Proceedings of ICBioMed 2025 Symposium: AI for Healthcare: Advanced Medical Data Analytics and Smart Rehabilitation
DOI: 10.54254/2753-8818/2025.AU27150

The Latest Pathological Mechanisms and Targeted Drugs Research of Attention Deficit Hyperactivity Disorder

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Abstract. A common neurodevelopmental disorder called attention deficit hyperactivity disorder (ADHD) is known to have a complex pathogenesis which still remains incompletely understood. Traditional research has focused on neuroinflammation, abnormal energy metabolism, neurotransmitter system disorders, and genetic mechanisms. ADHD affects 5%-7% of children and adolescents worldwide, with approximately 60% of patients experiencing persistent symptoms into adulthood, often accompanied by conditions like anxiety. In recent years, research focusing on neuroinflammation and energy metabolism has expanded, which led to new mechanisms such as the Immune-Metabolic-Circuit ternary pathological model, along with emerging therapeutic approaches including highly selective molecular entities and digital therapies, such as the triple reuptake inhibitor Centanafadine and the digital therapy EndeavorRx. However, current research has limitations: specific molecular pathways of pathogenesis are not fully elucidated, long-term efficacy of some drugs requires further verification, and there is insufficient research on individualized treatment. Future efforts should focus on molecular mechanisms to develop precise targeted drugs and combine multiple therapies to provide personalized plans. This article reviews traditional pathogenesis, recent research progress, the latest drugs, and treatment methods.

Keywords: ADHD, Immune-Metabolic-Circuit, triple reuptake inhibitor, non-pharmacological Interventions

1. Introduction

ADHD is characterized by core symptoms including impulsivity, uncontrollable movements, and inattention [1]. Globally, ADHD impacts 5%-7% of this population, with around 60% of those affected having symptoms that persist into adulthood. ADHD not only affects academic achievement and career development but also frequently co-occurs with conditions like anxiety and depression, imposing a heavy burden on individuals and families. Its complex pathogenesis involves multiple aspects including neuroinflammation, neurotransmitter system disorders, and genetic factors. Traditional studies have mainly focused on abnormalities in the levels of monoamine neurohormones such as dopamine and norepinephrine (NE). Imbalances of these transmitters in key brain regions like the prefrontal cortex and hippocampus are confirmed as core mechanisms underlying deficits in attentional regulation and impulsive behavior. Recent studies have found that emerging targets such as the serotonin system and BDNF-TrkB pathway are also involved in the

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disease process, offering critical insights into new dimensions of the disorder, including abnormal neural plasticity and neuronal developmental defects. At the same time, environmental factors such as inflammation and obesity can exacerbate ADHD symptoms through genetic overlap, immune activation, and interactions. Notably, interactions between environmental risks, such as prenatal infection and early adversity, and susceptibility genes like DRD4 have emerged as a focus of recent research. With the rapid development of targeted drugs and non-pharmacological therapies (such as digital therapy, repetitive transcranial magnetic stimulation, cognitive-behavioral intervention, etc.), in-depth exploration of the pathogenesis of ADHD is crucial for optimizing treatment plans. This not only enhances the precision of existing therapies but also lays the groundwork for developing novel interventions and achieving personalized treatment. Despite many breakthroughs in current research, the heterogeneous characteristics of ADHD still bring challenges to etiological exploration and treatment. Elucidating subtype-specific pathological mechanisms will be a key direction for future research. This article will review the latest pathological mechanisms and research progress of targeted drugs for attention deficit hyperactivity disorder.

2. Pathogenesis of ADHD

2.1. Traditional pathogenesis of ADHD

Studies on neuroinflammation revealed that the changes of inflammatory cytokine levels of ADHD patients can impact neuronal activity by activating the hypothalamic-pituitary-adrenal (HPA) axis, impairing cognitive control and executive functions [2]. Another key feature is abnormal energy metabolism whereby mitochondrial dysfunction in ADHD patients reduces ATP production, which lowers axonal dopamine (DA) vesicle loading. This triggers excessive reactive oxygen/nitrogen species (ROS/RNS), damaging neuronal membrane fatty acids and disrupting neural signaling. Monoamine neurotransmitter regulation is critical to ADHD pathogenesis. Widespread dopamine receptor/transporter dysfunction leaves synaptic cleft dopamine insufficient, affecting prefrontal cortex motivation and attention regulation. Abnormal NE transporter function lowers extracellular NE, causing behavioral control and emotional issues. 5-hydroxytryptamine (5-HT) receptor dysfunction disturbs 5-HT-dopamine system dynamics, influencing ADHD development. Genetics strongly influence ADHD onset (heritability 70-80%). Identified candidate genes (e.g., DAT-1/SLC6A3, DRDs, DbH) relate to neurotransmitter systems; their polymorphisms or abnormal expression increase ADHD risk by impairing neurotransmitter synthesis, transport, or signaling. Epigenetics may also mediate environmental influences on ADHD risk.

