

The Role of Epigenetic Mechanisms in Substance Use Disorders: An Overview

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Abstract

“Substance use disorder” (SUD) is a common, chronic, remitting/relapsing group of psychiatric disorders having devastating effect not only on the individual but also impose socio-economic burden on their families and the society at large. They are often accompanied with numerous maladaptive behaviors and a persistent and compulsive, uncontrolled use of substance. Interestingly, they have moderate to high heritability and seem to be modulated by both genes and environment. Recent researches suggest that interactions of environmental and genetic factors designate the significance of epigenetic mechanisms, which have been found to occur in SUDs. This review makes an attempt to provide an overview regarding the various types of epigenetic modifications and their application in relation to SUDs.

Keywords: Epigenetics; Substance use disorder; DNA; Histones; Micro RNA

Introduction

Substance use disorders are a group of psychiatric disorders influenced by various genetic, neurobiological, social and environmental factors. Researches have revealed that some common heritable genetic components may predispose an individual to substance dependence which is estimated to be as high as 20–50% [1]. However, researchers have also elucidated the inter-linked nature of genetic and environmental factors in order to clarify the idea that some specific biological factors and broader biosocial influences interact intricately to develop a predisposition or perpetuate substance abuse/dependence [2]. Although unclear, the interactions between various genotypes and environmental influences point toward an important role for epigenetic mechanisms in drug dependence. Nevertheless, this epigenetic perspective can be a more novel and precise way of explaining the chronicity of psychiatric conditions including SUDs. So what do we mean by epigenetics? According to Jaenisch and Bird, epigenetics is broadly defined as “a series of biochemical processes through which changes in gene expression are achieved throughout the lifecycle of an organism without a change in DNA sequence” [3]. These changes can be immediate or delayed and may be passed on to daughter cells, or to successive generations through the process of cell division. In simpler terms, it is the vector through which environment interacts with an individual’s genome to determine all aspects of function and resilience in terms of health and disease (Figure 1). More specifically, covalent modifications of chromatin (DNA-histone protein complex), present in the cell nucleus is referred to as epigenetics. Epigenetic mechanisms perpetuate transient modulation as well as lasting variation in gene expression. The possible impact of the environment on epigenetic regulation has attracted substantial interest in researchers. Undoubtedly, a proportion of stress-exposed genetically vulnerable individuals do go on to develop SUDs which clearly represent low resilience factors and a high gene-environment interactions [4]. Stable epigenetic changes may become ideal mediators to produce changes in the functionality of the brain along with poor resilience factors for the development of substance use disorder.

Mechanism of Dependence

Substance abuse/dependence may be a resultant of impulsive→compulsive use of the substance. There are frequent episodes of abstinence which may/may not follow relapse. There are identifiable

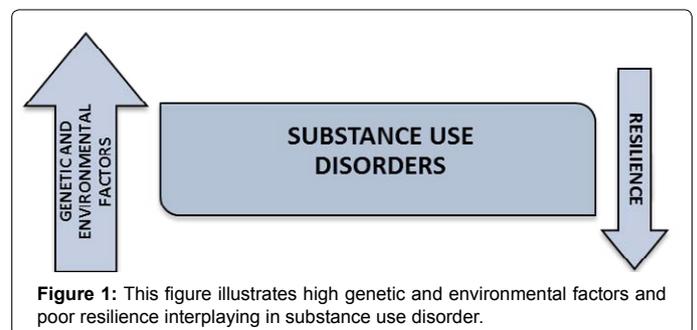


Figure 1: This figure illustrates high genetic and environmental factors and poor resilience interplaying in substance use disorder.

neurobiological mechanisms of dependence and much has been attributed to the abnormal reward circuitry. Drug-induced changes in gene expression in various brain reward systems, such as the nucleus accumbens (NAc), prefrontal cortex (PFC) and ventral tegmental area (VTA), represent one of the mechanism thought to contribute to dependence [5]. Changes in gene expression have been implicated in transition from chronic exposure to drug, to drug dependence; for example, increased transcription factor Δ FosB to several folds in the NAc is seen following chronic drug exposure and has been implicated in the transition to a dependent state [6]. Moreover, altered expression of specific genes, such as activator of G-protein signaling 3 (AGS3) and brain-derived neurotrophic factor (BDNF) are involved in drug relapse in rodents [7]. Moreover, conditioned responses and an environmental context-dependency to the behavioral sensitization are also apparent. Chronic cocaine not only induces a variety of long-term biochemical and physiological effects, but also induces changes in the neurotransmitter GABA in the ventral striatum (nucleus accumbens) due to the modification in the dendritic spines. These GABAergic neurons have regulating effects on both glutamatergic neurons of pre-

