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The Neural Mechanism of NMDA Receptor Hypofunction in Schizophrenia

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Abstract. Schizophrenia is a chronic and severe mental disorder, but its pathological mechanisms remain incomplete. While the traditional dopamine hypothesis can explain positive symptoms, its therapeutic effects on negative symptoms and cognitive impairment are limited. This article, through literature review and systematic integration, elucidates the multi-level neural mechanisms of NMDA receptor hypofunction in schizophrenia, covering the molecular, cellular, and neural circuit levels. The study found that NMDA receptor dysfunction originates from multiple factors, including abnormal expression of receptor subunits and epigenetic factors. These changes preferentially damage parvalbumin-positive (PV+) interneurons, leading to cortical excitation/inhibition imbalance, and dysfunction of multiple circuits, ultimately manifesting as the multidimensional symptom spectrum of schizophrenia. However, evidence challenges the classic hypothesis that "PV+ neuron NMDA receptor dysfunction is the core starting point of the disease," suggesting that the pathological mechanisms of schizophrenia may involve the synergistic effects of multiple cell types and brain regions. It provides a theoretical framework for a deeper understanding of the pathophysiological mechanisms of schizophrenia, and also offers important insights for developing new therapies targeting the glutamatergic system.

Keywords: schizophrenia, NMDA receptor, hypofunction, neural mechanisms

1. Introduction

Schizophrenia includes positive symptoms (hallucination and delusion), negative symptoms (avolition and anhedonia), and cognitive symptoms (impaired working memory and reduced willpower), but the pathological mechanism has not been fully elucidated to date. The traditional Dopamine Hypothesis succeeds in explaining positive symptoms, and the developed drugs such as risperidone and olanzapine can effectively treat positive symptoms, but there is no significant improvement in negative and cognitive symptoms.

N-methyl-D-aspartate (NMDA) receptors, as excitatory glutamate receptors in the central nervous system, play an important and indispensable role in synaptic plasticity (the basis of memory formation) [1]. A large number of clinical studies have shown that patients with schizophrenia have extensive NMDA receptor dysfunction, which is consistent with the patients' multiple symptoms. According to research by scholars such as Coyle, a type of non-competitive NMDAR antagonist (ketamine) can induce positive, negative, and cognitive symptoms that are similar to schizophrenia

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[2]. Studies by Kantrowitz have found that cognitive dysfunction in schizophrenia patients can be improved by enhancing NMDA receptor function [3]. These all point out that NMDAR low function is likely to be one of the core pathological mechanisms of schizophrenia. Researchers such as Jauhar integrated the NMDA receptor hypothesis and the dopamine hypothesis to form a complete pathological mechanism [4].

This article uses the method of literature analysis and review to sort out the neural mechanisms of NMDA receptor dysfunction in schizophrenia, mainly covering the mechanisms of molecules, cells, and overall neural circuits. The significance of this article lies in systematically sorting out the latest research results in NMDA receptor disorders, providing a theoretical framework for an in-depth understanding of pathological mechanisms, and at the same time providing new guidance and inspiration for the treatment of schizophrenia.

2. The origin and evidence of NMDA receptor hypofunction hypothesis

2.1. Neurobiological basis: physiologicla functions of NMDA receptors

N-methyl-D-aspartate (NMDA) receptors (NMDARs) are ionotropic glutamate receptors primarily distributed in the hippocampus, prefrontal cortex, and cerebral cortex. They exhibit voltage-dependent and dual-ligand-dependent gating: at resting membrane potential, magnesium ions (Mg^{2+}) block the NMDA ion channels. Therefore, activation of NMDARs requires membrane depolarization to remove magnesium ions (Mg^{2+}), allowing glutamate to bind to the subunit GluN2, and glycine co-agonist to bind to the subunit GluN1. This enables the influx of sodium ions (Na^{+}) and calcium ions (Ca^{2+}) and the efflux of potassium ions (K^{+}).

