Effect of DNA Methylation and Environmental Factors on Drug Addiction

ABSTRACT

Substance addiction remains a significant social and medical issue, influenced by both environmental and genetic variables.~~Substance addiction is still a major social and medical issue. Environmental and genetic variables both have an impact on it.~~ The interplay between genetic and environmental factors demonstrates the importance of the epigenetic mechanism. Given its ability to influence enduring alterations in gene expression, epigenetic regulation provides a compelling hypothesis for the persistent behavioral abnormalities associated with drug addiction. Epigenetic mechanisms, including DNA methylation, significantly influence drug addiction and substance abuse. Environmental factors such as parental influence, cultural norms, media representation, and learned physical associations alsocontribute to addiction. This chapter will focus on the effect of DNA methylation and environmental factors on drug addiction. Understanding these variables could potentially provide interpretive tools for the future diagnosis and management of addiction.~~Comprehending these variables could potentially yield interpretive instruments for the future diagnosis and management of addiction.~~

Keywords: Epigenetics, Drug addiction, DNA Methylation, Environmental Factor

1. INTRODUCTION

Substance addiction, which includes alcoholism and illegal drug use, is a severe issue marked by obsessive drug seeking and persistent hazardous use despite detrimental effects [1]. Addiction rises from a confluence of hereditary and environmental elements that interact to create a cumulative, irreversible, and lifelong effect, much like other complicated illnesses [2]. Addictive drugs stimulate the brain's natural reward system through the release or synaptic accumulation of the neurotransmitter dopamine [3,4]. More importantly, the genesis of drug addiction is the result of several environmental variables coming together (like real exposure to illicit drugs) and inherited predisposition (such as genetic polymorphisms influencing the characters related to drug-seeking behavior and dependency). Research on families, twins, and adoptions suggested that the heritability of drug addiction is contributed from moderate to high (ranging from 30 to 70 percent) by shared and non-shared surrounding factors [5]. Numerous evidence suggest that gene expression occurs in abnormal patterns at different regions of the brain related to drug addiction, such as the prefrontal cortex, the nucleus accumbens, the amygdala, and the ventral tegmental area [6,7,8]. The interaction of genetic and environmental factors signifies the role of epigenetic mechanisms.

Epigenetics encompasses the biochemical modifications responsible for changes in gene expression throughout an organism's lifecycle, independent of alterations in the DNA sequence. This includes reversible modulation of gene expression primarily driven by DNA methylation and histone modification [9]. Various epigenetic mechanisms, including DNA methylation, histone modifications, and chromatin rearrangement, play a crucial role in long-term regulation of gene expression, serving as a molecular memory for genes and their interactions with the environment [10].~~Epigenetics defines biochemical modifications through which gene expression alterations are found throughout an organism's lifecycle without a variation in DNA sequence, as well as reversible modulation of gene expression caused mainly by DNA methylation and histone modification. [9]. Different epigenetic mechanisms, such as DNA methylation, histone modifications, and chromatin rearrangement, have influenced long-term gene expression regulation, providing molecular memory for genes and environmental interactions [10].~~ Researchers have demonstrated that epigenetic variables have a significant role in the vulnerability to specific common neuropsychiatric phenotypes associated with addiction, such as schizophrenia [11] and depression disorders [12]. Other evidence also suggested that long-lasting neuroplasticity changes observed in drug addiction may be partially regulated by epigenetic alterations [13]. Numerous findings indicate that exposure to external environmental factors has the potential to impact epigenetic modifications globally or at specific genomic loci [14]. Given that epigenetic modifications are transmitted mitotically in somatic cells, they present a potential mechanism through which the influence of external environmental stimuli at specific developmental stages can lead to enduring behavioral changes. Of particular interest in the context of addictive behavior, there is a wealth of evidence suggesting that drugs of abuse directly influence epigenetic processes, and these alterations may contribute to the molecular underpinnings of addiction. DNA methylation is viewed as a more enduring epigenetic modification compared to histone tail modifications, which are considered more readily reversible. ~~Numerous~~

~~discoveries show that exposure to external environmental factors can impact epigenetic modifications globally or at specific loci [14]. Since epigenetic modifications are transmitted mitotically in somatic cells, they offer a potential method via which the influence of outside environmental stimuli at particular developmental stages can result in long-term behavioral changes. Especially interesting to addictive behavior, there is various evidence that drugs of abuse directly affect epigenetic processes and that these alterations may contribute to the molecular basis of addiction. DNA methylation is viewed as a more stable epigenetic alteration than histone tail modifications, which are considered easily reversible.~~

