Dopamine Pathway Disorders in Adolescent ADHD and Core Targeted Therapeutic Strategies

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***Abstract*—Attention Deficit Hyperactivity Disorder (ADHD) is one of the most common neurodevelopmental disorders among adolescents worldwide. The growing disease burden of adolescent ADHD has attracted extensive academic attention. Cumulative empirical evidence identifies dopamine-pathway dysfunction as the core biochemical mechanism underlying adolescent ADHD pathogenesis. Genetic and epigenetic regulatory processes jointly modulate these pathological alterations and drive disease progression. This review synthesizes recent studies published from 2021 to 2026, focusing on dopamine-related molecular abnormalities, including elevated expression of the dopamine-transporter protein encoded by the DAT1 gene and regulatory effects of DNA methylation on gene transcription. It further elaborates on the molecular mechanisms of action for two first-line clinical medications targeting the dopaminergic system. Based on a comprehensive synthesis of existing literature, this review highlights key limitations in current research. Major drawbacks include over-reliance on studies of isolated single-neurotransmitter pathways and insufficient analysis of environmental risk factors such as prolonged exposure to short-form digital media. This review proposes targeted directions for future research, including epigenetic-biomarker-based early-screening approaches and individualized medication strategies tailored for adolescents. It establishes clearer logical links between basic molecular research and clinical practice, and provides theoretical support for future biological early-intervention research on adolescent ADHD.**

***Keywords*—adolescent Attention Deficit Hyperactivity Disorder (ADHD), dopamine pathway, Dopamine Transporter 1 (DAT1) gene, DNA methylation, targeted medication**

I. Introduction

ADHD is a prevalent adolescent neurodevelopmental disorder with rising clinical concerns. Cross-regional epidemiological studies report a global adolescent ADHD prevalence of 5%–7%, with male adolescents showing two-to-three-fold higher diagnostic rates than female adolescents [1]. Frequent short-form-media exposure may exacerbate inattention via altered dopaminergic regulation [2]. Existing research on adolescent ADHD is more limited than that on child ADHD. Pubertal hormonal shifts and prefrontal-cortical maturation reshape ADHD manifestations; adolescents mainly present internalized symptoms instead of childhood-typical hyperactivity, so teenager-specific dopamine regulatory mechanisms remain under-summarized. Short-video exposure may worsen pre-existing symptoms in genetically vulnerable adolescents, rather than directly triggering ADHD.

This review retrieved publications from PubMed, Web of Science, and CNKI using the search terms adolescent ADHD and the dopamine pathway. Most included literature spans 2021–2026; classic foundational genetic papers from 1998 and 2009 are included for background. Studies limited solely to children or adults were excluded. This review integrates evidence on dopamine transporters, susceptibility genes, and first-line targeted treatments to elaborate dopamine-related pathological pathways in adolescent ADHD, bridging basic molecular findings and clinical practice for epigenetic early-screening and personalized adolescent medication.

II. Molecular Mechanisms of Adolescent ADHD

A. Dopamine Dysregulation

Dopamine is a key neurotransmitter modulating attention, impulse control, and reward-related behaviors. Dysregulated dopamine-signaling forms the core biochemical basis of adolescent-ADHD clinical symptoms [3]. After dopamine is released into the synaptic cleft, the Dopamine Transporter (DAT) re-uptakes extracellular dopamine into presynaptic neurons. The DAT1 gene is one of the best-characterized ADHD susceptibility genes, though not the sole causal factor. DAT1 variants increase DAT protein expression and accelerate synaptic dopamine clearance, lowering dopamine availability and weakening signaling in the striatum and prefrontal cortex, which produces persistent attention and self-regulation deficits.

The prefrontal cortex governs planning, self-restraint, and long-term-goal maintenance, while the striatum mediates reward feedback and behavioral motivation. Adolescent ADHD patients with high DAT expression have low dopamine levels in both regions. When completing tasks that require sustained executive control, they receive insufficient reward feedback from slow

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long-term learning outcomes and tend to seek fast-paced, low-effort stimulation.

