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REVIEW ARTICLE

# The Role of Epigenetics in the Pathogenesis and Potential Treatment of Attention Deficit Hyperactivity Disorder

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**Abstract:** There is increasing evidence that dysregulated epigenetic mechanisms of gene expression are involved in the pathogenesis of attention deficit hyperactivity disorder (ADHD). This review presents a comprehensive summary of the current state of research on the role of epigenetics in the pathogenesis of ADHD. The potential role of epigenetic drugs in the treatment of ADHD is also reviewed. Several studies suggest that there are epigenetic abnormalities in preclinical models of ADHD and in ADHD patients. Regarding DNA methylation, many studies have reported DNA hypermethylation. There is evidence that there is increased histone deacetylation in ADHD patients. Abnormalities in the expression of microRNAs (miRNAs) in ADHD patients have also been found. Some currently used drugs for treating ADHD, in addition to their more well-established mechanisms of action, have been shown to alter epigenetic mechanisms of gene expression. Clinical trials of epigenetic drugs in patients with ADHD report favorable results. These data suggest that abnormal epigenetic mechanisms of gene expression may be involved in the pathogenesis of ADHD. Drugs acting on epigenetic mechanisms may be a potential new class of drugs for treating ADHD.

**Keywords:** Attention deficit hyperactivity disorder, childhood, genetics, epigenetics, pathogenesis, treatment.

## 1. INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder that affects children, adolescents, and adults around the world [1]. ADHD in children is characterized by inattention, hyperactivity, impulsivity, or a combination of these symptoms, which adversely affect everyday functions like learning to read and making friends [2]. ADHD is the most common neuropsychiatric disorder among children affecting 9.5% of all US children between 6 and 17 years old [2]. Initially, it was thought that ADHD is solely a childhood disorder and the diagnosis of adult ADHD was uncertain. However, now it has been established that among 40 to 60% of children with ADHD, the disorder persists into adulthood [3]. ADHD in adults differs from that in children partly because of a greater reduction in hyperactivity symptoms than symptoms of inattention. Reduction in hyperactivity can manifest as restlessness, while the persisting symptoms of inattention can manifest as difficulties in performing tasks like keeping appointments and meeting deadlines. ADHD in adults can result in work problems like frequent job changes, interpersonal problems like marital issues, and coexisting psychiatric disorders like major depression and anxiety disorders (ADs) [3].

## 2. ROLE OF HEREDITARY FACTORS IN ATTENTION DEFICIT HYPERACTIVITY DISORDER

Family, twin, and adoption studies indicate that ADHD has a marked hereditary component [2]. The heritability of the disorder has been estimated to be 76%, making it one of the most heritable psychiatric disorders [4]. Genome-wide association studies (GWAS) have identified several genes associated with ADHD. These include common variants as well as rare variants [5, 6]. There is thought to be genetic overlap between ADHD and other neuropsychiatric disorders like schizophrenia, bipolar disorder, and ADs [5]. However, precisely how the genetic variants contribute to the disorder is unclear, and to date, genetic testing has not made it into clinical practice [6, 7]. In recent years there is also increasing evidence that epigenetic mechanisms of gene expression are dysregulated in ADHD patients, a field that has been reviewed elsewhere [8, 9]. The present article updates the data on the role of epigenetics in ADHD and discusses the potential pharmacological modification of dysregulated epigenetic mechanisms in the treatment of this disorder. The cited literature was retrieved from searches in PubMed and Google Scholar.

## 3. CURRENT TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER

Drugs used for the treatment of ADHD include CNS stimulants like amphetamines and methylphenidate. These drugs are generally recommended as first-line pharmacological treatment.

They act by increasing extracellular levels of the neurotransmitters dopamine and norepinephrine in the synaptic cleft [10]. Drugs that do not stimulate the CNS include atomoxetine, extended-release clonidine, and extended-release guanfacine [10]. Atomoxetine inhibits the reuptake of norepinephrine and dopamine. Clonidine is a centrally acting $\alpha_2$ adrenergic receptor agonist, and guanfacine stimulates postsynaptic

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$\alpha_{2A}$ receptors [10]. Psychotherapy is also very important in the treatment of patients with ADHD and is known to complement pharmacotherapy [1].

