Review Article

# The Epigenetics of Drug Addiction

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**ABSTRACT**

Drug addiction is still a significant medical and societal issue. Drug addiction susceptibility is influenced by genetic, environmental, social, and biological variables. The importance of epigenetic mechanisms, which have been discovered to occur in reaction to drug use or as underlying variables in chronic substance misuse and relapse, is particularly highlighted by the interconnections of environmental and genetic factors. The term "epigenetics" refers to heritable, potentially reversible changes in gene expression that do not entail changes to the DNA sequence. This review covers the many types of epigenetic changes and their significance to drug addiction to understand whether epigenetics is a predisposing factor for, or a response to, developing an addiction to drugs of abuse.

**Keywords:** Epigenetics, Drug Addiction, Opioid, Alcohol, DNA methylation.

## INTRODUCTION

Epigenetics is the study of heritable, possibly reversible changes in gene expression that take place without changing the DNA's sequence. DNA methylation and chromatin remodeling are the two main mechanisms that regulate epigenetic inheritance. Epigenetic changes can be passed down to daughter cells or to succeeding generations through meiotic or mitotic inheritance. They can also occur instantly or slowly accumulate. These epigenetic changes could be the result of genetic imprinting, chronic drug use, or pharmacotherapies for addiction.[1-4] A crucial process in addiction is memory consolidation in the hippocampus and storage in the cortex, both of which may be impacted by changes in DNA methylation. The neuroplasticity changes seen in drug addiction are relevant to the role of important DNA methylation enzymes, such as DNA methyltransferases, in regulating the induction of synaptic plasticity in the hippocampus. Changes in CpG methylation can persist or quickly reverse.[5,6] The DNA regions known as CpG sites or CG sites are those where a cytosine nucleotide is followed by a guanine nucleotide in a straight line along its 5' 3' orientation. CpG islands are genomic areas with a high frequency of CpG sites. The cytosine nucleotide is followed by a guanine nucleotide at the CpG sites, also known as CG sites, in a linear pattern along the 5'-3' orientation of the DNA molecule. CpG islands are genomic areas with a high frequency of CpG sites.

### How does epigenetics work?

Different epigenetic modifications have an impact on gene expression. Several epigenetic modifications include:

#### *DNA Methylation:*

The process of DNA methylation involves the addition of a methyl group to DNA. This group is typically introduced to specificregions of DNA, where it prevents proteins from attaching to DNA and "reading" genes. Demethylation, a procedure, can be used to get rid of this chemical group. Genes are typically "turned off" by methylation and "turned on" by demethylation.

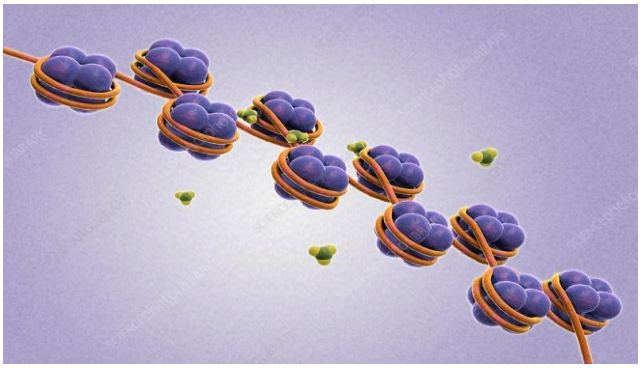

**Figure 1:** DNA histones and epigenetics

#### *Alteration of Histones:*

Histone proteins are wrapped around DNA. When histones are firmly packed together, proteins that "read" the gene have difficulty accessing the DNA, and the gene is turned "off." More DNA is exposed or not wrapped around a histone when histones are loosely packed, and this allows proteins that "read" genes to access it, turning the gene "on." Histones can have chemical groups added or subtracted to make them more or less tightly or loosely packed, which turns genes "on" or "off."

#### *Non-Coding RNA:*

Coding and non-coding RNA is produced using instructions found in your DNA. Proteins are created using coding RNA. In order to prevent the coding RNA from being used to produce proteins, non-coding RNA attaches to the coding RNA along with some proteins. This helps control the expression of genes. In order to "on" or "off" genes, non-coding RNA may also enlist proteins to change histones.

