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The Mechanism of Neuroinflammatory Response in the Pathogenesis of Attention Deficit Hyperactivity Disorder and the Traditional Chinese Medicine Regulatory Strategies

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Abstract: Neuroinflammation plays a crucial role in the attention-deficit hyperactivity disorder (ADHD) pathogenesis. ADHD patients exhibit an imbalance of pro-inflammatory and anti-inflammatory factors, abnormal activation of microglia and astrocytes and the oxidative stress-inflammation vicious cycle. Maternal immune activation and HPA axis disorder interfere with fetal neurodevelopment and also increase the risk. TCM believes that the pathogenesis of the ADHD is "kidney essence deficiency and marrow sea insufficiency", which deeply corresponds to the neuroinflammation framework. Chinese herbal monomers (such as baicalin, magnoculine, and eucommiine) and compound formulas (such as Anshen Dingzhi Ling, and Bu Shen Kai Qiao Fang) can regulate signaling pathways such as MAPK/NF-κB and NLRP3, inhibit glial cell activation, reduce pro-inflammatory factors, repair the blood-brain barrier, and improve ADHD-like behaviors. Acupuncture combined with conventional drugs can alleviate hyperactivity, impulsivity, and learning problems, but the quality of evidence needs to be improved. In the future, more high-quality evidence-based research needs to be explored.

Keywords: Neuroinflammatory; Traditional Chinese Medicine; Attention Deficit Hyperactivity Disorder.

1. Introduction

The global prevalence of ADHD among children is 5% - 7% and the prevalence among children aged 6 - 17 is 5.29%. The ratio of males to females is approximately 2.4:1, but the ratio in clinical referrals can reach 4:1. About 60% - 70% of children with ADHD continue to have symptoms into adulthood. ADHD not only causes inattention, hyperactivity, and impulsivity, but also increases the risks of academic failure, peer conflicts, and family disputes, as well as impairing social skills and making patients vulnerable to bullying [1]. Additionally, ADHD children often have emotional problems or emotional disorders. Epidemiological studies show that the proportion of children with ADHD experiencing mood instability is 38%, which is 10 times that of ordinary children; 25% - 45% of ADHD children exhibit emotional dysregulation. ADHD patients have an increased risk of the traffic accidents, substance abuse, obesity, and suicide attempts, with an increased all-cause mortality rate. Early identification and comprehensive treatment can improve prognosis, but those without standardized intervention continue to suffer from persistent impairment in quality of life, self-esteem, and interpersonal relationships, imposing a heavy burden on families and society [2].

The clinical treatment of ADHD mainly adopts a comprehensive intervention model, covering various means such as psychological education, psychological behavior therapy, special education support, functional training, and medication. However, this model has problems such as unsatisfactory efficacy and a long treatment cycle. Moreover, the side effects of medication are prominent, causing heavy care and economic burdens [3].

With the rapid development of the neuroimmunology, more and more evidence indicates that neuroinflammatory responses characterized by immune dysregulation and abnormal pro-inflammatory states are increasingly attracting attention in the pathogenesis of ADHD. It is also worth noting that the regulation of neuroinflammation cannot be achieved by a single target, but requires multi-pathway and multi-level integrated intervention. This precisely aligns with the treatment philosophy of traditional Chinese medicine. TCM, with its overall regulatory pattern of syndrome differentiation and treatment and good safety, demonstrates unique advantages. Some TCM compound prescriptions and acupuncture therapy have shown clear anti-inflammatory and neuroprotective effects. Therefore, exploring the scientific connotation of tTCM treatment of ADHD from the perspective of neuroinflammation can provide new ideas for the exploration of the pathogenesis and comprehensive intervention.

2. The Mechanism of Neuroinflammation in the Pathogenesis of ADHD

2.1. Imbalance in Inflammatory Factor Levels Interferes with Neurotransmitter Metabolism and Brain Development and Maturation

The study found that the levels of IL-6 in the children's serum were elevated, while the levels of TNF-α were decreased. Moreover, the increase in IL-13 and IL-16 was positively correlated with the severity of inattention, hyperactivity, and oppositional behavior. These inflammatory factors can interfere with the neural transmission of the

dopaminergic pathway, alter the metabolism of dopamine and norepinephrine in the prefrontal cortex, and thereby damage cognitive functions such as attention and working memory. Additionally, a high inflammatory state during the maternal pregnancy period (such as elevated IL-6) will increase the risk of the offspring developing ADHD, suggesting that perinatal inflammatory exposure, by affecting the development of the neurotransmitter system, becomes an important cause of ADHD [3-5].

