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Influence Mechanism of Wendan Decoction on Cognitive Function of Schizophrenia: From Neurotransmitter to Signal Pathway

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Abstract: Schizophrenia is a serious mental disorder, often accompanied by significant cognitive impairment, which seriously affects the quality of life and social function of patients. As a traditional Chinese medicine prescription composed of *Pinellia ternata*, *Pericarpium Citri Reticulatae* and *Poria cocos*, recent studies have shown that Wendan Decoction has potential benefits in improving the cognitive performance of patients with schizophrenia. This paper reviews the mechanism of Wendan Decoction in improving the cognitive ability of patients with schizophrenia, focusing on its effects on neurotransmitter regulation, signal pathway regulation and neuroprotection. By integrating the existing experimental research and clinical observation data, this paper analyzed the intervention effect of Wendan Decoction active ingredients on the core pathophysiological process of schizophrenia, revealed its possible target and molecular mechanism, and provided new theoretical basis and ideas for the treatment of cognitive dysfunction in schizophrenia with traditional Chinese medicine.
Keywords: Wendan Decoction; Schizophrenia; Cognitive function; Neurotransmitters; Signal path; Neuronal plasticity

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1. Introduction

Schizophrenia is a complex mental disease, and cognitive dysfunction is one of its core symptoms, which seriously affects the social function and quality of life of patients. Although antipsychotics have a certain effect on positive symptoms, their effect on improving cognitive function is limited [1]. As an important prescription of traditional Chinese medicine, Wendan Decoction has been widely concerned in recent years. Clinical practice shows that Wendan Decoction has good effect in improving the mental symptoms and cognitive function of patients with schizophrenia [2]. Its components, such as dannanxing, *Pinellia ternata* and *Glycyrrhiza uralensis*, can improve brain function and neural plasticity by regulating neurotransmitters such as dopamine and glutamate.

In addition, the cognitive impairment of schizophrenia is closely related to brain-derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF) and other biomarkers. Wendan Decoction may promote the recovery of cognitive function by enhancing the expression of these factors [3]. Its mechanism also involves the regulation of immune inflammatory response, improving chronic inflammatory state, and then affecting cognitive function [4]. There is a close

relationship between chronic inflammation and cognitive impairment.

This article focuses on the influence mechanism and target of Wendan Decoction on cognitive function of schizophrenia, aiming to provide scientific basis for new treatment strategies and bring new ideas and methods for the treatment of schizophrenia.

2. Composition and pharmacological basis of Wendan Decoction

2.1. Classic prescriptions of Wendan Decoction and the efficacy of various herbs

The main ingredients of Wendan Decoction include *Pinellia ternata*, *Pericarpium Citri Reticulatae*, Zhuru, *Fructus aurantii Immaturus*, etc. *Pinellia ternata*, as a key medicinal material, has the effects of resolving phlegm, relieving cough, reducing stress and stopping vomiting. It can improve cognitive function and emotional state by regulating the levels of neurotransmitters such as dopamine and 5-hydroxytryptamine [5]. *Pericarpium Citri Reticulatae* can regulate Qi, strengthen spleen, eliminate food and phlegm, and its active ingredients can regulate the permeability of blood-brain barrier and improve the function of central nervous system. Zhuru has the function of clearing heat and resolving phlegm, regulating GABAergic and glutamatergic systems, and alleviating anxiety and depression symptoms. *Fructus aurantii Immaturus* can relieve Qi depression, eliminate accumulation and remove stagnation, and improve cognitive function and emotional performance by regulating the hypothalamus pituitary adrenal (HPA) axis and other neuroendocrine systems.

2.2. Modern pharmacological research on the main active ingredients of Wendan Decoction

Modern pharmacological studies have shown that the main active components of Wendan Decoction include flavonoids, alkaloids and volatile oil compounds. Flavonoids such as quercetin and kaempferol have antioxidant and anti-inflammatory activities, which help to alleviate neuroinflammation. Caffeine in alkaloids can excite the central nervous system and improve attention and memory. Volatile oil components show neuroprotective effect, which can regulate the synthesis and release of neurotransmitters and improve the metabolic function of neurons [5]. These components can penetrate the blood-brain barrier, play a neuroprotective role in the central nervous system, regulate the release and metabolism of neurotransmitters, and improve emotional and cognitive functions.