## 4. OUTLINE OF EPIGENETICS

Epigenetics, other than, or in addition to, genetics, is at present an active area of research in both biology and medicine. It involves molecular mechanisms like DNA methylation, DNA hydroxymethylation, histone modifications, and non-coding RNA (ncRNA)-mediated regulation of gene expression. Epigenetic mechanisms of gene expression can be modulated by factors in the environment, and epigenetic mechanisms of gene expression are thought to be a link between the genome and the environment [11]. There is increasing evidence that epigenetic mechanisms of gene expression are dysregulated in human disease, especially common chronic disorders. Indeed, epigenetics has been referred to as the epicenter of modern medicine [12]. There is also increasing evidence that abnormal epigenetic mechanisms of gene expression contribute to the pathogenesis of common psychiatric disorders [13, 14].

## 5. SCOPE FOR EPIGENETICS IN ATTENTION DEFICIT HYPERACTIVITY DISORDER

Several lines of evidence suggest that abnormalities in epigenetic mechanisms of gene expression are involved in the pathogenesis of ADHD: **1**. There are differences between the two sexes with regard to ADHD, with males being more commonly affected than females [5]. **2**. The concordance rate in monozygotic twins for ADHD falls far short of 100%, suggesting a role for epigenetic factors in its pathogenesis. The concordance rate in monozygotic twins has been estimated to range from 59 to 92% [15]. **3**. Environmental factors are known to be involved in the pathogenesis of ADHD. Such factors can more easily act by altering epigenetic mechanisms of gene expression than the DNA sequence of genes, suggesting a role for epigenetic mechanisms in the pathogenesis of ADHD. **4**. As described below, there is experimental evidence for abnormal epigenetic mechanisms of gene expression in patients with ADHD. **5**. As described below, some of the currently used drugs for treating ADHD have been shown to alter epigenetic mechanisms of gene expression.

## 6. ROLE OF DNA METHYLATION IN THE PATHOGENESIS OF ATTENTION DEFICIT HYPERACTIVITY DISORDER

Several studies have found abnormalities in DNA methylation associated with ADHD. Zhang *et al.* [22] exposed male C57BL/6 mice to 2mg/kg of nicotine for 5 weeks and then mated them with wild-type females (Table **1**). The offspring of male mice were subjected to behavioral tests at 8 weeks after birth. It was found that paternal nicotine exposure led to hyperactivity of the offspring. It was also found that paternal nicotine exposure caused a rise in total DNA methylation of *Dat*, the gene encoding the dopamine transporter (DAT1) in murine spermatozoa, and the hypermethylation could imprint in the brains of the offspring mice, leading to hyperactivity in the offspring. Abnormalities in DNA methylation have also been found in peripheral tissues of ADHD patients in comparison to control subjects (Table **2**). Of note, many of the studies cited in Table **2** and investigating DNA methylation found hypermethylation of DNA, an epigenetic change that correlates with a decrease in gene expression. For example, Meijer *et al.* [34] observed no epigenome-wide significant differences in single CpG site methylation between patients with persistent ADHD and healthy controls or patients with remittent ADHD. However, hypermethylated regions in the *APOB* and *LPAR5* genes were associated with ADHD persistence compared with ADHD remittance. Sigurdardottir and colleagues [41] attempted to determine possible differences in norepinephrine transporter (NET) promoter methylation between 23 ADHD patients and 23 healthy controls. The authors found significant differences in methylation levels at many CpG sites between the two groups. A defined segment of the NET promoter (region 1) was found to be hypermethylated in ADHD patients in comparison to controls.

### 6.1. Role of Histone Modifications in the Pathogenesis of Attention Deficit Hyperactivity Disorder

Relatively little work has been done on the role of histone modifications in the pathogenesis of ADHD. Ookubo and colleagues [18] examined epigenetic changes in the developing brain of thyroid hormone receptor-β deficient mice, a mouse model of ADHD. The authors found that the expression of acetylated histone H3 was low in the dorsal raphe of the mice, and histone deacetylase (HDAC) 2/3 proteins were widely increased in the mesolimbic system of the mice. Xu *et al.* [43] conducted a pair-matching case-control study of epigenetic abnormalities in blood samples obtained from Chinese Han children. The authors found that there was increased expression of HDAC1 in the ADHD patients compared to healthy controls, suggesting to the authors that there was decreased histone acetylation in the patients.

