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Research Progress of Spironolactone as an Antagonist of NRG1-ERBB4 Pathway in the Treatment of Cognitive Impairment in Schizophrenia

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Abstract

Cognitive dysfunction is one of the core symptoms of schizophrenic patients. The prognosis of patients' cognitive function is closely related to the overall social function. The use of antipsychotic drugs to improve the cognitive impairment of schizophrenic patients is not yet ideal. The NRG1-ERBB4 signaling pathway acts on the prefrontal cortex. Abnormality of this pathway can affect cognitive function. Currently, spironolactone as an antagonist of nrg1-erbb4 signaling pathway, it is used in the clinical treatment of patients with schizophrenia. This article reviews spironolactone as an NRG1-ERBB4 signaling pathway antagonist that significantly improves cognitive dysfunction in patients with schizophrenia., and further provides theoretical and clinical basis for clinical treatment of cognitive dysfunction.

Keywords

Schizophrenia; NRG1-ERBB4; Spironolactone; Cognitive dysfunction

Schizophrenia is a severe crippled chronic mental illness characterized by positive symptoms (hallucinations and delusions), negative symptoms (social withdrawal) and cognitive impairment (executive function and memory impairment) [1,2]. According to a study by Yueqin Huang et al. [3] in 2019, the lifetime prevalence rate of schizophrenia spectrum disorder in China is 0.7%. Among them, cognitive dysfunction is one of the core symptoms of schizophrenia, the cognitive function of patients is closely related to the outcome of their overall social function. Cognitive impairment is very common in patients with schizophrenia, many areas have been impaired, including language, attention, processing speed, working memory, visual memory, executive function and social cognition [4,5]. Due to the unknown pathogenesis of schizophrenia spectrum disorder and the lack of specific biomarkers, although antipsychotics can improve the positive symptoms of patients, they have little effect on negative symptoms and cognitive impairment [6-8]. The improvement of cognitive dysfunction has a far-reaching impact on the treatment of schizophrenia, but due to professional knowledge, resources and time constraints, we seldom evaluate it in clinical practice, and the therapeutic effect of antipsychotics is not obvious. Therefore, it is necessary to develop and explore more targeted therapies for cognitive disorders in schizophrenia. Some related studies have shown that the NRG1/ERBB4 signaling pathway has the potential to become a new therapeutic target for the treatment of schizophrenia. Screening among drugs approved by NIH-NCC, spironolactone, a glucocorticoid receptor antagonist, was found to be an inhibitor of ERBB4 activity and reduced the level of ERBB4 phosphorylation in human xenogeneic T-47D cells and Nrg1 transgenic mice in vitro. Nrg1 transgenic schizophrenic mice treated with spironolactone showed positive symptoms and improved working memory function [9]. This article expounds the related studies on spironolactone in the treatment of cognitive impairment of schizophrenia in recent years, in order to provide further reference for the treatment of cognitive impairment of schizophrenia.

The Role of NRG1-ERBB4 Pathway in Schizophrenia

A study of Nrg1 and ErbB1 in patients with schizophrenia

The neuroregulatory protein (Nrg) plays an important role in the dynamic balance between nerve growth and development and normal brain activity. Nrg is a growth factor containing epidermal growth factor (EGF) domain expressed in the nervous system, which is encoded by 6 genes (Nrg1-Nrg6), among which Nrg1 is the most typical [10-12]. Nrg1

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exists in many organs and plays different roles in each organ. It is important for the growth and development of mammary gland, heart, central nervous system and peripheral nervous system. It mainly exists in hippocampal and cortical neurons [13,14]. It is also essential to participate in nerve repair, myelin remodeling, glial growth and development, synaptic transmission and neuronal plasticity, the development of GABA intermediate neurons and the expression of dopamine, serotonin receptor and monoamine transporter [15,16]. Nrg1 participates in neuronal protection mainly through PI3k/Ark [17], aquaporin-4 (AQP-4) [18] and nuclear factor kappa B (NF- κ B) [19]. Nrg1 has been widely studied in models of schizophrenia, epilepsy, cerebral ischemia and neurodegenerative diseases [20-23]. Recent studies have found that Nrg1 is one of the susceptibility genes of schizophrenia, Nrg1 plays a role mainly by activating ErbB receptor tyrosine kinase [24].