2.2. Abnormal Activation of Glial Cells Leads to Dysregulation of Synaptic Pruning and Dysfunction of Circuits

The excessive activation of microglia and astrocytes is the core feature of neuroinflammation. PET studies have shown that the activation signals of microglia in the dorsolateral prefrontal cortex and orbitofrontal cortex of ADHD patients are significantly enhanced, and the activation degree is positively correlated with the severity of symptoms; inhibiting the abnormal activation of microglia can improve inattention. Activated microglia release pro-inflammatory factors and excessively prune synapses, disrupting the stable environment of neurons; astrocytes affect synaptic plasticity by upregulating thrombospondin-1 (TSP1), leading to abnormal regulation of attention and impulse control. The activation of MAPK/NF-κB signaling pathway is a key molecular pathway mediating abnormal activation of glial cells, and inhibiting this pathway can alleviate neuroinflammation and improve ADHD-like behaviors [3,4,6].

2.3. Maternal Immune Activation and HPA Axis Dysfunction iInterfere with Fetal Neural Development

Maternal infection during pregnancy or autoimmune diseases can increase the risk of ADHD in offspring through the maternal immune activation pathway. Inflammatory cytokines in the mother's body (such as IL-6, TNF-α) can directly pass through the placenta, causing an increase in inflammatory levels in the fetal brain and affecting key developmental processes such as neuronal proliferation, migration, and synaptic pruning. At the same time, inflammatory factors can activate the HPA axis, leading to elevated levels of glucocorticoids. High concentrations of glucocorticoids binding to high-density receptors in the prefrontal cortex cause dendrite atrophy, impairing executive function and error monitoring ability. Animal experiments have also shown that exposure to inflammation during the neonatal period (such as increased IL-4) reduces normal synaptic pruning by microglia, resulting in excessive connectivity of neural circuits and manifested as hyperactivity and impulsive behavior [3,4].

3. ADHD-related Neuroinflammation in TCM

Although there is no concept of "neuroinflammation" in TCM, its etiological and pathological explanations of ADHD resonate profoundly with the modern framework of neuroinflammation.

TCM holds that the disease location of ADHD is brain, with the core pathogenesis being "kidney essence deficiency, marrow sea insufficiency, and developmental delay," leading to delayed maturation of the prefrontal cortex and abnormal myelination. Kidney essence deficiency places the brain tissue in a low-energy reserve state, making it vulnerable to inflammatory insults; myelination defects can activate microglia, releasing pro-inflammatory cytokines, which in turn inhibit myelin repair, forming a vicious cycle of "kidney deficiency – brain developmental lag – neuroinflammation" [7-10].

"Yin quiescence deficiency, Yang hyperactivity excess" is the fundamental pathogenesis of ADHD. Modern diet and stress exacerbate "Yang hyperactivity consuming Yin," corresponding to an imbalance in dopamine D1/D2 receptors and dysregulation of synthesis/clearance. In neuroinflammation, pro-inflammatory cytokines belong to "Yang hyperactivity / fire pathogen," while anti-inflammatory cytokines (IL-10) belong to "Yin quiescence." Spleen-stomach deficiency leads to the upward floating of "Yin fire," causing chronic low-grade neuroinflammation, which explains the hyperactive and impulsive symptoms [11,12].

Deficiency of kidney essence affecting the heart, liver, and spleen: Hyperactivity of heart fire leads to irritability and poor concentration; hyperactivity of liver yang leads to impulsivity and anger; spleen deficiency with dampness retention generates phlegm that clouds the orifices, resulting in learning difficulties. Hyperactivity of heart and liver fire corresponds to sympathetic overactivity, hyperfunction of the HPA axis, and elevated cortisol levels, promoting peripheral and central inflammation. Spleen deficiency with dampness retention is associated with gut microbiota dysbiosis and the activation of microglia via the gut-brain axis. Acupuncture regulates the autonomic nervous system and inhibits pro-inflammatory factors, reflecting the anti-inflammatory mechanism of "kidney-brain interaction" [8,10,12].