### 6.2. Role of Non-coding RNAs in the Pathogenesis of Attention Deficit Hyperactivity Disorder

The role of ncRNAs in the pathogenesis of ADHD has also received attention. To date, attention has mainly focussed on one type of ncRNAs, microRNAs (miRNAs), which are ncRNAs comprising 19-24 bases. miRNAs typically silence gene expression by inhibiting the translation of messenger RNA (mRNA) into protein. As shown in Table **1**, in preclinical models of ADHD, abnormalities of miRNAs have been detected. As shown in Table **2**, to date, several miRNAs have also been found to be dysregulated in ADHD patients in comparison to control subjects. At present, we are in the early stages of this research area. However, the available data suggests that dysregulated miRNAs modulate the expression of genes like those encoding DAT1 and dopamine receptor 1 (DRD1) that have been associated with the pathogenesis of ADHD. Dysregulation of such miRNAs could alter the normal functioning of these molecules in the brain contributing to the development of ADHD. It also appears that there are alterations of levels and functioning of miRNAs in animal models of ADHD and in peripheral tissues of ADHD patients. Hence, peripheral miRNA levels could potentially serve as biomarkers for ADHD.

**Table 1. Epigenetic changes in preclinical models of attention deficit hyperactivity disorder.**

| Tissue/Model | Epigenetic Change | References |
|---|---|---|
| Prefrontal cortex of rat | miRNA let-7d involved in ADHD | [16] |
| Cerebral cortex of mice | Chronic exposure of male mice to ethanol before mating produces ADHD-like features in offspring probably epigenetically | [17] |
| Developing brain of THR-β deficient mice | Decreases expression of acetylated histone H3 in dorsal raphe; Increases expression of HDACs 2/3 in mesolimbic system | [18] |
| Rat prefrontal cortex | Abnormal expression of miRNAs | [19] |
| Rat hippocampus | Different expression of miRNAs | [20] |
| Rat lateral ventricle | Aberrant miR-384-5p affects learning and memory | [21] |
| C57BL/6 mice | Paternal nicotine exposure induces hyperactivity in offspring by hypermethylation of DAT gene | [22] |
| *In Silico* | Prediction that several candidate SNPs in miRNA target genes may play major roles in ADHD | [23] |

**Abbreviations:** DAT: Dopamine transporter; HDAC: Histone deacetylase; miRNAs: microRNAs; SNPs: Single nucleotide polymorphisms; THR-β: Thyroid hormone receptor- β.

### 6.3. Epigenetic Effects of Currently-used Drugs in Attention Deficit Hyperactivity Disorder

It is interesting that some of the currently used drugs for treating ADHD, in addition to their well-established mechanisms of action, alter epigenetic mechanisms of gene expression (Table **3**). For example, the sympathomimetic drug and CNS stimulant amphetamine have been shown to decrease global DNA methylation [58] and increase histone H4 acetylation [56,57] in the brain. Amphetamine has also been shown to affect the expression of miRNAs in preclinical studies [62]. Biagoni *et al.* [63] found that exposure of C57 black/6J mice to high and/or prolonged doses of methamphetamine produces a long-lasting increase in striatal α-synuclein levels. This was found to be associated with persistent demethylation of the α-synuclein gene promoter in the corpus striatum. The CNS stimulant methylphenidate was shown to influence DNA methylation of the dopamine D4 receptor gene in an 8 week open-label trial in youth with ADHD [61] and the expression of long non-coding RNAs (lncRNAs) in the prefrontal cortex in rats [59]. Atomoxetine has been shown to affect serum levels of miRNA-let-7 in children with ADHD [53]. More details of the epigenetic effects of currently used drugs in ADHD are given in Table **3**.

### 6.4. Clinical Trials of Epigenetic Drugs in Attention Deficit Hyperactivity Disorder

The antiepileptic and mood-stabilizing drug valproic acid (VA), and its sodium salt sodium valproate, are known to have HDAC inhibiting effects at therapeutic concentrations [64]. In this context, it is of interest that VA has been shown to have beneficial effects in ADHD patients. Miyazaki and colleagues [65] showed that extended-release sodium valproate gives a favorable response in 3 ADHD patients with giant somatosensory evoked potentials. Blader and co-workers [66] showed that sodium valproate reduces aggression in children with ADHD. Toriolli *et al.* [67] showed that VA reduces ADHD symptoms in boys with fragile X syndrome. Another epigenetic drug undergoing preclinical and clinical trials for ADHD treatment is vafidemstat, which is developed by the pharmaceutical company Oryzon [68]. Vafidemstat is a KDM1A inhibitor. KDM1a is a flavin adenine dinucleotide (FAD)-dependent amine oxidase that acts primarily as a lysine demethylase. KDM1A is thought to be involved in many biological processes, including neurogenesis and the regulation of neuron progenitor cell proliferation and terminal differentiation. Recent data from a phase IIa clinical trial support vafidemstat as an emerging therapeutic option for the treatment of agitation and aggression in psychiatric disorders, including ADHD [68]. More details on clinical trials of epigenetic drugs in ADHD are given in Table **4**.