NMDAR is an obligatory heterotetramer ion channel composed of four subunits. Its basic configuration consists of two GluN1 subunits and two GluN2 subunits or two GluN3 subunits. GluN1 is the essential core for NMDAR function, while GluN2 determines the gating kinetics and pharmacological properties of the ion channel [5]. Moreover, different GluN2 subunits have different functions [6]. In addition, the incorporation of the GluN3 subunit can reduce calcium ion permeability and weaken the magnesium ion blocking effect. NMDAR regulates neural circuits through calcium ion (Ca^{2+}) signaling. Mature neurons can perform bidirectional synaptic plasticity, including long-term potentiation (LTP) and long-term depression (LTD). The influx of calcium ions (Ca^{2+}) activates protein kinase II (CaMKII), promoting AMPA receptor membrane insertion and enhancing the synapse (LTP). However, when the signal intensity of the influx of calcium ions (Ca^{2+}) is moderate, it activates phosphatase to internalize AMPA receptors, thereby weakening the synaptic connection (LTD) [7].

2.2. Origin of the hypothesis: ketamine and PCP evidence

Ketamine (2-chlorphenyl-2-methylamino-cyclohexanone) is a non-competitive NMDAR antagonist and a structural derivative of phencyclidine (PCP). It was developed in 1962. Both are dissociative anesthetics. However, Ketamine has higher safety and can overcome the neurotoxicity and severe mental side effects of PCP (confusion, etc.), so it has become a safer alternative drug, especially in clinical human experiments. Ketamine has analgesic, amnestic and antidepressant properties, has been listed as an essential drug by the World Health Organization, and is widely used in veterinary clinical anesthesia. Due to its risk of abuse and hallucination, it is classified as a controlled substance in a large number of countries (it is classified as a Category III controlled substance in the United States) [8].

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Inspired by the hallucinogenic effects of PCP drugs, Javitt and Zukin reported in their review that after joint analysis of PCP binding sites and NMDA receptors, it was found that the related psychiatric symptoms that can be triggered by PCP abuse perfectly match all symptom profiles of schizophrenia, including positive, negative, and cognitive symptoms.

2.3. Findings supporting the hypothesis

2.3.1. Clinical findings

The above-mentioned individuals abusing PCP and ketamine drugs are the initial clinical findings of schizophrenia, and the ingestion of phencyclidine and ketamine in schizophrenia patients will aggravate their symptoms [9]. In addition, according to statistics, 6.5% of patients who meet the diagnosis of schizophrenia and are sick for the first time test positive for anti-NMDAR antibodies. Another report page shows that 8% of schizophrenia patients (115/1441) have detected anti-NMDAR antibodies [10].

In addition, patients with schizophrenia often have electroencephalogram abnormalities, such as abnormal gamma wave oscillations. One of the gamma waves with 30-100Hz is considered to be related to the cognitive symptoms of schizophrenia. Cortical gamma oscillation refers to the higher-frequency rhythmic electrical activity generated by the synchronous discharge of the cerebral cortex neuron group, and is controlled by the calcium-binding protein-containing γ-aminobutyric acid (GABA) interneurons on pyramidal neurons [11,12]. It is worth noting that NMDA receptor antagonists (such as ketamine) can selectively block NMDA receptors on PV+ interneurons, resulting in weakened GABAergic inhibition, which in turn causes enhanced cortical activity and abnormal γ-band oscillations. This finding provides direct evidence for the NMDA receptor hypofunction hypothesis [13].

2.3.2. Cadaver findings

Tissue studies of human postmortem brains have been important in providing evidence supporting the hypothesis of low NMDA receptor function, and most results point to low NMDAR function in schizophrenia. One of the analyses found that GluN1 mRNA, GluN1 protein and GluN2C mRNA expression were significantly decreased in the prefrontal cortex of schizophrenia patients, although there were no statistically significant changes in the GluN2 and GluN3A subunits. In another study, it was found that GRIN1 mRNA encoding the NMDAR NR1 subunit in the dentate gyrus of the hippocampus was significantly reduced, GluN1 levels were selectively reduced, and there was left-lateralization.