Gene expression can alter over time due to the mitotic stability of DNA methylation patterns. However, these patterns also exhibit a discernible degree of adaptability over time, allowing cells to adapt to shifting internal and external influences. [15]. Research has shown that DNA methylation status also regulates the neuroplasticity brought on by abusing drugs, and it may have a significant impact on the onset and symptoms of drug addiction [16, 17]. A consistent adaptation, in line with the persistent and experience-driven nature of addiction, involves the lasting epigenetic changes to the DNA of affected neurons [7].~~One constant adaptation, proportionate to experience-driven and persistent nature of addiction, entails enduring epigenetic alteration to the DNA of impacted neurons [7].~~ Through conformational alteration to chromatin shape and accessibility, these alterations affect transcription without directly changing the nucleotide sequence. These changes can affect underlying transcription levels ofgenesdifferently, priming/desensitizing particular genes for stimulation or suppression in response to drugs, or triggers or regulating splice variant expression [8, 9]. Since addiction does not develop until after repeated exposure to an addictive substance, the causes of addiction can only be fully understood by identifying the inherited and environmental predisposing variables along with the dynamic neurobiological alterations brought on by long-term drug exposure.

2. DNA METHYLATION AND ADDICTION

DNA methylation is the process of introducing a methyl groupto the C5 position of cytosine (5-mC) [18]. DNA can be modified by an enzyme called DNA methyltransferases (DNMTs), which facilitate the addition of a methyl group to the cytosine and is traditionally observed at cytosine-guanine dinucleotide (CpG) residues [9]. DNA methyltransferase 1 (DNMT1) maintains DNA methylation through the replicative process, which copies an existing 5mC onto the complementary DNA strand after cell division [19]. DMNT3a and DMNT3b are considered de novo methyltransferases, responsible for methylating previously unmethylated cytosines to establish a pattern of DNA methylation [20,21]. The identified forms of cytosine modification can return to an unmethylated state through base excision repair, glycosylation, or deamination. In addition to other functions, DNA methylation is necessary for healthy organismal development, genetic imprinting, X chromosome inactivation, and tissue-specific gene expression [22]. DNA methylation is believed to be a gene expression repressive modification. A group of proteins translates DNA methylation status to gene regulation by attracting regulatory complexes to promoters and enhancers. Methylation at particular cytosine-guanine dinucleotides (CpG islands) ~~has~~ impede~~d~~s transcription factors binding to target regions by assembling multiple corepressor complexes. MeCP2 and MBD1 are methyl-binding domain-containing proteins that attract repressive complexes to methylated DNA. These proteins also stabilize other corepressors, such as HDACs, near gene promoters. DNA methylation at gene promoters can impact the transcription factor CREB's binding because the consensus cAMP response element (CRE) sequence has a

CpG island that, when methylated, inhibits CREB from binding to its target sequences [23]. The 5-hydroxymethylcytosine moiety might be an epigenetic mark different from 5-methylcytosine [24, 25].

Increasing research has started to elucidate the role of DNA methylation in drug addiction. Furthermore, studies have shown that the enzyme DNA methyltransferase 3a (DNMT3a), ~~an enzyme that methylates DNA,~~ plays a direct function. ~~Reports haveshown that~~A decreased in DNMT3a activity ~~in the Nucleus~~ accumbens causes~~d~~ increased behavioral reactions to cocaine, which can be achieved through either pharmacological suppression or viral-mediated enzyme knockdown [26]. Researchers discovered aberrant DNA methylation patterns in the promoter regions of several genes in both drug and alcohol addicts as well as animal models. Furthermore, they demonstrated a significant correlation between DNA methylation and alcohol and nicotine dependency in women, particularly at the monoamine oxidase-A (MAOA) gene [27].~~Researchers found promoter regions of several genes to exhibit aberrant DNA methylation patterns in drug and alcohol addicts or animal models. Also, they showed a substantial correlation between DNA methylation with alcohol and nicotine dependency in women at the monoamine oxidase-A (MAOA) gene [27].~~ Another discovery revealed~~s~~ that heroin users' blood and brain tissue had increased levels of methylation at CpG-rich islands within the opioid receptor gene (OPRM1) [28, 29, 30]. Compared to individuals who are not taking opioid painkillers, researchers have shown increased methylation levels in patients undergoing long-term treatment, suggesting that prolonged opioid exposure has pharmacological effects [28]. A study also indicate~~d~~s increased DNA methylation at the OPRM1 (opioid receptor mu 1) gene promoter of methadone-maintained former heroin addicts, leading to a decrease in OPRM1 gene expression in lymphocytes [29]. Blood samples from alcohol-dependent people also showed higher levels of DNA methylation in the HTR3A serotonin receptor gene [31]. A finding concluded the severity of alcoholics' drinking patterns correlated negatively to DNA methylation of a cluster of CpGs associated with the promoter region of the NR2B (NMDA receptor 2B) gene [16]. In a separate study, researchers identified hypermethylation of the Arginine Vasopressin (AVP) gene associated with alcoholism. Conversely, DNA hypomethylation was observed in the promoter region of the atrial natriuretic peptide (ANP) gene [32]. Additionally, researchers demonstrated that inhibiting DNMT activity led to alterations in the methylation profiles of the reelin and BDNF promoters—two genes linked to the modulation of synaptic plasticity in the adult hippocampus [33]. Collectively, these findings underscore the impact of drug use on gene expression through DNA methylation.~~In another research, the Arginine Vasopressin (AVP) gene was found to be hypermethylated with alcoholism; in contrast, DNA hypomethylation is observed at the promoter area of the atrial natriuretic peptide (ANP) gene [32]. Researchers also demonstrated that DNMT activity inhibition alters the methylation profile of the reelin and BDNF promoters, two genes linked to the generation of synaptic plasticity in the adult hippocampus [33]. All these findings show how the use of drugs alters gene expression by DNA methylation.~~