2.2. Recent research about the pathogenesis of ADHD

2.2.1. The Immune-Metabolic-Circuit (I-M-C) ternary pathological model

At the immune level, maternal immune activation and intestinal flora imbalance lead to an increase in peripheral Th17 cells. Oxidative stress is caused when IL-17 activates microglia after crossing the blood-brain barrier. At the metabolic level, impairment of mitochondrial function results in a decline in the NAD+/NADH ratio, which leads to a decrease in SIRT1 deacetylation activity. This inhibits PGC-1α, triggering an energy crisis in dopamine (DA) neurons. At the circuit level, downregulation of H2R expression in parvalbumin (PV) neurons reduces GABA release, thereby disinhibiting downstream dopamine (DA) burst firing and inducing behavioral phenotypes [3].

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2.2.2. 5-hydroxytryptamine transporter (SERT/SLC6A4)

SERT is responsible for the reuptake of 5-hydroxytryptamine, and its dysfunction can lead to an imbalance in 5-hydroxytryptamine levels. Studies have shown that changes in the expression and activity of SERT are related to the severity of ADHD symptoms and may become a new therapeutic target. 5-HT and DA are co-released in the orbitofrontal cortex, and SERT inhibition can synergistically enhance the DA signal [4].

2.2.3. 5-HT2A receptor (HT2A)

A member of the 5-hydroxytryptamine receptor family, 5-HT2A receptor is mainly located in brain regions such as the cerebral cortex and hippocampus. These brain regions play significant roles in emotions, cognition, and behavioral control. From the perspective of neurotransmitter regulatory mechanisms, the 5-HT2A receptor can interact with 5-HT2A receptors on dopaminergic neurons, influencing the synthesis, release, and reuptake processes of dopamine. Once the function of the 5-HT2A receptor becomes abnormal, this balance will be disrupted, leading to dysregulation of dopamine activity. By regulating dopaminergic neural transmission, 5-HT2A receptor antagonists have been shown to alleviate the hyperactive and impulsive symptoms of patients with ADHD through some clinical trials and relevant animal experiments. The mechanism of action may be through blocking the 5-HT2A receptor, correcting the abnormality of dopamine activity, and restoring the normal function of brain neural circuits [5].

2.2.4. Synaptic plasticity-related molecules

Synaptic plasticity serves as the foundation of memory and learning. The dysfunction of AMPA and NMDA receptors is associated with ADHD. For the long-term potentiation (LTP) and long-term depression (LTD) processes associated with learning and memory, the NMDA receptor which has high permeability to calcium ions, performs an indispensable regulatory function. The AMPA receptor mainly mediates rapid excitatory synaptic transmission, and its functional state directly affects the efficiency of neural signal transmission between neurons. Researchers observed, for instance, that in spontaneous hypertensive rats (SHR), a commonly used animal model of ADHD, synaptic transmission in the hippocampus mediated by NMDA receptors was reduced, and the rats showed greater sensitivity to NR2B-specific blockers. This suggests that the subunit composition and function of this receptor have changed. Regulating the activity of these receptors may improve synaptic transmission efficiency and alleviate ADHD symptoms [6].

3. Latest drugs under research

3.1. Triple reuptake inhibitor centanafadine (EB-1020)

Centanafadine acts as a triple reuptake inhibitor, the IC50 concentrations of which are 38 nM for DAT, 6 nM for NET, and 83 nM for SERT. Centanafadine has the ability to block the reuptake of three substances serotonin, norepinephrine, and dopamine at the same time. By raising the amounts of these three neurotransmitters present in the synaptic cleft, Centanafadine brings about all-around improvements in the key symptoms of ADHD patients, including issues with hyperactive behaviors, impulsive actions and attention. Data from Phase III clinical research (trial identifier NCT05257265, involving 459 participants) demonstrated that the drug had a effective treatment impact on symptoms assessed by the ADHD-RS-5 scale. Specifically, the group given 328.8 mg of

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Centanafadine showed a much larger reduction in total raw scores compared to the placebo group, with the scores being –18.50 [0.93] versus –14.15 [0.93], and the statistical significance was confirmed (p = .0006) [7].

