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Dizocilpine (MK-801): The Dual Potential of a Non-Competitive NMDA Receptor Antagonist in Psychiatric Pharmacology

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Abstract. NMDA receptors play a very crucial role in the central nervous system. They are essential for neural transmission, synaptic plasticity, as well as learning and memory. If these receptors malfunction, it can cause various mental disorders. Deszomzipine, as a non-competitive NMDA receptor inhibitor, It has a very prominent influence on the occurrence and development of many mental illnesses. This article mainly conducts a review of it, focusing on the pharmacological characteristics of dezocepine, including its chemical structure and mechanism of action. It also focuses on exploring its application as a research tool in understanding the function of NMDA receptors and simulating related disease models, in order to provide theoretical basis for exploring its potential therapeutic drug value.

Keywords: Dizocilpine; NMDA receptors; nervous system; synaptic plasticity.

1. Introduction

The NMDA receptor (N-methyl-D-aspartic acid receptor), full name N-methyl-D-aspartate receptor, belongs to the glutamate receptor family and is a heteropolymer composed of multiple subunits[1]. It is an important excitatory neurotransmitter receptor in the central nervous system. The NMDA receptor has three coding genes, which encode three subunits: NR1, NR2, and NR3. Among them, the NR1 subunit is the basic unit that constitutes the ion channel, while the NR2 subunit is a regulatory subunit.[2]. The NR1 subunit has a glycine binding site that is essential for forming a functional receptor. Without the expression of this subunit, newborn mice die within a few hours of birth due to respiratory failure. The NR1 subunit has 8 splice variants, which can be formed by rearranging combinations of the 3 exons of the NR1 encoding gene, and it is expressed almost throughout the brain. The NR2 subunit includes four subtypes (NR2A-D). This subunit has a glutamate binding site that regulates receptor activity. The expression of this subunit is regional and time-specific; NR2B and NR2D are widely expressed in the whole brain tissue during embryonic development, while NR2A and NR2C are expressed in the brainstem and cerebellum tissue after adulthood, respectively. In the NMDA receptor complex, NR2 determines the channel's conductivity, kinetic properties, and sensitivity to drugs.NR3 is composed of two subtypes, NR3A and NR3B.NMDA receptors have a high permeability to calcium ions. When activated, they can produce calcium influx, which activates a series of downstream signaling factors involved in signaling between nerve cells[3]. Functional NMDA receptors must contain the NR1 subunit, and multiple NR2 subunits co-assemble with NR1 to form a tetramer.

Dizocilpine (MK-801), also known as dextrorphan maleate, is a non-competitive NMDA receptor antagonist that can reduce receptor function by blocking NMDA receptors. It plays an important role in the treatment of neurological diseases.[4]. The NMDA receptor is related to glutamate, and its receptors are widely distributed in the central nervous system. MK-801, as a non-competitive antagonist of the NMDA receptor, primarily exerts its effects by blocking the NMDA receptor.[5]. Dysfunction of NMDA receptors can lead to a disruption of the balance between the glutamate system and the dopamine system. Antagonism of NMDA receptors can result in insufficient inhibition of cortical GABA interneurons on midbrain glutamatergic neurons, thereby stimulating striatal dopaminergic neurons and promoting dopamine release. Janus et al. [6] administered MK-801 to adolescent rats and subsequently evaluated their cognitive function as well as synaptic growth in hippocampal neurons. The experimental results indicated that MK-801 administration in adolescent rats resulted in significant cognitive deficits and severe impairment of synaptic growth in

hippocampal neurons. These findings closely mirror the cognitive and synaptic abnormalities observed in patients with schizophrenia. This suggests that MK-801 may induce cognitive dysfunction by disrupting synaptic growth mechanisms in neural cells, thereby offering a potential avenue for research on animal models of schizophrenia pathogenesis.Konecny et al.[7] highlighted that MK-801 and its structural analogs, particularly NMDA antagonists, have attracted considerable attention in Alzheimer's disease (AD) treatment research. Their most recent study revealed that Dizocilpine derivatives can effectively block NMDA receptors while avoiding the common psychiatric side effects associated with the parent compound, Dizocilpine. Almeida et al.[8] explored the proteomic alterations elicited by MK-801 in brain slices cultured from adult human donors and examined the impact of both typical and atypical antipsychotics on these MK-801-induced changes. Their findings indicated that MK-801 significantly diminished the signaling of NMDA glutamate receptors in human brain slice cultures. Utilizing mass spectrometry-based proteomics and systems biology approaches, the study identified that the proteomic changes induced by MK-801 implicated a variety of signaling pathways associated with the pathophysiology of schizophrenia. These pathways included Ephrin signaling, opioid signaling, melatonin signaling, Sirtuin signaling, interleukin 8 signaling, endogenous cannabinoid signaling, and synaptic vesicle cycling, among others.