### 6.5. Clinical Implications of the Role of Epigenetics in Attention Deficit Hyperactivity Disorder

From the above, it is apparent that dysregulated epigenetic mechanisms of gene expression contribute to the pathogenesis of ADHD. However, much more work needs to be done in order to get a clearer picture of the role of epigenetics in ADHD. Regarding the epigenetics of ADHD, a relevant issue is whether data in the brains of patients can be inferred from data in their peripheral tissues like blood and saliva (Table **2**). Ideally, the study of epigenetic changes in ADHD patients should be done on their brain tissues. However, due to practical reasons, this is difficult. On the other hand, data on epigenetic mechanisms from peripheral tissues are known to provide useful information on epigenetic mechanisms in brain tissues [69]. There are websites available that enable the interpretation of epigenetic data from peripheral tissues in the context of the brain [70, 71].

Better knowledge of the role of epigenetics in the pathogenesis of ADHD could help in the clinical management of ADHD patients in two ways. One way pertains to the clinical diagnosis of ADHD patients. At present, patients with ADHD are diagnosed based on clinical grounds, namely, history and clinical examination [1]. Biomarkers for the diagnosis and prognosis of ADHD will be useful for the clinical practitioner. One possible type of biomarkers are

**Table 2. Epigenetic changes in human peripheral cells in attention deficit hyperactivity disorder.**

| Tissue | Epigenetic Change | References |
|---|---|---|
| Blood | DNA methylation related to early childhood malnutrition implicated in ADHD | [24] |
| Blood, Saliva | Hypermethylation of DRD4 gene associated with deficits in ADHD | [25] |
| Blood | Methylation of 5-HT3A gene linked with ADHD | [26] |
| Saliva | Methylation of VIPR2 associated with ADHD | [27] |
| Buccal cells | DNA methylation related to event-related brain potentials and ADHD behavior | [28] |
| Blood | Potential role for DNA methylation in genes related to cortical circuits | [29] |
| Blood | DNA methylation related to GABA, DA, and 5-HT genes implicated in ADHD | [30] |
| Blood | Peripheral DAT1 promoter methylation may predict striatal DAT availability in ADHD. | [31] |
| Blood cells | Identification of risk variants for ADHD that correlate with differential cis-methylation | [32] |
| Blood | Many DMRs detected | [33] |
| Blood | DNA methylation associated with ADHD traits | [34] |
| PBMCs | One CpG site and 4 regions differentially methylated | [35] |
| Saliva | Possible DNA methylation biomarkers for ADHD | [36] |
| Umbilical cord blood | Methylation of GFI1 is a mediator of association between prenatal smoking and ADHD at 6 years | [37] |
| Blood | DNA methylation in LIME1 and SPTBN2 is associated with ADHD | [38] |
| Blood | DNA methylation changes may be useful biomarkers | [39] |
| Blood/Saliva | Association between COMT gene methylation and response to treatment in ADHD | [40] |
| Blood | Association of NET methylation with *in vivo* NET expression and ADHD symptoms | [41] |
| Blood | DNA methylation in TARBP1 gene associated with ADHD | [42] |
| Blood | Increases expression of HDAC1 | [43] |
| Blood | Changes in several miRNA levels | [44] |
| Serum | Elevated miRNA Let-7d level | [45] |
| PBMCs | Pri-miR-34b/c and miR-34b/c associated with ADHD | [46] |
| Blood | AGO1, a miRNA biosynthesis candidate gene, associated with ADHD | [47] |
| Blood | miRNAs may be useful as biomarkers | [48] |
| Serum | Low levels of miR-142-3p and miR-378 | [49] |
| Blood | miRNAs are involved in ADHD pathogenesis | [50] |
| PBMCs | Aberrant profiles of expression of miRNAs | [51] |
| Serum | Aberrant expression of miRNAs | [52] |
| Serum | Changes in expression of miRNA-let-7 | [53] |
| Leukocytes | Expression of miRNAs affects brain development | [54] |
| Blood | Three miRNAs differentially expressed | [55] |

**Abbreviations:** COMT: Catechol-O-methyltransferase; DAT1: Dopamine transporter; DMR: Differentially methylated regions; DRD4: Dopamine receptor 4 subtype; GABA: Gamma amino butyric acid; HDAC1: Histone deacetylase 1; 5-HT: Serotonin; miRNAs: microRNAs; NET: Norepinephrine transporter; $TARBP_1$: TAR (HIV1) RNA-binding protein1; VIPR2: Vasoactive intestinal polypeptide receptor-2.

