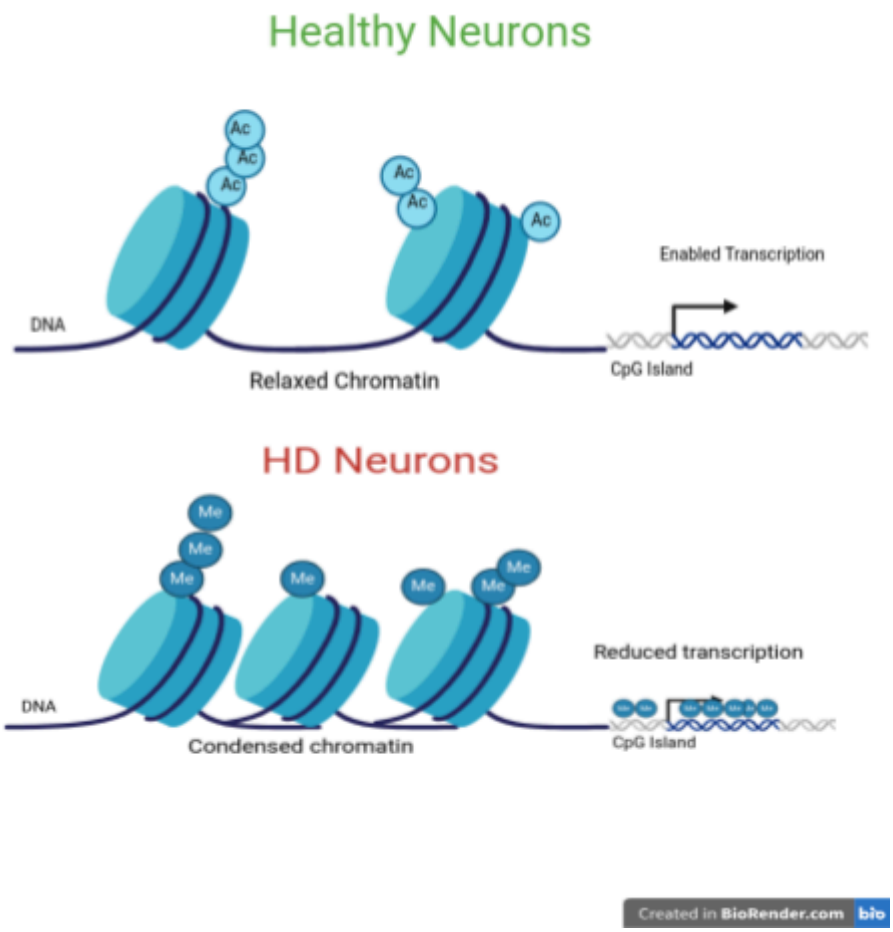

Figure 5. Differences of epigenetic mechanisms active in healthy neurons compared to the neurons of Huntington patients. In healthy neurons, genes can be transcribed at a higher rate due to the acetylation of histone proteins. In neurons of Huntington patients, it was observed that due to the unusually high number of methylation on the chromatin, there was a reduced rate of transcription on the CpG island. CpG islands are areas on the genome that contain a lot of cytosine and guanine nucleotides. Adapted from [10].

Conclusions

The diverse and meticulous mechanisms of epigenetics such as DNA methylation, histone acetylation, ncRNAs, and RNA editing, can regulate gene expression without needing to make changes to the DNA blueprint itself. Prospects suggest that epigenetics could be leveraged for tailored medical approaches targeting specific, extensively researched conditions. Each individual possesses a distinctive epigenetic profile that can change for their specific needs and requirements. Nevertheless, there are lingering questions pertaining to the efficacy of therapeutic intervention in epigenetics and the potential risks associated with interfering with this intricate system, given its inherent connection with other essential molecular and cellular processes.

References

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Glossary

Chromatin: chromatin is the material that makes up chromosomes, composed of DNA wrapped around histone proteins.

Euchromatin: the uncondensed form of chromatin, where RNA transcription is accessible for gene expression.

Heterochromatin: the condensed form of chromatin, caused by methyl groups being added onto the chromatin. RNA transcription is not accessible, and gene expression is repressed.

Methylation: an epigenetic mechanism where methyl tags are added to the chromatin, causing it to condense; resulting in the repression of gene expression.

DNA methyltransferase enzymes (DNMTs): the primary enzymes that catalyze the transfer of a methyl group onto the chromatin.

Histone acetylation: an epigenetic mechanism where acetyl groups are added onto histone proteins; chromatin relaxes, making the DNA accessible for transcription, and promoting gene expression.

Histone acetyltransferase enzymes (HATs): the enzymes that facilitate the addition of acetyl groups onto histone proteins.

Non-coding RNAs: ncRNAs are RNA segments that do not code for proteins. Instead, they can regulate the activity of genes by binding to other RNAs. ncRNAs influence gene expression and promote plasticity and other homeostatic processes.

miRNAs: microRNAs are a type of ncRNA that regulate gene expression. miRNAs can repress or activate target genes by working with RNA-binding proteins.

snoRNAs: small nucleolar RNAs are a type of ncRNA that promotes developmental and adult functional complexity. In eukaryotes, snoRNAs serve in modifying ribosomal RNA (rRNA).

RNA editing: a process in which RNA is used to modify and regulate protein-coding genes;; useful in processes such as neural transmission and presynaptic vesicle release.

ADAR enzymes: adenosine deaminases are enzymes that mediate RNA editing by acting of RNAs. These enzymes swap out one nucleotide for a different one, changing the sequence's identity.

Plasticity: organisms being able to change their gene expression based on their environment or circumstances; reversible and dynamic.

DNA methylation inhibitors: DNA methylation inhibitors disrupt the transfer of methyl groups onto chromatin, disrupting synaptic plasticity and hippocampal learning and memory. DNA methylation inhibitors can reactive genes that should be silenced; overexpression and unintentional expression of certain genes.

Alzheimer's disease: the most common form of dementia that affects the elderly population; characterized by ongoing and progressive neurodegeneration in specific regions of the brain; this degeneration leads to memory impairment and progressive cognitive dysfunction.

Amyloid β peptide: a protein fragment derived from a larger protein called amyloid precursor protein (APP); accumulation of Aβ peptide in the brain is associated with Alzheimer's disease.

Huntington's disease: a genetic disorder that causes brain cells to gradually lose function and die, impacting the areas of the brain responsible for controlling voluntary movement and memory.

HTT gene: the HTT gene codes for the Huntingtin protein. A mutation in the HTT gene is the cause of Huntington's disease.

Homeobox genes: a group of genes that regulate development in organisms, including cell differentiation and morphogenesis.