3.2. Serdexmethylphenidate/dexmethylphenidate (SDX/d-MPH)

Dexmethylphenidate belongs to the category of dopamine precursor medications, featuring a sustained-release structure that lowers the chance of drug misuse.Through increasing the amount of dopamine in the brain, Dexmethylphenidate strengthens the ability to control behaviors and attention, which shown favorable safety and effectiveness when used to treat ADHD. In an SDX/d-MPH open-label safety study (NCT03460652, n=282) in ADHD children aged 6–12 years, demonstrated that d-MPH exhibited sustained efficacy with tolerable side effects, such as decreased appetite (n≈44), upper respiratory tract infection (n≈23), nasopharyngitis (n≈19) and decreased weight (n≈18) [8].

3.3. TAK-653 (AMPA receptor positive allosteric modulator)

In a clinical trial, 24 healthy volunteers were randomly divided into placebo group, 0.5 mg and 6 mg TAK-653 groups. Through a series of professional scales and assessment tools, key indicators such as the attention index of the patients were measured regularly to objectively and accurately evaluate the efficacy of TAK-653. Both TAK-653 groups increased saccadic peak velocity (19.49 [5.98, 32.99], P = 0.02 for 0.5mg, 15.40 [1.91, 28.90], P = 0.06 for 6mg). The 6mg TAK-653 group also improved adaptive tracking (%) (1.68 [0.51, 2.84], P = 0.02) and smooth pursuit eye movements (%) (2.32 [0.37, 4.27], P = 0.05). These data clearly indicate that TAK-653 can significantly enhance the attention level of adult ADHD patients, contrasting sharply with the placebo group ($P < 0.05$). In actual performance, patients taking TAK-653 significantly reduced the number of distractions in scenarios requiring concentration, could complete tasks more attentively, and greatly improved efficiency and quality. The results proved that volunteers in the TAK-653 group had significant improvement in the attention index [9].

4. Non-pharmacological interventions

4.1. Repetitive Transcranial Magnetic Stimulation (rTMS)

Repetitive transcranial magnetic stimulation targets the right prefrontal cortex to enhance connectivity within the cognitive control network, improving the attention and executive functions of patients with ADHD. A meta-analysis of five RCTs with 189 participants shows that compared with the control groups, the rTMS group was more effective for improving sustained attention in ADHD patients (p = 0.001). Moreover, its further analysis also showed that rTMS was more effective for improvement of processing speed, but seems to have no effect on enhancing executive or memory function. This treatment method is non-invasive and has good tolerance, providing a new option for physical therapy of ADHD [10].

4.2. EndeavorPx digital therapy

EndeavorRx is an FDA-approved digital therapy that improves the attention of ADHD patients through reinforcement learning. This therapy utilizes a gamified training model to enhance patients' treatment compliance and opens up new avenues for non-pharmacological treatment of ADHD. The

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adaptive game based on reinforcement learning shows that in a 3rd phase RCT involving 600 children, after 4 weeks of intervention, the test signal detection power of the attention variable (TOVA) increased by 0.93 standard deviations, and the therapeutic effect persisted for 1 month [11]. It was accepted for special review under the Innovative Medical Device Channel by National Medical Products Administration (NMPA) in September 2024.

5. Conclusion

The pathogenesis of ADHD is complex, involving interactions among multiple factors such as neuroinflammation, energy metabolism, neurotransmitter systems, and genetics. While traditional research has focused on abnormalities in monoamine neurotransmitters like dopamine and norepinephrine, recent studies have revealed emerging mechanisms including the Immune-Metabolic-Circuit ternary pathological model, serotonin system, BDNF-TrkB pathway, and synaptic plasticity-related molecules, providing a more comprehensive perspective for understanding the disease. Notable advancements have been made in recent times in studies related to both emerging and classic targets, and this progress has served as a foundation for developing targeted drugs. The latest investigational drugs and treatment methods show promising application prospects, such as Centanafadine which improves symptoms through triple reuptake inhibition, dexmethylphenidate which is safe and effective with low abuse potential, TAK-653 which enhances attention, LM22A-4 which target emerging pathways, as well as non-pharmacological interventions including rTMS and EndeavorRx digital therapy, each with its own advantages. However, current research has limitations: the specific molecular pathways of pathogenesis have not been fully elucidated, the long-term efficacy and safety of some therapeutic drugs require further verification, and there is insufficient research on individualized treatment for patients with different subtypes, age groups, and comorbidities, along with a lack of precise biomarkers for predicting therapeutic effects. Future research should focus on the molecular mechanisms to develop more precise targeted drugs, combine multiple treatment methods to provide personalized treatment plans, strengthen long-term follow-up studies to improve efficacy and safety data, and pay attention to the needs of special populations. All of these efforts have a final objective, which is to improve life quality of patients and enhance treatment efficacy.

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