2.3. Pharmacodynamic characteristics of Wendan Decoction

The pharmacodynamic characteristics of Wendan Decoction are reflected in the synergy of its overall compatibility. The compatibility of *Pinellia ternata* and *Pericarpium Citri Reticulata*e can promote the spleen and stomach function, improve the drug absorption capacity, and improve the mental symptoms caused by spleen and stomach disorders. The combination of Zhuru and Zhishi can clear away heat, detoxify, unblock Qi, and improve mood and cognitive status. On the whole, Wendan Decoction can regulate the balance of neurotransmitters, improve the permeability of blood-brain barrier, and enhance the anti-inflammatory ability of nervous system. Research shows that Wendan Decoction can affect nervous system function and improve cognitive ability through MAPK signaling pathway and other channels [5]. This multi-dimensional regulatory mechanism not only alleviates symptoms, but also promotes the overall rehabilitation of patients in the treatment of mental diseases.

3. Pathophysiological basis of cognitive impairment in schizophrenia

3.1. Abnormal neurotransmitter system and cognitive impairment

The cognitive impairment of schizophrenia is closely related to the imbalance of neurotransmitter system, involving the abnormalities of dopaminergic system, glutamate and γ - aminobutyric acid (GABA) and other key transmitters. The unstable state of dopaminergic system may lead to attention and executive dysfunction [6]. As the main excitatory

neurotransmitter, glutamate dysfunction and NMDA receptor dysfunction will lead to the decline of neural plasticity and aggravate cognitive impairment [7]. The dysfunction of GABA system is manifested as inhibitory nerve conduction deficiency, which further aggravates the cognitive challenge. Regulation of these neurotransmitter systems has become a key therapeutic goal to improve cognitive function.

3.2. Neural plasticity and synaptic dysfunction

Neural plasticity is the basis for the brain to adapt to environmental changes and learn. Schizophrenic patients have abnormal synaptic function, which is manifested by decreased density of dendritic spines and changes in synaptic plasticity [7]. Changes in the number and morphology of dendritic spines will lead to the reduction of synaptic density, affecting information transmission and cognitive function. Abnormal expression of neurotrophic factors such as BDNF is closely related to synaptic dysfunction. The decrease of BDNF level may lead to the decrease of synaptic density and affect the maintenance and improvement of cognitive function [8]. Restoring the normal expression of BDNF is a potential strategy to improve synaptic function and cognitive ability.

3.3. Mechanism of neuroinflammation and oxidative stress

Neuroinflammation plays a key role in the pathogenesis of schizophrenia. Continuous activation of microglia will release pro-inflammatory factors such as tumor necrosis factor alpha α (TNF-α) and interleukin-6 (IL-6), which will trigger chronic inflammatory response and is closely related to cognitive dysfunction [9]. Elevated levels of oxidative stress will directly damage neurons and affect their survival and connectivity. Oxidative stress and neuroinflammation form a vicious circle, which together constitute the pathological basis of cognitive dysfunction in schizophrenia. Strategies to reduce oxidative stress and neuroinflammation may provide new therapeutic approaches for improving cognitive function.

4. Regulating effect of Wendan Decoction on neurotransmitter system

4.1. Regulation of dopamine system

Wendan Decoction can significantly regulate the dopamine system and affect the expression and function of D1 and D2 receptors. Studies have shown that Wendan Decoction can improve cognitive function and psychiatric symptoms, enhance dopamine signaling and alleviate positive symptoms by regulating D1 and D2 receptors. In addition, Wendan Decoction also affects the synthesis, release and metabolism of dopamine, improves nerve conduction efficiency, and provides biological basis for its application in the treatment of schizophrenia.

4.2. Intervention on glutamatergic system

The effect of Wendan Decoction on glutamatergic system is mainly reflected in the regulation of NMDA receptor function. Abnormal glutamate activity is an important factor in the pathogenesis of schizophrenia, and the dysfunction of NMDA receptor is closely related to cognitive impairment. Wendan Decoction may improve cognitive ability and relieve symptoms of patients with schizophrenia by regulating NMDA receptor activity. At the same time, it may affect glutamate glutamine metabolic cycle, promote glutamate metabolism and its clearance from synaptic space, reduce neurotoxicity, and improve synaptic health.