**What influences your epigenetics?**

One of the primary epigenetic pathways affecting gene expression is the methylation of cytosines at the 5′ position of the cytosine pyrimidine ring in CpG dinucleotide sites. DNA methylation is required for X chromosome inactivation, tissue-specific gene expression, genomic imprinting, and the development of healthy organisms. The process of designating genes for silencing has evolved from the methylation of CpG sites in promoter regions, which typically results in a reduction in gene expression. In addition to normal aging and development, your environment and behaviors also have an impact on how your epigenetic makeup changes as you age.

**1. Growth and epigenetics**

Epigenetic alterations start to take place before birth. Despite sharing the same genes, your cells all appear and behave differently. Epigenetics plays a role in determining which function a cell, such as a heart cell, neuron cell, or skin cell, will have as you grow and develop.

An example would be nerve versus muscle cells:

Despite sharing the same DNA, your muscle and nerve cells function differently. Information is sent from a nerve cell to other cells in your body. The structure of a muscle cell contributes to your body's mobility. Due to epigenetics, a muscle cell can turn "on" genes that generate proteins necessary for its function and "off" genes necessary for a nerve cell's function.

**2. Age and epigenetics**

Your epigenetic makeup evolves over time. Your epigenetic makeup at birth is different from what it is when you are a child or an adult.

On study of newborns, for instance a newborn, a 26-year-old, and a 103-year-old had their DNA methylation levels tested at millions of locations. Age causes a reduction in DNA methylation. The DNA methylation of a newborn was highest, that of a geriatric was lowest, and that of a youngest was in the middle of those two ranges.

**3. Versatility and Epigenetics**

Not all epigenetic modifications are long-lasting. In response to adjustments in behavior or environment, some epigenetic modifications can be added or eliminated.

*Smokers, non-smokers, and former smokers in a case study:*

Smoking may alter epigenetic processes. Smokers typically have less DNA methylation than non-smokers at specific regions of the AHRR gene, for instance. For heavy and chronic smokers, the disparity is higher. Former smokers may experience enhanced DNA methylation at this gene after stopping smoking. They may eventually attain levels resembling those of non-smokers. It is possible for this to occur in certain situations in less than a year, but the amount of time depends on how much and for how long the smoker smoked before stopping.

**Drug Addiction**

The persistence of the drug-addicted state is probably a result of drug-induced changes in gene expression throughout the reward circuitry of the brain. The regulation and stability of drug-mediated neuronal gene programs, as well as the subsequent spread of addictive behaviors, are directly impacted by chromatin remodeling, according to recent studies examining the molecular mechanisms governing drug-induced transcriptional, behavioral, and synaptic plasticity.

Addiction, a relapsing chronic brain disease, is a major medical and social problem. Opioid use is three times more common in India than it is worldwide. The most popular drug used is alcohol, followed by marijuana and opioids. The male-to-female ratio is 17:1, and the prevalence of alcohol use is 4.6%. Cannabis use is 2.8%, and opioid use is 2.1%. In terms of harmful and dependent use, 19% of alcohol users are dependent, whereas 0.25% of cannabis users are dependent. Opioids are used by 2.1% of the population, with heroin accounting for 1.14%, pharmaceutical opioids accounting for 0.96%, and opium accounting for 0.52%. Dependent use is the most prevalent usage pattern among users.

The three drugs that are used most frequently nationally are opium (afeem), heroin, and prescription opioids. Sedatives are only used recreationally or for non-medical reasons by 1 million people, or less than 1% of the population. But what's more worrying is how frequently it affects kids and teenagers. Child addiction is a bigger issue in Uttar Pradesh, Madhya Pradesh, Maharashtra, Delhi, and Haryana. Cocaine (0.10%), stimulants like amphetamine (0.18%), and hallucinogens (0.12%) have the lowest prevalence of current use in the country.

The process of becoming addicted to drugs happens in stages, beginning with the first use, moving on to regular use, and concluding with addiction and relapse. Addiction is characterized by the emergence of physiological dependence on the drug that is required for a person to function normally, the emergence of tolerance that necessitates higher doses of the drug to produce the same effect, and the emergence of withdrawal symptoms. Drugs used to treat addiction alter physiological functions, keep an addict in that state, and affect withdrawal and relapse.

Addiction susceptibility and chronic addiction are influenced by convergent biological, social, environmental, and genetic factors. Twin studies suggest that there are heritable genetic factors that contribute to drug addiction. These genetic factors, along with nongenetic factors, explain 20–50% of the variation in the likelihood of developing a drug addiction. ports the notion that various biosocial influences interact with specific biological factors, has helped to clarify the connections between these determinants.