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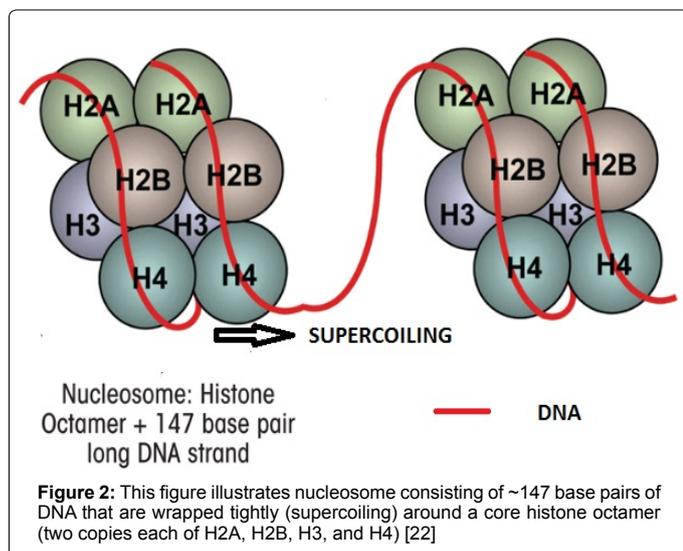
frontal cortex and dopaminergic neurons in the nucleus accumbens [8]. Hence, it appears that epigenetic mechanisms are regulated by substance abuse in brain's reward regions and might contribute to drug-related behaviours.

Epigenetic Regulation in SUDs

In many studies, environmentally induced changes in gene expression are associated with altered DNA methylation patterns or with altered histone modifications [9]. Interestingly, the possibility of an epigenetic contribution to psychiatric disorders, specifically schizophrenia, autism and substance use disorder has been increasingly focussed upon for an attractive molecular hypothesis.

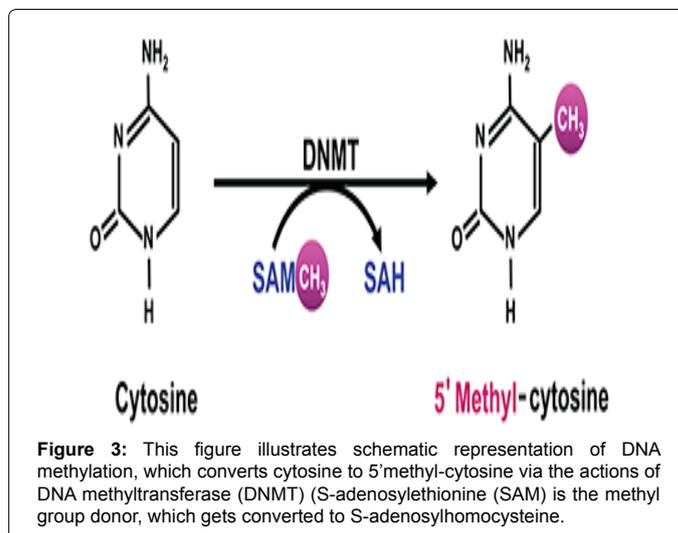
Histone modification

The nucleotides of DNA in a mammalian genome have extraordinary degree of compactness and organization within the chromatin. The nuclear material is composed of DNA, histones and non-histone proteins [3]. The fundamental unit of chromatin is the nucleosome consisting of ~147 base pairs of DNA that are wrapped tightly (supercoiling) around a core histone octamer (two copies each of H2A, H2B, H3, and H4) (Figure 2). This highly condensed structure has control over gene expression, which occurs partly by gating the access of transcriptional activators to DNA [10]. The histone proteins assemble at one end called the carboxy (C) terminal to form the histone core, with the other end, in the amino (N)-terminal "tail" region, projecting out from the histone core. The post-translational histone modification occurs at the (N) terminal and includes acetylation, phosphorylation and methylation of histones. This diversity of histone modifications supports the "histone code hypothesis," which hypothesizes that the sum of modifications at a particular gene defines a specific epigenetic state of gene activation or silencing [11]. Histone acetylation is catalyzed by histone acetyltransferases and reversed by histone deacetylases (HDACs), which generally drives a more permissive (open) state of chromatin and an increased gene expression. Histone methylation, catalyzed by histone methyltransferases (HMTs) and reversed by histone demethylases (HDMs), can either activate or repress gene transcription (increased or decreased gene expression) depending on the amino acid residue undergoing methylation. Histone acetylation and thus chromatin remodelling may regulate a protein called cyclic-AMP responsive-element-binding (CREB) protein. This protein helps modulate the transcription of certain genes by binding to a specific sequence on the DNA. Importantly, CREB binding protein