Current studies have shown that there are four subtypes of ErbB receptor tyrosine kinase (ErbB1-4), among them ErbB2, ErbB3 and ErbB4 combine with Nrgs to form homodimers or heterodimers, and mediate Nrgs signal transduction by activating different kinase pathways [13]. In the brain, ErbB4 is the most abundant in all ErbBs and is the main receptor of Nrgs [25-27]. Shopping Huang et al [28] have shown that the only known receptor in ErbBs that can bind to Nrg1 in the brain is ErbB4.ErbB4 not only binds to the receptor but also acts as a tyrosine kinase., according to gene linkage analysis and association studies, there is a great relationship between ErbB4 variation and schizophrenia [29]. Many studies have shown that the changes of the NRG1/ErbB4 signal pathway are closely related to the pathogenesis of schizophrenia, and the pathogenesis of schizophrenia in children may be related to the variation of NRG1/ErbB4 signal pathway [30-33]. It can be seen that the effect of ErbB4 on schizophrenia is mainly through the combination with NRG1. Because the etiology of schizophrenia is unknown, it is necessary to develop and explore more targeted drug therapy for schizophrenia. In recent years, the research on the relationship between NRG1/ErbB4 signal pathway and schizophrenia has become the focus of many researchers.

Study of NRG-1/ErbB signal pathway in patients with schizophrenia

NRG-1/ErbB signaling pathway plays a very important role in the development of central nervous system and brain function of infants during embryo and after birth [34,35]. It has been reported that the change of NRG1-ERBB4 pathway is an important cause of neuropsychiatric diseases (schizophrenia, epilepsy, autism, etc.) [36,37]. Genetic studies have confirmed that NRG1 and homologous receptor ERBB4 are susceptible genes for schizophrenia, and changes in the NRG/ERBB4 signaling pathway are associated with positive, negative and cognitive symptoms [38,39]. Several autopsy studies have also reported an increase in the expression of NRG1 in patients with schizophrenia [40,41]. In addition, hyperphosphorylation of NRG1-ERBB4 in the brain of patients with schizophrenia has been found postmortem [42]. In patients with schizophrenia, a large number of oligodendrocytes in the prefrontal lobe are lost, resulting in abnormal myelin formation [43,44], and the loss of myelin sheath can lead to schizophrenia and cognitive impairment. Wenping Guo et al. [45] confirmed that during the development of schizophrenia, the expression of NRG-1 decreased during demyelination of oligodendrocytes and increased to normal level during myelination regeneration, while the expression of ErbB4 increased during demyelination and myelination regeneration of oligodendrocytes. These results suggest that NRG-1/ErbB4 signal pathway plays an important role in myelination and demyelination of oligodendrocytes in prefrontal cortex. Prefrontal lobe dysfunction is the site of cognitive impairment in patients with schizophrenia, especially the cause of working memory impairment [46,47]. To sum up, it can be seen that the abnormality of NRG-1/ErbB4 signal pathway will lead to the change of cognitive function in patients with schizophrenia. We can find a new target to block the NRG1/ERBB4 signal pathway and provide a new choice for the treatment of schizophrenia.

Preclinical Study of Spironolactone as an Antagonist of NRG1-ERBB4 Signal Pathway in the Treatment of Schizophrenia

Molecular mechanism of spironolactone as an antagonist of NRG1-ERBB4 signal pathway in the treatment of schizophrenia

A preclinical study published by Wehr et al. [48] showed that when they applied this strategy for screening, they found that the glucocorticoid antagonist spironolactone, as an inhibitor of ERBB4 activity, effectively reduced the level of ERBB4 phosphorylation in vitro and in vivo, and normalized the changes of excitatory/inhibitory neurons of cortical projection changes, which can be used as a drug to improve schizophrenia-related behavior. Functional impairment of prefrontal cortex is a potential mechanism of cognitive impairment. Abnormal NRG1-ERBB4 signaling pathway can affect the cortical circuits formed between inhibitory intermediate neurons and excitatory pyramidal neurons. The corresponding imbalance between inhibition and excitation is believed to be the cause of cognitive impairment observed in mouse models with and without function [49]. Spironolactone was used to treat heart failure or aldosteronism more than 50 years ago. In their preclinical studies, spironolactone induced an increase in inhibitory neurotransmission in brain slice culture, which supported the ERBB4-mediated inhibitory intermediate neuron function model. In order to test the behavior improvement, spironolactone was used to treat Nrg1 transgenic mice for a long time, and it was tested in the experiment of schizophrenia-related behavior in animals. It is worth noting that the working memory function and positive symptoms of Nrg1 transgenic mice treated with spironolactone were significantly improved [48]. From animal experiments, we found that spironolactone can improve the cognitive dysfunction of schizophrenia, and has a certain effect on positive symptoms, but the clinical application needs to be further confirmed.