The prefrontal cortex continues to develop until approximately age 25. Mild dopamine declines harmless for adults can disrupt adolescent neural-circuit development, so dopamine fluctuations exert stronger long-term impacts on adolescent neural networks.

Reward-circuit abnormalities driven by dopamine dysregulation explain certain behavioral tendencies in modern adolescents. Repeated short-form-media engagement brings instant gratification and short-term dopamine surges, raising the brain's reward threshold. Ordinary activities like reading and studying fail to meet this threshold and lead to concentration difficulties [2]. Such environmental factors cannot independently cause ADHD; they amplify pre-existing symptoms in genetically susceptible adolescents.

DAT1 variants accelerate synaptic dopamine removal. Repeated stimulation changes postsynaptic dopamine-receptor sensitivity in vulnerable teenagers. Even with reduced media use in later adolescence, reward thresholds may not return to normal, creating a vicious cycle of inattention. These molecular abnormalities arise from combined heritable gene variants such as DAT1 and dynamic epigenetic modifications, discussed below.

B. Other Neurotransmitter Abnormalities

Despite dopamine dysfunction being the main research interest, several neurotransmitter systems interact with each other, and all work together to produce the manifestation of adolescent ADHD. Noradrenaline works together with dopamine to regulate sustained attention and alertness. In the brain, weak noradrenergic signaling reduces the ability of the brain to exclude irrelevant external stimuli, and patients become easily distracted by visual and auditory stimuli around them. Additionally, altered metabolism of 5-HT is primarily involved in emotional regulation and impulsive behavior. Thus, it is not surprising that many adolescent ADHD patients tend to show mood swings and hasty decision-making [4].

There are significant gaps in the current research. Previous studies have typically focused on particular neurotransmitter pathways in isolation. A complex network of crosstalk between dopamine, noradrenaline, and 5-hydroxytryptamine has not been systematically explored. Many research models examine only a single neurotransmitter and cannot replicate the actual biochemical environment found in teenagers' brains under pathological conditions.

Noradrenergic neurons and dopaminergic neurons are synaptically interconnected in the adolescent prefrontal cortex. Dopaminergic neurons will also be indirectly inhibited when not enough noradrenaline is released. But the synergistic regulatory relationship between the two types of neurons in living brain tissue of adolescents is neglected in most cell experiments in vitro, so the experimental results are not consistent with the real pathological characteristics of the brain tissue.

C. Molecular Pathways and Metabolic Regulation

Beyond the direct transport function of DAT protein, metabolic enzymes, such as Monoamine Oxidase (MAO), participate in the degradation and recycling of monoamine neurotransmitters within synaptic circuits. Elevated DAT expression accelerates dopamine reuptake and reduces synaptic dopamine availability in patients with ADHD. Some studies have theoretically proposed that reduced MAO activity may counteract the excessive clearance of dopamine caused by overactive DAT transporters. Lower MAO enzymatic activity could slow the oxidative breakdown of reabsorbed dopamine inside presynaptic neurons, which might partially maintain intracellular dopamine reserves and relieve extreme neurotransmitter depletion in the synaptic gap. However, this compensatory metabolic balance is incomplete and insufficient to reverse the core dopamine deficit observed in adolescent ADHD brains, which explains why enzyme-level metabolic adjustments cannot fully offset pathological DAT overexpression.

All these neurotransmitter transport and metabolic pathway abnormalities are partially shaped by genetic variation and epigenetic modification, which are explored in the subsequent section on hereditary regulatory mechanisms.