4.3. Impact on other neurotransmitter systems

Wendan Decoction can also regulate GABAergic system and 5-hydroxytryptamine (5-HT) system. As the main inhibitory neurotransmitter, GABA dysfunction is associated with anxiety disorder and schizophrenia. Wendan Decoction may play a sedative and anti-anxiety role by increasing the synthesis and release of GABA, enhancing the sensitivity of GABA receptor, and improving emotional and cognitive function. At the same time, Wendan Decoction can regulate 5-HT system, improve emotion and cognitive ability, so as to enhance the overall therapeutic effect.

4.4. Key signaling pathway intervention

4.4.1. PI3K/Akt/mTOR signaling pathway

The components of Wendan Decoction can activate PI3K/Akt/mTOR signaling pathway and promote the proliferation and differentiation of neurons. By improving PI3K activity, Wendan Decoction promotes Akt phosphorylation and activates downstream mTOR protein kinase, which plays a key role in neurogenesis and synaptic plasticity [10]. Synaptic plasticity is the basis of learning and memory. Wendan Decoction may play a positive role in improving the cognitive function of patients with schizophrenia by regulating this pathway.

4.4.2. CREB-BDNF pathway

Wendan Decoction can promote CREB phosphorylation and increase BDNF expression. BDNF is a key regulator of neural plasticity, which is involved in many aspects of learning and memory. CREB phosphorylation can more efficiently bind to BDNF gene promoter region and promote transcription, which is of great significance for neuron survival, differentiation and synapse formation [10]. Wendan Decoction may play a key role in improving the cognitive impairment of patients with schizophrenia by regulating this signal pathway.

4.4.3. Wnt/β-catenin signaling pathway

The regulatory effect of Wendan Decoction on Wnt/β - catenin signaling pathway has attracted much attention. The components of Wendan Decoction can affect the stability of β - Catenin and promote neuron formation by regulating the activity of Wnt signaling pathway. Studies have shown that Wendan Decoction may activate Wnt pathway and improve β - Catenin nuclear translocation by inhibiting the antagonists of Wnt signaling pathway [10]. After β-Catenin enters the nucleus, it promotes the expression of downstream target genes related to neurogenesis, which is of great significance for the recovery and improvement of cognitive function.

4.5. Neuroprotective effect of Wendan Decoction

4.5.1. Anti oxidative stress

Wendan Decoction has a clear antioxidant stress effect, which can enhance the activity of endogenous antioxidant enzymes such as superoxide dismutase (SOD) and catalase (CAT), promote free radical scavenging, and reduce oxidative damage [11]. In addition, Wendan Decoction can also alleviate mitochondrial dysfunction, improve mitochondrial membrane potential, enhance the activity of respiratory chain complex, enhance the energy production ability of cells, provide a better living environment for nerve cells, and help to alleviate the related symptoms of patients with schizophrenia.

4.5.2. Anti neuroinflammatory effect

Wendan Decoction has a significant effect in combating neuroinflammation, which can effectively inhibit the excessive activation of microglia, reduce the release of inflammatory factors such as TNF - α and IL-6, and alleviate neuroinflammation [12]. At the same time, Wendan Decoction can regulate the dynamic balance between the expression of pro-inflammatory cytokines and anti-inflammatory cytokines, promote the expression of anti-inflammatory factors such as transforming growth factor beta (TGF-β) and interleukin-10 (IL-10), inhibit the expression of pro-inflammatory factors, and reduce the damage caused by neuroinflammation to the nervous system.

4.5.3. Promoting neurogenesis and synaptic remodeling

Wendan Decoction has a positive promoting effect on hippocampal neurogenesis. Studies have shown that Wendan Decoction can promote the proliferation and differentiation of hippocampal neural stem cells and increase the generation of new neurons by activating BDNF signaling pathway, so as to improve cognitive ability [13]. In addition, Wendan Decoction

can also increase the number of dendritic branches and synapse formation of neurons, enhance the connectivity of neural networks, and improve the efficiency of information transmission. The improvement of synaptic remodeling helps to enhance learning and memory ability, and provides biological basis for the improvement of cognitive function in patients with schizophrenia.

5. Clinical evidence of Wendan Decoction in improving cognitive function

Randomized controlled trials (RCTs) are the key design in the study of Wendan Decoction improving cognitive function. Preliminary studies have shown that Wendan Decoction has a positive effect on the cognitive function of patients with schizophrenia. Some studies have pointed out that Wendan Decoction can improve cognitive ability by regulating the neurotransmitter system. Mini Mental State Examination (MMSE) and Wisconsin Card Sorting Test (WCST) are commonly used to quantify the changes. The existing literature shows that Wendan Decoction can improve the cognitive score and reduce the positive and negative symptoms, suggesting that it may have a good effect in cognitive intervention, which needs to be further verified by systematic analysis and multi center RCT.

