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A Review on Biological Mechanisms of Negative Symptoms in Chronic Schizophrenia

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Abstract: Research about the negative symptoms of chronic schizophrenia (SZ) is still lagging behind, in order to more comprehensively and systematically understand the biological and molecular mechanisms behind them, as well as to explore more valuable research directions and treatment options. By summarizing the results of previous studies and exploring them at the levels of neurobiology, genetics, molecular biology and microbiology, the authors provide a preliminary review of the new research progress in recent years. The authors hypothesize neurodevelopmental disorders by thoroughly investigating the anatomical features of various brain regions and the corresponding abnormalities in neurotransmitters. This paper then provides a relatively fresh perspective by summarizing the potential pathogenic mechanisms in terms of the brain-gut axis and metabolic syndrome. Ultimately, it is determined that the pathophysiology of chronic schizophrenia is associated with multiple biological mechanisms within the body, primarily arising from neurological abnormalities within the brain. On the basis of this, the author provides a conceptualization of the pathophysiology and a potential course of treatment.

Keywords: Schizophrenia, Negative Symptoms, Biology, Pathogenesis

1. Introduction

Schizophrenia is a group of severe mental disorders divided into positive symptoms and negative symptoms with unclear etiology; chronic SZ is the kind of schizophrenia with predominantly negative symptoms. Clinically, negative symptoms mainly refer to the decline or lack of normal psychological and mental functions. However negative symptoms are implicit, so they are harder to treat than positive ones. Additionally, as the disease worsens, positive symptoms like hallucinations become less common and mental degradation is a growing phenomenon that is frequently misdiagnosed. [1]. At present, research has found a link between damage to brain structures and pathogenesis. The expression of multiple neurotransmitters, hormones and related genes may participate in the pathogenesis of negative symptoms of chronic SZ. In recent years, neuroimaging and magnetic resonance imaging research has provided a valuable line for revealing the pathological mechanism of negative symptoms. Therefore, this article outlines the biological mechanism of the onset of negative symptoms that may exist in the chronic SZ group, discusses it from the level of neurobiology, genetics, molecular biology, etc., and makes a preliminary review of the relevant research progress in recent years. Understanding these basic pathological processes can be used for exploring more accurate

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evaluation and providing new targets for more effective treatment [2,3].

2. Overview of Negative Symptoms of Chronic Schizophrenia

2.1. Overview

In clinical terms, negative symptoms mainly refer to the decline or absence of normal psychological and mental functions, mainly in the three aspects of emotional response, social function and cognitive function. In 1982, Andreason N.C. divided the diagnosis of negative symptoms of SZ into five aspects, and then in 2005, the National Institute of Mental Health further selected five dimensions for the assessment of negative symptoms of schizophrenia: affective flattening, attention impairment, alogia, avolition-apathy, non-socialization [4].

Crepelin proposed that negative symptoms reflect most essential pathological changes in schizophrenia, and this conclusion has also been widely recognized by the academic community. However, the recent research on negative symptoms lags behind positive symptoms, and its biological mechanisms are still not clear. This article will sort out and summarize the possible biological mechanisms based on previous studies on negative symptoms of chronic SZ [5].

2.2. Differences from Positive Symptoms

Regarding the difference between negative symptoms and positive symptoms, there are mainly three theories put forward by important scholars. Henri examined schizophrenia in 1961 from a pathological perspective, hypothesizing that negative symptoms could be the main symptom and positive symptoms would be compensatory responses brought on by normal mental processes [6]. In the 1980s, Crow TJ divided schizophrenia into two types. Type II was mainly negative symptoms, which obtain more significant brain organic changes that would lead to more serious disease outcomes [7]. After that, Andreason N.C. distinguished primary and secondary negative symptoms, of which secondary refers to diseases related to or caused by positive symptoms, emotional symptoms, adverse drug reactions, environmental deprivation, and other treatment-related factors [8].