The phenotype of ADHD shows a dynamic evolution: In the early stage, the "syndrome without identifiable pattern" represents inflammatory compensation; in the middle stage, the "kidney essence deficiency pattern" features pro-inflammatory factors inhibiting dopamine function, leading to attention deficits; in the late stage, the "kidney deficiency with liver hyperactivity pattern" involves complement activation and oxidative stress damaging the prefrontal cortex-striatal circuit, resulting in loss of impulse control. Among Western medications, methylphenidate (tending to reduce fire) is effective for hyperactivity and impulsivity, while atomoxetine (tending to nourish yin) is effective for attention deficits, confirming that "yang patterns are easy to treat, yin patterns are difficult to cure." Early intervention targeting "kidney essence deficiency and inflammatory initiation" is key to halting disease progression [7,11].

4. Research Progress on the Regulation of Neuroinflammation by TCM Compound Formulations

4.1. Chinese Herbal Combinations

In recent years, TCM compound prescriptions have demonstrated unique advantages in the research related to ADHD. An animal experiment aimed to evaluate the therapeutic effect and anti-inflammatory mechanism of the Anshen Dingzhi Ling (ASDZL) on ADHD. The results proved that in the open field test, the movement distance of the ASDZL group was reduced by approximately 41% compared to the model group, the central zone stay time decreased by 56%, and the standing times decreased by 48%;

in the Morris water maze test, the escape latency of the ASDZL group was significantly shortened on the 4th-5th days (from 47.2 seconds to 28.5 seconds on the 5th day), and the number of platform crossings increased by 2.1 times. ELISA showed that ASDZL reduced IL-1β (down by 38%), IL-6 (down by 45%), TNF-α (down by 51%), and MCP-1 (down by 42%) in serum and brain tissue, and increased anti-inflammatory factor IL-10 (up by 86%). Immunohistochemistry confirmed that ASDZL inhibited the activation of microglia (Iba1+ cells reduced by 53%), astrocytes (GFAP+ reduced by 47%), and mast cells (tryptase+ reduced by 62%). Electron microscopy and Western blot showed that ASDZL upregulated the expression of ZO-1 and occludin by approximately 2-3 times and inhibited the phosphorylation of MAPK (p-p38, p-JNK) and NF-κB (p-IκBα, p-p65) pathways [13].

Another animal study using the Bushen Kaiqiao Formula (BSKQF) focused more on microglial cell polarization and synaptic plasticity. In terms of design, BSKQF was divided into low, medium, and high dose groups. The positive drug was methylphenidate, and behavioral tests included the EPM and Y-maze to assess impulsivity and attention. The results also showed dose- and time-dependent behavioral improvements; in addition, it was found that M1 type microglia in the prefrontal cortex significantly increased, and BSKQF could reverse this; ELISA confirmed a decrease in IL-1β and IL-6; transmission electron microscopy also observed ultrastructural damage to the BBB (irregular endothelial cell nuclei, blurred basement membrane, and edema of astrocyte foot processes), which recovered after treatment. From the mechanistic perspective, BSKQF not only inhibits the NF-κB pathway (p-p65, p-IκBα), but also for the first time reveals its inhibition of NLRP3/caspase-1 inflammatory body activation and reduction of TNF-α; moreover, Golgi staining and Nissl staining showed neuronal atrophy and decreased dendritic spine density in SHR, and the morphology and synaptic plasticity of neurons significantly improved after BSKQF treatment. All of these confirmed the crucial role of neuroinflammation in ADHD and provided a basis for multi-target intervention by traditional Chinese medicine formulas [14].

4.2. Acupuncture

Acupuncture, as an important non-drug therapy component of traditional Chinese medicine, is gradually being recognized by modern research for its value in the treatment of ADHD. Domestic scholars have explored the multi-level mechanisms of acupuncture in treating ADHD, which exert therapeutic effects through regulating the secretion of monoamine neurotransmitters, promoting cerebral circulation to improve blood supply, regulating cell apoptosis, and inhibiting inflammatory states, among other pathways [10]. A systematic review and meta-analysis（14 randomized controlled trials, 1185 patients) howed that compared with using conventional drugs alone, acupuncture combined with conventional drugs could significantly improve behavioral problems, learning problems hyperactivity-impulsivity and hyperactivity symptoms, while there was no significant improvement in anxiety and psychological somatic symptoms; compared with using conventional drugs alone, using acupuncture alone could also improve learning problems (MD 9.70, 95%CI 5.44 - 13.96), hyperactivity-impulsivity (SMD -1.43, 95%CI -1.79 to -1.07), hyperactivity (MD -5.26, 95%CI -6.55 to -3.98), and total efficacy rate (RR 1.17, 95%CI 1.08 - 1.26). The study also mentioned that acupuncture may alleviate ADHD symptoms by regulating neurotransmitters such as dopamine and norepinephrine, improving cerebral blood flow, and enhancing the function of the prefrontal cortex, but the quality of the included studies was low (lack of blinding, allocation concealment, etc.), and the evidence was limited, and it is not recommended for routine use [15]. A meta-analysis published in 2025 also mentioned that for children who are intolerant to drugs, acupuncture may provide an alternative option, but the quality of the evidence is insufficient, and no rigorous randomized controlled trials need to be designed to verify this [16].