The effects of gene-environment interactions are still being studied, but there may be more genetic influence on manifested phenotypes than traditional nature-nurture

studies would suggest. According to interactions between genotype and environmental factors, epigenetic mechanisms may affect both the acute response to drugs as well as the development of drug addiction. The persistence of mental illnesses and the challenges in creating pharmacotherapeutic treatments for persistent behavioral disorders lend credence to this epigenetic point of view.

**Opioids**

**Table 1:** Epigenetic modifications in drug abuse.

| Gene | Treatment | Response |
|---|---|---|
| **OPRM1** | Chronic | Reduced OPRM1 mRNA content and increased OPRM1 promoter methylations were linked in vitro. |
| | Chronic | Two OPRM1 promoter region CpG sites were hypermethylated in lymphocyte DNA of Caucasian former heroin addicts |
| | Chronic | In the lymphocyte DNA of Caucasian former heroin addicts, two CpG sites in the OPRM1 promoter region were discovered to be hypermethylated. |
| | Chronic | Leukocyte DNA from male opioid addicts has seven OPRM1 CpG sites that are hypermethylated. |
| | Chronic | OPRM1-promoter CpG site hypermethylation in the sperm of male opioid addicts |
| | Acute | male offspring had increased exposure to morphine and developed tolerance to it more quickly, while female adult offspring of dams treated with morphine for 10 days prior to mating displayed increased anxiety-like behavior. |

The majority of opioid analgesics, heroin's bioactive byproducts (6-monoacetylmorphine and morphine), as well as endogenous ligands enkephalins and endorphins, all act on the opioid receptor, which is encoded by the OPRM1 gene.[7] In vitro research has revealed a correlation between lower levels of OPRM1 mRNA and higher levels of histone deacetylation.[8,9] (The DNA is wrapped more securely around the histone cores when the histone tails are deacetylated, which makes it more difficult for signaling pathways to attach to the DNA. This process which is known as gene silencing, results in lower levels of gene expression) and promoter methylation. The transcription factors Sp1, Brg1, and BAF155 bind to the OPRM1 promoter region during the differentiation of P19 cells and activate OPRM1.[10] Histone deacetylase dissociated simultaneously with the repressors mSin3a, Brm, and MeCP2. While having no impact on morphine dependence or tolerance, sodium butyrate does improve the conditioned place preference and locomotion sensitization brought on by the drug. The activation of OPRM1 expression and the recruitment of Brg1 may facilitate the dissociation of MeCP2 with concurrent histone modification.[11]

Former heroin addicts who are Caucasian and Hispanic may have hypomethylation in the OPRM1 promoter region due to a negative feedback mechanism that reduces the expression of OPRM1 and, consequently, the levels of the opioid receptor. Reduced transcription and consequently lower levels of the opioid receptor are caused by DNA methylation of the OPRM1 promoter.[12,13] This is corroborated by a report indicating that methadone maintenance subjects had fewer opioid receptors in their blood. The OPRM1 gene may be silenced by Sp1 and other transcription factors if CpG sites in the OPRM1 promoter are over methylated.[14]

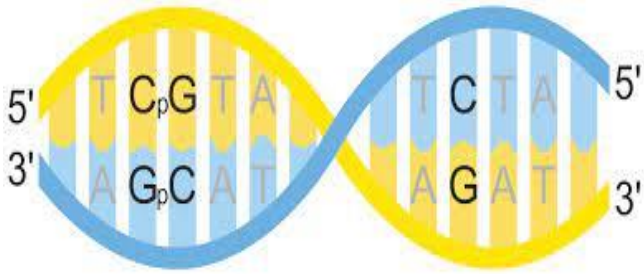


**Figure 2:** CpG site

**Alcohol**

After both brief and prolonged use, alcohol causes epigenetic changes. Chronic ethanol treatment has been shown to cause demethylation of CpG islands in the NMDA receptor NR2B subunit gene NR2B and an increase in NR2B expression in mouse cortical neurons.[15]