3. Biological Mechanism of Chronic Schizophrenia

3.1. Neurobiology

3.1.1. Brain Anatomy

With the progress of science and technology in recent years, the research on functional brain imaging of schizophrenia has been supported by a number of advanced technologies such as PET, SPET, fMRI, CT, etc., which have made more comprehensive progress in brain anatomy and targeted research on pathological changes of brain organs [9]. The most consistent structural abnormalities found in schizophrenia can be summarized as the enlargement of the ventricles, the atrophy of the cerebral cortex and the reduction of the gray matter in various brain areas. Through Pandurangi`s research, the clinical symptoms of patients with early ventricular enlargement are principally manifested as negative symptoms [10].

According to various research reports, the abnormal or damaged brain areas with negative symptoms of schizophrenia is mainly focus on the area related to cognitive and memory function. Its pathological characteristics are mostly the reduction of gray matter volume and gray matter concentration, which will lead to certain neurodegeneration changes and progressive loss [11-14]. In a broad sense, the results support the following three models: schizophrenia is caused by frontal striaticular dysfunction, frontal temporal lobe dysfunction and frontal edge dysfunction [15].

The frontal lobe, hippocampus, temporal lobe edge system, lower parietal lobus, and island lobe

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are the main brain areas that show pathological characteristics, and their functions are also concerned with social cognition, advanced thinking, declarative memory, etc. [16-20]. Hence, the diagnosis of patients with negative symptoms of chronic SZ will have the features of the five dimensions mentioned above, which corresponds to the function of the abnormal brain area and there exists a connection of mutual influence, mutual restriction and progressiveness between them. In addition, different degrees of organic injure have been detected in the amygdala, the accus cortex, the thalamicum, the basal ganglion, the strium region and the cerebellum, but the cause and uniformity of its pathogenesis have not been discovered [21-23].

Pathological characteristics of reduced connection between brain fibers and white matter have also been exposed in the brains of patients with negative symptoms. These pathways are mainly focused on connecting speech, auditory and memory-related limbic systems; there are also pathways related to language and emotion processing present lesion with varying degrees, such as corpus callosum, uncinate fasciculus, inferior frontal occipital fasciculus and other connective fibers [3,11,15]. According to more research statistics, chronic SZ will demonstrate more severe neurodegenerative changes and white matter damage [16].

It is an enormous process that explore the pathological of neurobiology, which involves biological abnormalities in various brain regions and the connection between various neurological processes. Some scholars have found that different negative symptoms have close correlation with the activation of functions in different areas of the brain: social retreat is related to the hippocampus, the temporal upper gyrus and bilateral thalamus, but the lack of pleasure is related to the amygdala. Consequently, ascertaining a clear physiological process requires a more innovative perspective and more in-depth research [3].

3.1.2. Neurotransmitters

The anatomical anomaly of the cranial nerve is a biological abnormality, but neurotransmitters also exhibit the pathogenic cause of this anomaly. Studies have shown that there is also a gap between neurotransmitters in patients with chronic SZ and non-patients, and these pathways are mainly concentrated in the brain regions of dispersive modulation system associated with cognition and memory.

Currently, it is known that there are four pathways of dopamine (DA) in the brain, of which the production of positive symptoms of schizophrenia is related to the excessive DA content in the midbrain-edge dopamine pathway, and the relative reduction of central DA function and concentration will cause certain negative symptoms. This deficiency may be primary or secondary caused by antipsychotic drug blocking [3,22]. Recent studies have found that 5-hydroxytryptamine(5-HT) may also play an important role in the middle cerebral-cortical pathway: the 5-HT receptors dominate this pathway than the DA receptors. If the 5-HT concentration is increased, it will have antagonistic effect on DA. Not only does this concept make theoretical sense, but clinical trials and PET technologies also support it [24].

Glutamic acid-mediated N-methyl-D aspartic acid (NMDA) receptors are associated with the limbic system and thalamus. The reduced level of this neurotransmitter will lead to abnormal memory generation mechanism in the hippocampus. Gamma-aminobutyric acid (GABA) is an inhibitory neurotransmitter in the brain, and the synchronization of nerve oscillation is the fundamental mechanism of its participation function. Research has shown that gamma-oscillation synchronization is abnormal in patients with prominent negative symptoms of schizophrenia.