3. ENVIRONMENTAL FACTOR AND ADDICTION

Environmental influence plays a vital role in addiction. For example, urban locations, which have a higher proportion of juveniles and illicit drug sales than rural settings, exhibit an approximately five-fold increase in the genetic impact on alcohol intake [34]. Results imply that exposure to external environmental influence could affect epigenetic processes globally or at particular loci [35]. Primary research and experiments on

DNA methylation changes that occur postnatally could give some ideas on the fundamental principles that control the role of epigenetics as an environmental mediator. DNA methylation profile varies due to nutritional, chemical, physical, and psychosocial factors (e.g., stress exposure). The role of epigenetic processes in modulating the phenotypic effects of environmental stimuli is supported by evidence that genetically similar animals and identical twins can experience epigenetic variation due to environmental factors [36, 37]. According to a study, adolescents with lower socioeconomic status have higher levels of DNA methylation at the serotonin transporter gene's promoter region in blood cells, which predicts alterations in risk-related brain functions and makes these people more vulnerable to addiction [38]. Slight modifications in methylation have been observed in blood samples from both human and mouse offspring born to mothers exposed to alcohol consumption during pregnancy [39]. These alterations appear to be associated with relevant metabolic genes. In a significant study, specific genomic sites exhibited methylation changes in adipose tissue when mice were exposed to a high-fat diet, leading to the induction of obesity and other diabetes-like signs [40]. Thus, environmental interventions on the epigenome provide a mechanism for understanding gene-environment interactions implicated in neurological illnesses, including those underlying susceptibility to addiction [41]~~Slight modifications in methylation have been observed in human and mouse blood samples from offspring born to mothers exposed to alcohol consumption [39] during pregnancy, and these changes appear to be associated with relevant metabolic genes. One significant study identified sites in the genome that undergo methylation changes in adipose tissue after exposing mice to a high-fat diet, thereby inducing obesity and other diabetes-like signs [40]. Thus, the epigenome's environmental intervention offers a mechanism for the gene-environment interactions currently found in neurological illnesses, including those underlie an addiction's susceptibility [41].~~

4. CONCLUSION

DNA methylation and its surrounding influences play a pivotal role in drug abuse. However, a more efficient and reliable preclinical research approach, along with studies focusing on locus-specific alterations in DNA methylation, is needed to fully comprehend the intricacies of DNA methylation in drug addiction. Once identified, the genes impacted by DNA methylation can be cross-referenced with locations affected by histone modifications to gain a comprehensive understanding of the interactions between these drug-induced epigenetic modifications and the control of gene expression.

Chemical agents that modify DNA methylation may serve as effective candidates for medical treatment, given the dynamic and reversible nature of epigenetic systems. With a deeper understanding of the mechanisms behind the addiction process, researchers can develop potent pharmaceutical medications and diagnostic biomarkers for the treatment and prevention of addiction, relapse, and other neurological disorders.

DNA methylation profiling offers insights into an individual's environmental exposure history. The field of drug addiction and overuse epigenetics provides a molecular understanding of the issue. To achieve this goal, studies utilizing genomic technologies, such as whole-genome and gene-specific bisulfite sequencing, must ascertain how drug abuse affects DNA methylation modifications and gene expression.

~~DNA methylation and surrounding influence play a vital role in the abuse of drugs. However, it will take more efficient and reliable preclinical research, as well as studies concentrating on locus-specific alterations in DNA methylation, to fully understand the intricacies of DNA methylation in drug addiction. Once discovered, the genes impacted by DNA methylation can be cross-referenced with locations impacted by histone modifications to produce a thorough understanding of the interactions between these drug-induced epigenetic modifications and gene expression control. Chemical agents that modify DNA methylation may be effective candidates for medical treatment since epigenetic systems are dynamic and reversible. Researchers will be able to create powerful pharmaceutical medications and diagnostic biomarkers for the treatment and prevention of addiction, relapse, and other neurological disorders with a finer understanding of the mechanisms behind the addiction process.DNA methylation profiling can provide information about an individual's environmental exposure history. The field of drug addiction and overuse epigenetics offers a molecular understanding of the issue. To achieve this goal, studies utilizing genomic technologies, such as whole-genome and gene-specific bisulfate sequencing, must ascertain how drug abuse affects DNA methylation modifications and gene expression.~~

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