**Table 3. Epigenetic effects of currently used drugs in attention deficit hyperactivity disorder.**

| - | Effect | References |
|---|---|---|
| Amphetamine | Produces increased H4 acetylation in mouse striatum | [56] |
| Amphetamine | Enhances global H4 acetylation in rat striatum | [57] |
| Amphetamine | Causes a decrease in global DNA methylation | [58] |
| Methylphenidate | Distinct lncRNA expression profiles in the PFC of rats | [59] |
| Methylphenidate | DAT1 methylation associated with response | [60] |
| Methylphenidate | Interaction between effect of CpG7 methylation and prenatal maternal stress and treatment response | [61] |
| Atomoxetine | Changes in serum miRNA-let-7 in children with ADHD | [53] |
| Methamphetamine | Demethylation of SCNA gene promoter | [63] |

**Abbreviations:** DAT1: Dopamine transporter 1; H4: Histone 4; lncRNA: Long non-coding RNA; PFC: Prefrontal cortex; SCNA: α-synuclein.

**Table 4. Clinical trials of epigenetic drugs in attention deficit hyperactivity disorder.**

| Drug | Class | HDAC Class Target of Drugs | Finding | References |
|---|---|---|---|---|
| ER-Valproate | HDACi | I, IIa | Favorable response of ADHD with giant SEP | [65] |
| Sodium valproate | HDACi | I, IIa | Reduces aggression | [66] |
| VA | HDACi | I, IIa | Reduces ADHD symptoms in FXS boys | [67] |
| Vafidemstat | LSD1 inhibitor | NA | Reduces agitation/aggressiveness | [68] |

**Abbreviations:** ER-Valproate: Extended release valproate; FXS: Fragile X syndrome; HDAC1: Histone deacetylase1; LSD1: Lysine demethylase 1; NA: Not applicable; SEP: Somatosensory evoked potentials; VA: Valproic acid.

epigenetic biomarkers, and efforts are being made to identify such biomarkers [9, 72]. Another way by which the knowledge of epigenetics could impact the clinical management of ADHD patients would be the use of new drugs that act by correcting dysregulated epigenetic mechanisms of gene expression. As mentioned above and as given in Table **2**, DNA hypermethylation and increased activity of HDAC1 have been detected in peripheral tissues of ADHD patients. In this light, drugs that decrease DNA methylation and HDAC activity may be useful. Indeed as given in Table **4**, the antiepileptic and mood-stabilizing drug VA has shown favorable results in ADHD patients. As mentioned above, VA at therapeutic concentrations has HDAC inhibiting activity [64]. However, VA also has other possible mechanisms of action, like inhibition of nerve conduction. Moreover, it is a non-specific inhibitor of HDACs targeting class I and class IIa HDACs. More specific HDACi could show greater clinical efficacy. HDACi, in addition to causing histone acetylation due to inhibition of HDACs, are also known to cause DNA demethylation. This effect could be due to perturbation of the dynamic interplay between the acetylation of histone tails and DNA methylation [73]. This effect could also be due to raised levels of the demethylating enzyme ten-eleven-translocation methylcytosine dioxygenase 1 (TET1) [74]. Since, as discussed above, there is DNA hypermethylation in ADHD patients, this effect could also contribute to the possible efficacy of HDACi in ADHD.

An important issue regarding the use of VA is possible adverse effects (AE) on the brain. These can occur prenatally, during infancy, and during childhood [75, 76]. Among all antiepileptic drugs, VA has the greatest potential to cause these AE [75]. Indeed, some children treated with VA can develop clinical features resembling those of ADHD [77]. The exact mechanism of the AE on the brain due to VA is not clear, but could, in fact, involve epigenetic mechanisms [78]. In this light, the use of other HDACi with greater safety profiles and HDAC specificity than VA may be warranted. Indeed, the clinical use of HDACi in the treatment of patients with psychiatric disorders is being actively investigated [79].

## CONCLUSION

There is accumulating evidence that abnormal epigenetic mechanisms of gene expression are involved in the pathogenesis of ADHD. These abnormalities include abnormal DNA methylation, histone modifications, and ncRNA-mediated regulation of gene expression. However, at present, we are in the early stages of this field of research. A better and deeper knowledge of the abnormalities of epigenetic mechanisms in ADHD could lead to improvements in the clinical care of ADHD patients with the development of epigenetic biomarkers of the disease process and new drugs that target and correct the epigenetic abnormalities.

## CONSENT FOR PUBLICATION

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## CONFLICT OF INTEREST

The author declares no conflict of interest, financial or otherwise.

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