Abnormalities in NMDAR GMS modulators have been found in the peripheral tissues of schizophrenia patients, including reduced levels of SR and D-serine. Levels of another endogenous GMS antagonist (kynurenic acid) are increased in the brain tissue and cerebrospinal fluid of postmortem schizophrenia patients [14]. Another study found that glutamate levels were reduced in the hippocampus and prefrontal cortex, and the catabolism of N-acetyl aspartyl glutamate (NAAG) was reduced by measuring neuronal substances and enzymes such as glutamate in the postmortem brain NAAG is an endogenous NMDAR antagonist and mGluR3 agonist, and its level is regulated by glutamate carboxypeptidase II (GCP-II). In the study of Coyle and Bergeron, it was found that the level of NAAG increased, but the activity of GCP-II decreased.

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3. Multilevel neural mechanisms of NMDA receptor dysfunction

3.1. Molecular and cellular mechanisms

NMDA receptor dysfunction in schizophrenia stems from multiple factors affecting molecules and cells at multiple levels, leading to weakened receptor conduction, cortical disorder, or inhibitory failure, ultimately causing neural circuit disorder and resulting in mental illness. These factors include genetic and non-genetic mechanisms (such as transcription, translation, and translational modification).

One of the most popular areas of research in mental illness is epigenetics, including schizophrenia. Epigenetics refers to DNA molecular modifications (such as DNA methylation and various histone modifications) that can regulate gene activity (such as the frequency of gene transcription) but do not affect the DNA sequence [15]. Several studies have found that the epigenetic regulation of multiple genes, including GAD1 and RELN, is altered in patients with schizophrenia [16]. This provides clues that some epigenetic changes may directly lead to cognitive symptoms and neurodevelopmental abnormalities in schizophrenia. Another study suggests that chromatin modifications caused by histone deacetylases (HDACs) may be the basis for cognitive impairment in a variety of mental disorders [16]. Meanwhile, in animal studies, various epigenetic changes have been found to affect the expression of NMDAR subunits; in human studies, DNA methylation of the NR3B promoter sequence has also been altered in patients with schizophrenia. In summary, all the above research results suggest that the epigenetic regulation of NMDAR may cause pathological effects. However, there is currently no direct data to prove this, but its relevance cannot be denied.

3.2. Neural circuit level dysfunction

In the microcircuits of the cerebral cortex, gamma-aminobutyric-acid-ergic (GABAergic) interneurons expressing parvalbumnin (PV) have the characteristic of fast-spiking and contain a large number of GluN2A subunits on their cell membranes, making PV interneurons highly sensitive to changes in glutamate signals [17]. Under normal physiological conditions, the activation of NMDAR can maintain the high-frequency firing of PV neurons, ensuring that they can generate γ-cortical oscillations that meet the needs of the brain, which provides continuous and precise inhibitory control for downstream pyramidal neurons

When NMDA receptors are dysfunctional, a pathological-grade continuous response occurs. Due to the lack of sufficient excitatory drive in PV interneurons, their activity is reduced, resulting in a significant reduction in the release of GABA in the synaptic cleft, which is the disinhibition response [18]. Subsequently, pyramidal neurons lose their normal inhibitory control, causing the cortex to fall into a state of overexcitation, which ultimately manifests as an excitation-inhibition imbalance. But, E/I imbalance directly disrupts the generation of γ-oscillations(related to working memory and attention.), leading to disordered excitation of neural networks and a decrease in neural networking ability. In clinical manifestations, on the one hand, the overactivation of the hippocampal-ventral tegmental circuit or the mesolimbic pathway may also lead to increased dopamine release, corresponding to symptoms such as hallucinations and delusions in positive symptoms; the reduced network synchronization ability makes it impossible to effectively integrate information, and the decreased NMDAR function in cortical interneurons may lead to increased excitability of glutamatergic projection neurons, resulting in overstimulation of GABAergic interneurons in the ventral tegmental region, which in turn inhibits the dopamine pathway in the

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mesocortex [14], corresponding to cognitive deficits such as impaired working memory and poor concentration in patients. Post-mortem studies have reported GABAergic defects in schizophrenic patients.

4. Case study with knockout the NMDAR on PV interneurons

For a long time, the NMDAR low-function hypothesis has been studied, and it is believed that the expression of calcium-binding protein PV interneurons is the core pathological starting point of schizophrenia [19]. In order to study this hypothesis, several laboratories conditionally knocked out the gene modification of the GluN1 subunit, which is essential for NMDAR in mouse PV interneurons, and named it Grin1ΔPV [20]. However, the behavioral performance of the mice in schizophrenia-related tests showed a large number of differences. Other studies have reported that Grin1ΔPV mice have a protective effect against the hyperactivity induced by the NMDAR antagonist MK-801 [21].