Through the phenomenon that improvement of the negative symptoms of chronic SZ through the use of anticholinergic drugs, it is speculated that excessive choline release may lead to negative symptoms, but there is a deviation in the evaluation of symptoms caused by drug factors, thus the mechanism of choline is still controversial [11].

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3.2. Brain Electrophysiology

Defining definitively phenotypes has always been a major challenge in the study of schizophrenia [16]. A recent study examined three neurophysiological internal phenotypes and three neurocognitive internal phenotypes in order to explore the processing process of brain auditory information in patients with schizophrenia, and found that they are hereditary and have many correlations with the environment [21].

3.3. Neurodevelopmental Theory

There is evidence that early neurodevelopmental lesions may leave the brain susceptical to later neurodevelopmental processes and may interact with other environmental factors. Therefore, some scholars have put forward the theory of neurodevelopmental disorders of schizophrenia. The conclusion of this theory is that the brain continues to develop after birth, mature in adulthood. Changes in brain structure and susceptibility of brain function caused by brain injury in the early stage (prenatal or perinatal) will show corresponding symptoms after physiological maturity, whether it is myelin function, spontaneous electroencephalographic activity or cognitive function, and then presented as schizophrenia [20, 21].

4. Genetics

Several current studies have shown that the process of participating in the onset of chronic SZ involves multiple genes, so schizophrenia is a polygenic disease. And these genes play a significant role in the process of regulating neuron migration, neuronal growth, neuron maturation and neuron-interconnection, which corresponds to the theory of neurodevelopment [25]. It has shown that the damage of physiological models caused by the loss of epigenetic factors in the process of DNA glycosylation, DNA methylation, histone modification, and DNA transcription translation is the incentives that causes negative symptoms and damage mechanism of the epigenome, and the regulation of these genes is also affected by the environment [24]. It can be inferred that the direct cause of negative symptoms is abnormalities and disorders in the process of neurodevelopment, while genetic abnormalities are background factors and indirect induction factors.

Furthermore, some scholars have found that schizophrenia is familial aggregation, which means that the offspring of patients with schizophrenia also have structural brain abnormalities in the cortex and subcortical brain regions similar to the diagnosed diseases, and the risk of the disease is directly proportional to the similarity of the patient's genes [26].

5. Regulation Related to Metabolic Syndrome

When psychological problems are acute, there will be a tendency to somatic, and even cause some metabolic syndromes. Obviously, the internal environmental homeostasis in the body is also reacting to the psychology comparatively. As a result, we can consider whether there is a pathogenesis of chronic SZ that deserves attention from the perspective of triggering metabolic syndrome.

5.1. Endocrine

In recent years, more studies have found that there is a certain dysfunction in the hypothalamus-pituitary-gonad axis of patients with chronic SZ, and the hormones in this pathway will participate in the regulation of negative symptoms. And sex hormones have also been found to play an important role. For example, women's higher estrogen, prolactin and male testosterone have a certain protective effect on schizophrenia. Moreover, there are possible effects of thyroid hormones and melatonin, and some studies have found that negative symptoms of anti-thyroid antibody-positive patients are

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relatively abundant [3].

5.2. Protein

The regulation of gene abnormalities primarily occurs in the form of proteins, such as neuromodulation protein 1, anti-binding protein, etc. These proteins are primarily involved in signal transduction, cell migration and growth, myelin formation, presynaptic membrane function regulation, and γ-aminobutyric acid function. However, some proteases have also been shown to play a vital role in the regulation of negative symptoms [22,23].

5.3. Immune Inflammation

Immune inflammation mainly occurs on microglial cells in the brain region. Small glial cells are the immune function cells of the central nervous system and by activating the neuroinflammation caused by microglial cells, it will damage neurons. The neurodegeneration and developmental abnormalities caused by it have been proved to be closely related to the negative symptoms of schizophrenia [3,22].