Histone modifications	Transcription effects noted
Acetylation	Increased transcription
Methylation	Increased/Decreased transcription
Phosphorylation	Increased transcription

Table 1: Histone modifications and their effects on transcription.



is essential for both short-term and long-term memory formation and consolidation. CREB is involved in long-term memory formation, synaptic plasticity that has been associated with dependence. Alcohol-induced damage to nerve cells in the hippocampus and cerebellum has also been associated with decreased CREB functioning [12,13]. A well-established molecular model for long-term memory has been studied with a notion that the facilitatory neurotransmitter serotonin (5-HT) activates the cAMP-dependent protein kinase (PKA) to phosphorylate CREB-binding protein (CBP) and phospho-CREB leads to the induction of two immediate early genes, C/EBP and ubiquitin C-terminal hydrolase, as well as several late effector genes including eEF1A and the RII subunit of PKA. In addition to serving as a scaffold protein in CREB promoter complexes, the recruited CBP also has intrinsic histone acetyltransferase activity and can modify histones at promoters, resulting in the decondensation of DNA and thus enabling gene expression [14]. Interestingly, studies have often reported decrements in hippocampal BDNF caused by a repressive epigenetic mechanism involving trimethylation of histone H3K27 [15,16]. However, trimethylation of histone H3K27 cannot be reversed by antidepressant treatment despite increase in the hippocampal BDNF levels. Nonetheless, a lifelong persistence of the epigenetic marks related to stressors early in life is a likely mechanism for increased reactivity of animals and humans to subsequent stressors later in life. Early traumatic life experiences may exhibit life-long decrements in BDNF in the prefrontal cortex, based on increases in DNA methylation. Interestingly DNA methylation is also involved in cocaine-induced behavioral sensitization in mice, and the sensitized response is again blocked by the methylation inhibitor zebularine [17]. Global H3 and H4 acetylation levels in the Nucleus accumbens (NAc) are increased after a single exposure to cocaine and remain elevated with chronic administration [18,19]. An acutely increased histone acetylation generally increases behavioural response to seek cocaine, a more sustained increases in acetylation may have attenuating effects on cocaine's rewarding tendency. Moreover, acute, but not chronic, cocaine increases H4 acetylation at the c-Fos promoter and chronic cocaine increases H3 acetylation at the BDNF promoters in NAc (Table 1).

DNA methylation

The DNA consists of four bases, guanine, cytosine, adenine and guanine. Researchers have focussed particularly on cytosine as it has been the best understood and the most stable epigenetic modification for regulating the transcriptional agility of mammalian genomes. DNA methylation is pertinent for epigenetics, as a methyl group is added to position 5 (Figure 3) of the cytosine pyrimidine ring in a reaction catalysed by a group of enzymes called DNA methyltransferases (DNMTs). This occurs primarily but not always where a cytosine (C) occurs next to guanine (G) in the DNA sequence (CpG). The fundamental link between DNA methylation and the regulation of gene expression is demonstrated by the observed negative relationship between the level of promoter DNA methylation and the degree of expression of many genes [3]. The addition of a methyl group to CpG sites in the promoter regulatory regions of many genes displaces the binding of transcription factors and attracts a methyl-binding protein that initiates gene silencing. In particular, the methyl CpG binding protein 2 (MeCP2 protein) is important for the regulation of synaptic plasticity and dendritic spine maturation. This is an important protein, as newly methylated CpG islands influence transcription. Hence, DNA methylation plays a pivotal role in brain development, synaptogenesis and synaptic plasticity in differentiated neurons [20]. In substance use disorder MeCP2 is important, because changes in MeCP2 in the nucleus accumbens have been shown to contribute to the neural and behavioural responses and they also can control BDNF expression and cocaine intake [21]. Cocaine self-administration also increases MeCP2 expression in the NAc and dorsal striatum, and increase drug intake under some conditions [21]. Its effects has been studied on BDNF expression as MeCP2 also helps in regulating alcohol's addictive properties and BDNF expression is altered in various brain regions by acute and chronic exposure to alcohol [22].