4.1. Experiment methods and design

However, the experiments of Bygrave et al. questioned this hypothesis. The laboratory researchers used the PV-cre driver line and the Grin1-2lox response line to form PV+ neuron-specific GluN1 knockout mice (Grin1ΔPV). Unlike other models, this model has a high coverage. The PV-Cre driver line covers 96% of PV+ cells in the neocortex and 84% in the hippocampus. It can also achieve efficient knockout, reduce the loxP site spacing in the Grin1-2lox line, and make NMDAR more likely to be lost in the early developmental stage. In terms of behavioral assessment, the Grin1ΔPV mice were first comprehensively assessed, including recording and comparing the behavior of hyperactivity induced by different environments, prepulse inhibition (PPI), sucrose preference, learning behavior in the maze, object recognition, memory, and other tests. Secondly, the damage caused by MK-801 pharmacological blockade in the control group and Grin1ΔPV mice was tested and compared. In addition, the effects of MK-801 on Grin1ΔPV mice were evaluated. Grin1ΔPV and control mice were administered MK-801 via intraperitoneal injection, and then tests were performed and recorded, such as quantifying stereotyped behaviors, rigidity, etc. [20].

4.2. Results

Contrary to previous expectations, untreated Grin1ΔPV mice exhibited normal phenotypes in most behavioral tests. In cognitive function assessments, knockout mice showed no significant differences from the control group in working memory and other tasks. In sensory gating tests, no deficit was observed in pre-pulse inhibition (PPI), suggesting a normal sensory information filtering mechanism. Furthermore, pleasure-related behaviors were unaffected, and the sucrose preference test showed no significant difference between the two groups, indicating an intact reward system.

Another finding was that Grin1ΔPV mice did not exhibit a protective response to the NMDA receptor antagonist MK-801, but rather showed a sensitization effect. In terms of motor activity, knockout mice showed a reduction in beam interruption in the early stages of administration (0–60 minutes), which appeared to be "protective," but behavioral scores revealed that they actually exhibited severe catalepsy. This phenomenon was observed in all knockout mice, while the control group showed almost no such behavior. In the late stages (60–90 minutes), after catalepsy was relieved, knockout mice showed hyperactivity instead.

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Further neurophysiological recordings revealed that after treatment with 0.2 mg/kg MK-801, knockout mice exhibited abnormal 4 Hz delta oscillations (3–5 Hz) in the medial prefrontal cortex. These slow waves, which are usually only seen during sleep, may interfere with higher cognitive functions in the waking state, which is highly consistent with the abnormal neural oscillations in patients with schizophrenia. These results together indicate that the loss of NMDAR function in PV+ neurons not only fails to protect the body from the effects of NMDAR antagonists, but also makes them more sensitive to various schizophrenia-related deficits.

5. Conclusion

This article integrates evidence and origin for the NMDAR hypofunction hypothesis, encompassing multiple levels, including pharmacology, neuroscience, and autopsy studies, as well as its neural mechanisms of operation, offering significant theoretical and clinical implications. However, the research by Bygrave et al. presents a crucial challenge to the classic hypothesis. This study found that PV+ neuron-specific NMDAR knockout mice (Grin1ΔPV) exhibited mild phenotypes at baseline and did not show a protective response to MK-801, but rather a sensitization effect. This finding challenges the classic view that PV+ neuron NMDAR dysfunction is the core pathological starting point of schizophrenia, suggesting that the pathological mechanisms of the disease may be more complex, involving the synergistic effects of multiple cell types and brain regions.

This research contributes to the existing body of knowledge by systematizing evidence of the NMDA receptor hypofunction hypothesis, providing an integrated framework for understanding the complex pathological mechanisms of schizophrenia. However, this study is limited by a lack of support from original experimental data, and due to space limitations, the relationship between NMDA receptor dysfunction and specific clinical subtypes could not be explored in depth, which could be addressed in future research.

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