Spironolactone as an antagonist of NRG1-ERBB4 signal pathway in the treatment of schizophrenia

In recent years, the NRG1/ERBB4 signaling pathway has become the focus of discussion. Related studies have revealed that it is a part of the pathophysiology of schizophrenia, especially closely related to the occurrence of working memory impairment in cognitive impairment [50,51]. Animal experiments have shown that mouse models with high levels of NRG1 show similar behaviors to schizophrenia, such as reduced social interaction, increased activity and cognitive impairment [52,53]. Because the corticosteroid receptor expressed in the brain is related to the regulation of stress response, spironolactone has been studied in the treatment of depression, and it has been proved that spironolactone can increase the activity and curiosity of mice [54]. In addition, anxiety was partially improved in a small number of patients with bipolar disorder [55], which is consistent with the conclusion of Wehr et al. [48] that spironolactone can affect the anxiety behavior of Nrg1 mice. The related studies of spironolactone in schizophrenia, depression and bipolar disorder all showed that spironolactone improved the symptoms.

Side effects of spironolactone in the treatment of schizophrenia

Spironolactone is an FDA-approved drug that has been used as a safe and effective diuretic in patients for decades and has not shown significant side effects in treating mice [56]. However, for healthy human volunteers, short-term use of spironolactone can reduce memory recovery and is also reported to be harmful to the formation of near memory in mice [57,58]. Although the above studies have shown that spironolactone provides a new choice for the treatment of schizophrenia, because the drug may have a certain impact on the body, further studies are needed to confirm the feasibility of spironolactone as a drug for the treatment of schizophrenia.

Clinical Evidence of Spironolactone as an Antagonist of NRG1-ERBB4 Signal Pathway in the Treatment of Schizophrenia

The impairment of memory disorder in patients with schizophrenia is widespread, which involves every component of memory (including work, study, instantaneous, short-term and long-term). The most serious damage to patients with schizophrenia is working memory disorder. Working memory refers to the process in which information content can be retained in the brain for synthesis and planning, that is, the ability to temporarily store information for use. Memory impairment has a serious impact on the daily activities of patients, which is the basis of social function impairment. Therefore, for patients with schizophrenia, it is very important to find drugs to treat their cognitive impairment (working memory impairment). The rationality of spironolactone in the treatment of cognitive impairment of schizophrenia (Spiro-Treat) stems from the results of recent preclinical studies, which show that the glucocorticoid antagonist spironolactone can improve the behavioral defects associated with schizophrenia in Nrg1 transgenic mice by antagonizing ERBB4 receptor[48]. These findings support the view that spironolactone is effective in the treatment of patients with schizophrenia. The Spiro-Treat trial was the first to evaluate the treatment of corticosteroid receptor antagonist spironolactone as an antipsychotic. 90 patients were randomly divided into two intervention groups (spironolactone 100mg/d or 200mg) and a control group (placebo) and received treatment for three weeks. The changes of working memory were evaluated by n-back test (n-back test is a mature method for testing working memory [59]) before and after dry expectation. Spiro-Treat also studied the effects of the intervention group on verbal memory, complex visual scanning, movement speed, and sustained and selective attention. In summary, Spiro-Treat 's results show that spironolactone can effectively improve working memory impairment in patients with schizophrenia [60]. Working memory impairment is considered to be an important part of cognitive impairment in patients with schizophrenia [61]. The Spiro-Treat trial provides us with a new choice for clinical treatment of cognitive impairment in schizophrenia. Once this study is successful, it will go beyond the established concept of interfering with dopaminergic nerve transmission as a key approach to the treatment of schizophrenia.

Summary and Prospect

To sum up, the abnormality of NRG1/ERBB4 signal pathway plays an important role in the occurrence and development of schizophrenia, but its specific mechanism is more complex. Current clinical studies and in vitro experimental studies have shown that spironolactone is effective in the short-term treatment of cognitive impairment in patients with schizophrenia, but if long-term use of medium to large doses of spironolactone can lead to hyperkalemia and increase the risk of arrhythmia, especially in combination with antipsychotics that prolong QTc, this problem will be more prominent. Considering the potential risk of long-term use of spironolactone in schizophrenic patients receiving antipsychotic treatment, we can consider short-term use of spironolactone to restore mutated NRG1-ERBB4 signaling pathways.As there is no related research in China and a small number of foreign studies, in the later stage, we need to increase the number of cases and further verify its efficacy in order to intervene the cognitive dysfunction of patients with schizophrenia.

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