4.3. Other TCM Therapy

Massage therapy is one of the non-drug therapies with a long history in traditional Chinese medicine. In the treatment of ADHD, pediatric massage mainly achieves the goal of improving core symptoms by unblocking meridians, regulating qi and blood, and calming the mind and stabilizing the spirit. A systematic review and meta-analysis included 8 randomized controlled trials (RCTs) and 3 case series studies (n=787) to evaluate the efficacy and safety of massage therapy. The results showed that the meta-analysis of 4 RCTs indicated that massage was superior to Ritalin in improving the effective rate (the proportion of symptoms showing certain improvement) (RR=1.39, 95% CI 1.16-1.66, P=0.0004), but the heterogeneity was high (I^2=75%). A single RCT showed that massage significantly improved anxious passive behavior (MD=-11.7) and non-cooperative behavior (MD=-8.60), which was better than the control group with a waiting list [17]. In terms of practical promotion, the intervention plan of pediatric massage managed by parents at home is also being explored. A pilot RCT in China evaluated the feasibility of parents implementing pediatric massage for ADHD symptoms in preschool children, and the results showed that the acceptance of parents and children was generally high, and the implementation process had good feasibility [18].

"The ear is the gathering point of the meridians." The qi of all the meridians in the body converges at the auricle. By stimulating specific ear points, one can regulate the functions of the corresponding internal organs and meridians and balance yin and yang. In the treatment of ADHD, ear points are particularly suitable for children due to their simple operation, no trauma, and high acceptance by children. The clinical application is becoming increasingly widespread. A randomized controlled trial was conducted on 70 children aged 6-12 with ADHD. They were divided into an ear acupressure group (using carthamus tinctorius seeds to stimulate specific points) and a massage control group. The intervention lasted for 4 weeks and was followed up until the 8th week. The results showed that the behavioral problems in the intervention group significantly decreased, with a large effect size (Cohen's δ = 1.49). The improvement in attention problems was particularly obvious (δ = 1.88 at the 4th week and δ = 1.48 at the 8th week), indicating that ear acupressure can be used as an effective adjunctive treatment method. It seems to improve functioning of the mesolimbic-dopaminergic system by altering the activity of neurotransmitters, such as serotonin and dopamine [19].

At present, the regulatory mechanisms of massage and ear acupressure on neuroinflammation remain unclear and require further research to systematically elucidate.

5. Conclusion

This article systematically elaborates on the core mechanisms of neuroinflammation in ADHD, including interference of the inflammatory factors with neurotransmitter metabolism, the abnormal activation of glial cells leading to dysregulation of synaptic pruning, the amplification of neuroinjury by oxidative stress, as well as the influence of maternal immunity and the HPA axis disorder on fetal development. TCM demonstrates unique advantages in regulating neuroinflammation through holistic regulation and syndrome differentiation and treatment: Chinese medicine compound prescriptions can inhibit the inflammatory body through multiple pathways, promote the M2 polarization of microglia cells, and protect the blood-brain barrier; acupuncture,massage and ear acupressure, although with limited evidence, shows auxiliary efficacy. However, current research still has limitations: most are animal experiments or small-sample clinical studies, lacking high-quality randomized controlled trials; the direct targets and molecular mechanisms of the anti-inflammatory effect of traditional Chinese medicine are not yet clear; there is a lack of a precise syndrome differentiation system based on biomarkers.

Future research should place greater emphasis on interdisciplinary integration. By leveraging advanced technologies such as bioinformatics, single-cell sequencing, and neuroimaging, a comprehensive cognitive framework for the relationship between neuroinflammation and ADHD can be established. On this basis, efforts should be made to promote the precision and individualized development of TCM targeted treatment of ADHD through neuroinflammation.

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