Two possible mechanisms for the actions of MeCP2 in drug reward have been proposed. First, a reduction in MeCP2 prevents increase in the NAc dendritic spine density while increasing the number of GABAergic synapses. An increase in MeCP2 phosphorylation specifically in GABAergic interneurons in the NAc is also complemented to the above mechanism, which may regulate behavioural sensitization to substance use disorder. An alternative model suggests that MeCP2 represses the transcription of specific microRNAs (see below), resulting in reduced repression of brain-derived neurotrophic factor (BDNF), which is also a target for CREB. BDNF has previously been described to promote cocaine self-administration [23]. Although these models are not mutually exclusive, further work is necessary to integrate them with our growing understanding of the multiple brain regions and cell types that are involved in reward behaviours.

Role of micro RNA (miRNA)

MicroRNAs (miRNAs) comprise of species of short noncoding RNA which regulate post transcriptional gene expression. Recent studies have demonstrated that epigenetic mechanisms, including DNA methylation and histone modification, not only regulate the expression of protein-encoding genes, but also miRNAs. Conversely, another subset of miRNAs controls the expression of important epigenetic regulators, including DNA methyltransferases and histone deacetylases. This complicated network of feedback between miRNAs and epigenetic pathways appears to form an epigenetics-miRNA regulatory circuit to organize the whole gene expression profile. When this regulatory circuit is disrupted, normal physiological functions are interfered with, contributing to various disease processes [24]. miRNAs control gene expression by interfering with the intricate processes of mRNA

translation into a protein product and mRNA degradation. Researchers have found that substance dependence is associated with both up and down regulation of miRNAs mimicking the direction of each of these changes affecting the reward circuitry. It has also been implicated in gene regulation and synaptic plasticity [25]. Several genes implicated in addiction models such as Δ FosB, dopamine transporter, and glutamate receptor subunits, have also been related to drug-triggered alterations in specific miRNAs [26]. Moreover, miRNAs are altered in NAc after chronic cocaine use [27]. However, extensive researches on miRNA affected by chronic substance intake and its relationship have yet to be elucidated.

What is mito-epigenetics?

Mitochondria contain their own circular DNA that encodes for proteins, transfer RNAs, ribosomal RNAs and also non-coding RNAs. Mitochondrial DNA is particularly important as it produces and regulates formation of the reactive oxygen species (ROS). Moreover, production of ROS at mitochondria integrates cellular energy state, concentration of metabolites in the neurons and other upstream signaling events. These have important implications in cellular stress signaling, maintenance of stem cell populations and even cellular survival [28]. In fact, addictive drugs enhance ROS production and generate oxidative stress that in turn alters mitochondrial and nuclear gene expressions [29]. Very recently, an epigenetic focus has been directed towards mitochondria and evidence indicates that mitochondria are involved in epigenetic regulation of nuclear genome including the methylation status of mitochondrial genome [30,31]. The complex transcription and epigenetic regulation of mtDNA induced by addictive substances in the brain have received very little attention and requires in-depth exploration.

The Way Forward

Based on the current researches it is evident that there is an exponential growth of epigenetic research to understand the mechanisms underlying substance use disorder and their related behaviors. However, the major limitations in such researches are that they are conducted on rats and precise research on human subjects may require post-mortem human brain tissue. This is because epigenetic changes are often tissue or cell specific and thus most likely to be apparent in the brain areas in which addiction is primarily manifested. Unfortunately, the low and middle economic countries do not possess high-quality post-mortem brain samples that have been well characterized for substance dependence. Additionally, very little is known about how factors such as age, sex and environmental exposure influence epigenetic patterns, which requires proper matching of subjects. Despite the fact, much is anticipated in the future with regards to epigenetics in psychiatric disorders and more specifically SUDs.

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