6. Potential Impact Mechanism of Intestinal Microorganisms

The influence of intestinal microorganisms is also a hot topic in research on the pathogenesis of chronic SZ in recent years. The intestinal microbiome interacts with the central nervous system through the intestinal brain axis. The microbiota can affect and react to many behavioral and mental disorders by virtue of this communication, which involves neurons, endocrine systems and immune systems. And it works by exacerbating chronic inflammation and interfering with the host's energy homeostasis [27]. Intestinal microorganisms mainly affect negative symptoms of schizophrenia through the form of immune inflammation, which can produce corresponding neuroactive substances, which are transmitted through the vagus nerve pathway, causing pathological changes and impairment of cognitive function in the hippocampus and cortex [28].

7. Discussion

The future research direction of negative symptoms of chronic SZ can be divided into two directions: evaluation and treatment. In terms of evaluation, the factors of negative symptoms have an independent evolutionary trajectory and pathological basis in the development of schizophrenia. Thereupon, it is necessary to conduct behavioral, imaging, neurobiochemical, molecular genetics and other aspects of each symptom, and combine computer intelligence to evaluate the patient's mental activity and expressive processes in a more objective ways [4]. The evaluation of negative symptoms is limited to evaluation by others, which can improve the self-assessment tool and eliminate the misdiagnosis of environmental factors from the perspective of the patient's self-experience.

For treatment, according to the theory of neurodevelopmental disorders, therapist can intervene in the neurodevelopmental process as soon as possible. When the corresponding cerebral organic and neurodegenerative changes are diagnosed in the early stage, drugs or other neurotherapy programs can be used to prevent neurobiological mechanisms. Food therapy is also a treatment plan that can reduce the impact of drugs. According to the microbiology, dietary supplementation of prebiotics and probiotics may affect the function of the brain intestinal axis by changing the intestinal flora, thus improving the impact of internal environmental homeostasis on brain abnormalities.

However, the author believes that the combined diagnosis and treatment of traditional Chinese and Western medicine may be a new direction and foothold for the treatment of mental diseases in the future. Scholars have found that the treatment of schizophrenic drugs by traditional Chinese medicine is similar to that of traditional psychotherapy, but the effect of acupuncture on negative symptoms is

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more obvious[29]. At this stage, there are very few studies on the combination of traditional Chinese medicine and psychology, but it is very feasible for traditional Chinese medicine to treat mental diseases, and the treatment of traditional Chinese medicine is more balanced. It will simultaneously improve the psychological and physical condition and have less side effects.

This article aims to explore the biological mechanism behind the negative symptoms of chronic SZ. Understanding these basic pathological processes can provide new targets for the exploration of more accurate evaluation and more effective treatment. At the same time, it also combines modern medicine, traditional Chinese medicine with psychological diagnosis and treatment, and finds research and treatment methods that can improve the body and psychology at the same time in the progress of technology and thinking.

8. Conclusion

The author mainly discusses from the level of neurobiology, genetics, molecular biology, metabolic syndrome, etc., elaborates the clinical symptoms of chronic SZ, and summarizes the potential biological mechanisms of negative symptoms of chronic SZ in recent years. The understanding of the heterogeneity of schizophrenia may give impetus to the success of genetics and neurobiology research on schizophrenia.

Research in the field of chronic SZ is still in its infancy, also many studies are still stuck at a relatively hysteretic level, thus future study must combine basic knowledge of schizophrenia genetics with understanding of normal brain function. Schizophrenia is a significant brain dysfunction, and its neurobiological research may help illuminate the nature of normal thinking, perception and emotions. Testing these broader assumptions will require the integration of studies on biochemistry and cell biology, neuroimaging and human genotype-phenotype correlation.

This article can be used as a reference for research at this stage. Through the study of discovered and possible biological mechanisms, researchers can better understand the inner feelings of patients with schizophrenia and reconcept the definition of schizophrenia on the basis of a better understanding of the etiology and pathogenesis.

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