In terms of safety, Wendan Decoction showed better safety and lower incidence of side effects than traditional antipsychotics. Studies have shown that Wendan Decoction Combined with commonly used antipsychotics has no significant drug interaction and is well tolerated by patients. The safety data of long-term use of Wendan Decoction also showed that the overall tolerance of patients was good, and the side effects were lower than those of conventional drugs, which laid the foundation for its clinical promotion.

The individualized therapeutic potential of Wendan Decoction is reflected in the implementation of dialectical treatment according to the theory of traditional Chinese medicine, and the adjustment of specific symptoms and physical conditions of different patients. This treatment method makes Wendan Decoction show significant effect difference in the treatment of schizophrenia. With the continuous development of biomarker research, personalized medication based on biomarker guidance is expected to improve the clinical efficacy. Although the current relevant research is relatively limited, preliminary data show that individualized treatment may play a key role in future clinical practice, and promote the application of Wendan Decoction in the treatment of schizophrenia.

6. Future research directions and challenges

Multiomics technology provides a new perspective for the study of the mechanism of Wendan Decoction. Integrating genome, transcriptome, proteome and metabolome data, we can understand the mechanism of Wendan Decoction under single cell resolution, reveal its role in different cell types, help to determine the main targets and signaling pathways, and provide the basis for precise treatment [14]. Future research needs to strengthen the integration and analysis technology of multi omics data to fill the gap between basic research and clinical application.

On the basis of multi omics technology, the verification of key targets is the core of understanding the mechanism of Wendan Decoction. The network pharmacology method can identify the main active components and potential targets of Wendan Decoction. Studies have shown that its multi-component and multi-target characteristics make it have significant advantages in the treatment of schizophrenia, and the effect may be achieved by regulating signal pathways [5]. In the future, combined with bioinformatics and experimental verification, we can systematically verify the target of Wendan Decoction and its biological effects at the cellular level, providing a theoretical basis for the development of new therapeutic drugs.

Modern preparation technology plays a key role in improving the clinical effect of Wendan Decoction. Microcarrier technology and nano drug delivery system can improve drug solubility, stability and bioavailability. Optimizing the preparation form can effectively release the active ingredients of Wendan Decoction in vivo, and enhance the improvement effect of cognitive function in patients with schizophrenia. Nanotechnology encapsulates the active ingredients of Wendan

Decoction, which can improve drug stability, achieve brain targeted release, reduce side effects, and provide new ideas for the modernization of traditional Chinese medicine.

The treatment strategy of integrated traditional Chinese and Western medicine provides rich possibilities for Wendan Decoction in the treatment of schizophrenia. Studies have shown that Wendan Decoction Combined with traditional antipsychotics can produce synergy, enhance the therapeutic effect, and improve the cognitive function and emotional state of patients by regulating the dynamic balance of neurotransmitters [15]. Combined medication can not only reduce the dosage of traditional drugs, reduce side effects, but also improve the degree of cooperation of patients. Future research can explore the specific synergistic mechanism of Wendan Decoction and different antipsychotics, and optimize the combined medication strategy.

7. Conclusion

As a traditional Chinese medicine prescription, Wendan Decoction shows potential in improving cognitive function of schizophrenia. Studies have shown that Wendan Decoction provides biological basis for patients by regulating a variety of neurotransmitters (such as glutamate, GABA and dopamine), which is suitable for patients with poor response to a single drug. Its regulation of signaling pathways affects neural development and cell survival, which provides a new perspective for understanding schizophrenia. Although Wendan Decoction shows clinical effect, its molecular mechanism and large-scale clinical trial data still need to be further studied. Future research should optimize the administration strategy, combine traditional Chinese and Western medicine treatment, and provide personalized scheme. When synthesizing different research perspectives, we should objectively evaluate their benefits and limitations to guide future research directions. In conclusion, Wendan Decoction shows good prospects in improving cognitive function of patients, but further research is needed to maximize its clinical application.

About the author

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Disclosure statement

The author declares no conflict of interest.

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