III. Genetic and Epigenetic Mechanisms

A. ADHD Susceptibility Genes

There is clear evidence of familial clustering, suggesting a genetic risk factor for ADHD. Family aggregation of ADHD is well documented: first-degree relatives of affected individuals show a two- to three-fold increased risk, consistent with the genetic effects established in child cohorts [4] and subsequently extended to adolescent cohorts. The DAT1 gene is the most uniformly studied susceptibility gene. Initial basic research showed that there is a relationship between variant alleles of DAT1 and ADHD in children.

However, single-gene mutations alone cannot cause ADHD. It is now understood that no single susceptibility gene is sufficiently penetrant to cause symptoms, but that the development of ADHD requires the polygenic effects of a number of risk genes. In addition to DAT1, other candidate genes, including dopamine receptors (DRD2 and DRD4), have been linked to ADHD. However, this variability represents a blind spot, because population ancestry and Linkage Disequilibrium (LD) in each group can skew genetic results, and many studies do not control for them.

Genetic comparison experiments among population groups have revealed that the risk effect of the DRD4 variant is stronger in European and American adolescent populations, while the correlation signal in East Asian cohorts is weaker [5]. Such population-specific differences may reflect regional differences in disequilibrium of regional gene groups, indicating that genetic screening markers should be adjusted according to the regional population characteristics in clinical application of ADHD in adolescence.

B. Epigenetic Regulation

Epigenetics is the study of how environmental factors can affect gene activity without changing the DNA sequence, which helps fill the research gap between inherited genetic risk and acquired external exposure factors. DNA methylation is the most extensively studied epigenetic mechanism in ADHD. When methylation occurs in the promoter region of the DAT1 gene, it prevents the transcription of the gene and consequently reduces the amount of DAT protein produced. The methylation pattern of the DAT1 gene is also considered a potential biological marker of symptom severity and predicts individual responses to medication.

Adolescent brains are continually developing, and unlike adults, they are less mature. Epigenetic modifications during this developmental period thus have more long-lasting effects on neural function. DNA methylation can be dynamically altered by environmental factors such as chronic stress, sleep deprivation, and digital media exposure. Epigenetics thereby links inborn genetic susceptibility with environmental exposures acquired after birth. It may explain why people with the same predisposing genes develop very different diseases.

The adolescent period is a key window of Central Nervous System (CNS) epigenetic remodeling. DNA methylation during this critical time window may be programmed into adulthood and chronically influence how the dopamine pathway functions. Regular outdoor activities and limiting time watching short videos are examples of positive environmental interventions that, if applied to adolescents at high genetic risk, may reduce hypermethylation of the DAT1 gene and thereby alleviate the clinical severity of ADHD symptoms in susceptible individuals [2].

IV. Pharmacological Therapeutic Strategies

A. Stimulant Medications: Methylphenidate

Methylphenidate is the most used stimulant medication in the therapy of ADHD in adolescents. Its main molecular target is the dopamine transporter. The drug acts on the DAT protein, blocking the reuptake of dopamine, increasing the amount of dopamine in the synaptic clefts and normalizing the transmission of signals between brain circuits involved in reward processing and the control of attention [6, 7]. The clinical studies on this target population of adolescents support the fact that methylphenidate at the appropriate dose is effective in reducing inattentive and hyperactive-impulsive symptoms.

There is known to be variation in the response to treatment for individual patients. This is partly explained by differences in DAT1 gene genotype and DNA methylation levels between patients. Pharmacogenetic studies suggest that adolescents with certain DAT1 genotypes (e.g., the 10-repeat allele) may show greater therapeutic effects after taking methylphenidate [8]. Meanwhile, physicians should focus on standardized dose planning in teens. Adolescent nervous systems are still developing, so they may be more susceptible to unwanted side effects of certain drugs, especially at high doses, such as sleep disturbances and mood swings.

A dose escalation approach is typically used clinically for adolescents, starting from the lowest effective dose with minimal incremental increases; measurable sustained changes in attention and sleep quality usually emerge gradually during dose titration. Adolescents with low DAT1 expression respond poorly to methylphenidate. Raising doses only increases insomnia and irritability side effects without obvious therapeutic benefits, meaning genetic and epigenetic marker testing before prescription may be valuable.