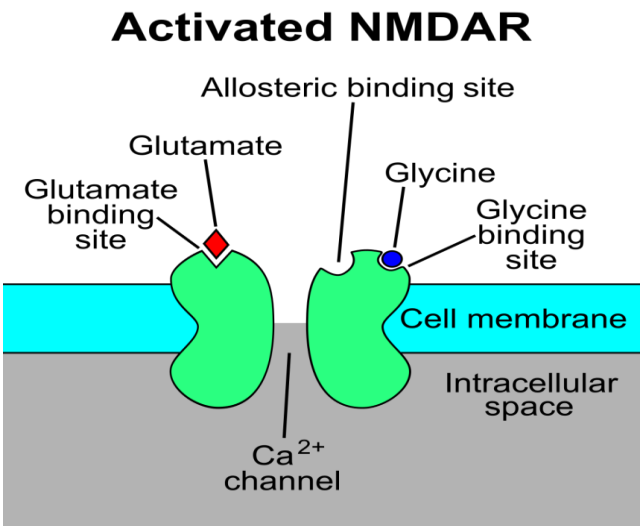


**Figure 3:** NMDA receptor activated

Illustration of a stylized NMDAR in action Both glutamate and glycine are present in the glutamate-binding site. The allosteric site, which when attached to a ligand modifies receptor function, is unoccupied. Two molecules of glutamate or aspartate and two molecules of glycine must bind to NMDARs.

In primary cortical neurons, chronic intermittent ethanol treatment and subsequent withdrawal were found to increase the expression of the NR2B genes along with an increase in the H3K9 acetylation of the NR2B promoter region. This rise was most likely brought on by a decrease in G9a, Suv39h1, and HDAC1-3 binding to the NR2B promoter rather than a change in the activity of global histone acetyltransferases or histone deacetylases. Moreover, acute ethanol treatment has been demonstrated to increase H3 and H4 acetylation and decrease histone deacetylase activity in the rat amygdala.[16,17] On the other hand, withdrawal from prolonged ethanol administration resulted in an increase in histone deacetylase activity in the same areas along with a simultaneous drop in H3 and H4 acetylation. In contrast to rats treated with trichostatin A (TSA), an inhibitor of histone deacetylase activity, in which anxiety-like symptoms did not emerge, these changes in histone acetylation during withdrawal were linked to increased anxiety in rats going through withdrawal.[18] Histone acetylation alterations may contribute to the anxiety brought on by ethanol withdrawal, which raises the possibility that histone deacetylase inhibitors may lessen the severity of alcohol withdrawal symptoms.[19]

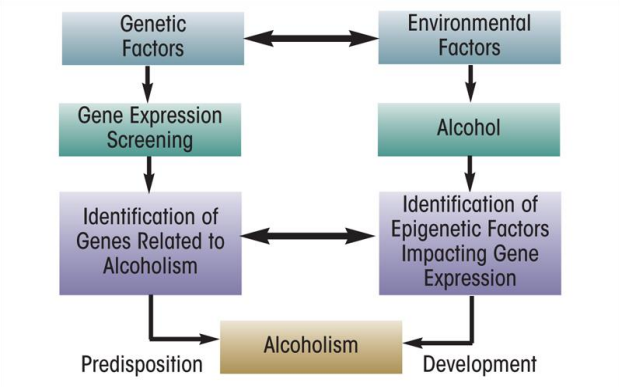


**Figure 4:** An improbable model for how hereditary and environmental influences interact to cause and contribute to alcoholism.

When compared to controls, the DNA of drinkers' lymphocytes exhibited hypermethylation. Despite having lower DNMT3b expression, there was a general increase in DNA methylation in alcoholic cells.[20] Alcoholics have been shown to have hypermethylation of the HERP gene, which is linked to higher homocysteine levels. Homocysteine increases the expression of endoplasmic reticulum chaperone proteins, which may protect the endoplasmic reticulum from stress.[21,22]

## CONCLUSION

Altered chromatin structure that influences gene expression and is brought about by addictive substances is the focus of modern epigenetic research. The early and long-term effects of a drug, the development of tolerance that leads to addiction, withdrawal symptoms, and relapse are all potentially impacted by these epigenetic factors. Initial reward-signaling pathways may be altered as a result of an epigenetic response to emotional stress and social challenges, predisposing one to a favorable response to drug use. Cocaine and c-fos activity in the nucleus accumbens show that additional epigenetic alterations that reverse the first acute drug response may occur with persistent drug use and addiction formation. It seems that rather than reflecting a biological propensity to become addicted, the epigenetic modifications linked to drug addiction are more likely to reflect an epigenetic reaction to substance use. Yet, research on the methylation changes in DNA linked to drug addiction raises the possibility that epigenetics may play a part in a person's greater susceptibility to addiction.

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