B. Non-Stimulant Medications: Atomoxetine

Atomoxetine is the first non-stimulant medication approved for the treatment of ADHD. It selectively inhibits the Noradrenaline Transporter (NET), which in turn indirectly enhances dopamine transmission in the prefrontal cortex. In particular, it is suitable for adolescent patients who cannot tolerate stimulant treatments or patients who have co-occurring symptoms of anxiety [9].

Atomoxetine is not a stimulant drug and its therapeutic effects do not occur immediately, but rather may build up gradually over an extended treatment period [9]. This characteristic reduces the risk of misuse or euphoric effects. Atomoxetine acts through different mechanisms of action than methylphenidate and so could treat different patient groups and provide a molecular basis for personalized clinical treatment plans for adolescents.

Adolescents make up a large proportion of ADHD clinical cases. For a subset of adolescents with comorbid anxiety or low drug tolerance, stimulant medications may paradoxically heighten inner tension and panic [9], so atomoxetine becomes the treatment of choice for this sub-population. It is a dual-acting drug that raises noradrenaline levels and moderately increases dopamine levels in the prefrontal cortex, easing inattention and anxiety at the same time and delivering broader clinical benefits for adolescents with complex comorbid ADHD.

C. Emerging Therapeutic Approaches

In addition to existing oral pharmaceutical therapies, researchers continue to investigate new lines of research for intervention. There are two main research streams, one being epigenetic therapies that aim to change the level of methylation of genes and the other being long-term behavior interventions that aim to change neural circuits [10]. Behavioral therapy provides prolonged attention control through repeated practice, with the opportunity to modify the sensitivity of reward circuits, which in turn somewhat indirectly modulates patterns of dopamine release.

But most of the new intervention approaches remain in the research lab and are not yet ready for use in adolescent clinical treatment. A number of epigenetic regulatory drugs have only been verified in animals. They have yet to be tested in large-scale clinical trials to see their long-term effects on developing adolescent brains.

Task segmentation training, delayed reward exercise, and media use restriction guidance are elements of

Cognitive Behavioral Therapy (CBT) specially optimized for adolescents. Long-term behavioral interventions may potentially stabilize the dopamine reward threshold in adolescents, serving as a possible complement to pharmacotherapy [10]. However, evidence for the incremental benefit of CBT added to standard medication and psychoeducation remains mixed [8, 11]. Whether combined schemes of medicine plus behavioral training could reduce symptom recurrence after dosage tapering requires further investigation.

V. Conclusion

This review identifies disrupted dopamine signaling as the core molecular mechanism of adolescent ADHD, with the DAT1 gene serving as one representative susceptibility gene rather than the single cause. Altered DAT1 function disturbs dopamine reuptake, alongside epigenetic regulation. Genetic vulnerability interacts with environmental factors like excessive short-video exposure to worsen epigenetic changes, while lifestyle interventions may relieve such dysregulation. Corresponding pharmacological treatments target these pathways to relieve symptoms for different patient subgroups. These findings have clear clinical implications. DAT1-related genetic and epigenetic differences may partly explain individual variation in treatment response. Epigenetic plasticity also supports lifestyle-based adjunctive interventions.

However, many genetic studies are limited to narrow population ancestry groups, which may bias analytical results. Most epigenetic evidence is correlational rather than causal, and many novel epigenetic drugs have only been tested on animal models without long-term human clinical data for adolescent brains.

Future research needs larger multi-ancestry cohort studies to verify gene-environment interactions in teen ADHD. Longitudinal trials may clarify whether lifestyle adjustments can stably modify DAT1 methylation. New epigenetic therapies, after sufficient safety verification, may help advance precision treatment for genetically susceptible ADHD adolescents.

Conflict of Interest

The author declares no conflict of interest.

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