This article will conduct a review of all the application values of the substance MK-801 as an NMDA receptor antagonist in the field of mental disorders. This article will explore in detail how MK-801 mediates the neuroprotective mechanism by blocking the NMDA receptor ion channel and its regulatory role in synaptic plasticity. This article particularly emphasizes its possible role in the treatment of mental disorders such as depression, anxiety and schizophrenia. The review also summarizes the rapid antidepressant effects and cognitive-enhancing capabilities of MK-801 demonstrated in experimental studies, while highlighting its limitations in terms of neurotoxicity and side effects. The review looks ahead to future directions for the development of safer and more effective NMDA receptor antagonists based on MK-801, with the aim of providing a solid theoretical basis for innovative treatment strategies for psychiatric disorders.

2. NMDA receptor antagonists

NMDA receptors are crucial in the maturation of the nervous system. This includes governing neuronal survival, the growth of dendritic and axonal architectures, and involvement in synaptic plasticity. They are pivotal in the establishment of neuronal circuits and are indispensable for learning and memory functions[9].The NMDA receptor is a ligand - gated ion channel. It has several distinct allosteric modulation sites and is highly permeable to Ca2+. These characteristics set it apart from other ligand - gated ion channels. Its activation leads to an increase in intracellular Ca2+ inward flow, which triggers a series of important cascade responses involved in the regulation of a variety of life activities such as synaptic plasticity, nervous system development, pain perception, and so on (Response process, how it affects calcium ion inward flow)[10]. When NMDA receptors function abnormally, it leads to the development of central nervous system and psychiatric disorders such as depression, schizophrenia, Parkinson's disease, and Alzheimer's disease[11].

In depression, glutamate signaling through NMDA receptor overactivation may trigger neuronal excitotoxicity and impair neural circuit function. The function of NMDA receptors may be abnormal in depressed patients. Beneyto et al. [12]found decreased expression of NMDA receptor subunits NR2B, NR1, and NR2A in the medial temporal lobe of depressed patients by examining the changes in glutamate receptor binding in the brains of cadavers with schizophrenia and affective disorders. This suggests that central glutamate receptor dysfunction in depressed patients may result in the inability to transport and metabolize intersynaptic glutamate in a timely manner, causing disorders of intersynaptic glutamate transmitter transmission, which may be an important part of the pathophysiological process of depression.

Anxiety disorders, on the other hand, are closely related to the regulation of fear memory and emotional responses by NMDA receptors, whose overactivity may amplify anxiety, while the modulatory effects of antagonists may significantly attenuate pathological fear responses[13]. Since depression and anxiety disorders are often co-morbid, and the close relationship between abnormal NMDA receptor function and depression has been confirmed, it is reasonable to hypothesize that abnormal NMDA receptor function may also play a role in the pathogenesis of anxiety disorders[14]. Noncompetitive NMDA receptor antagonists, such as ketamine, have demonstrated the potential for rapid relief of depressive symptoms by blocking receptor activity.

The role of abnormal NMDA receptor function in schizophrenia is supported by extensive research. In the pathomechanism of schizophrenia, NMDA receptor hypofunction leads to an imbalance in the glutamatergic system, which further affects dopaminergic neurotransmitter regulation and triggers cognitive deficits and positive symptoms[15]. Moghaddam and Javitt discuss the glutamatergic hypothesis or the NMDA receptor hypofunction hypothesis, which suggests that glutamatergic receptors, especially NMDA receptors in GABAergic interneurons function is impaired, leading to an imbalance between neuronal excitation and inhibition that induces the production of schizophrenia[16]. In addition, NMDA receptor antagonists are capable of triggering schizophrenia-like symptoms in healthy populations and exacerbating disease symptoms in patients with schizophrenia. MK-801 can increase the activity of acetylcholinesterase and monoamine oxidase in mice, suggesting that the mechanism of action of MK-801 may be related to changes in cholinergic neurons[17]. There is an interaction between the cholinergic and dopaminergic systems; acetylcholine can modulate dopamine neurotransmission through acetylcholine receptors, thereby inducing positive symptoms of schizophrenia[18]. To address cholinergic transmission deficits, the cholinergic receptor agonist xanomeline can alleviate schizophrenia-like symptoms in patients and animal models[19]. Prenatal supplementation of choline in mother rats can also alleviate the hyperactivity symptoms induced by MK-801 in adult offspring[20]. Additionally, inhibiting acetylcholinesterase to increase the content of acetylcholine can improve the positive symptoms relating to visual hallucinations in patients[21]. MK-801, functioning as a non-competitive NMDA receptor antagonist, is capable of effectively simulating schizophrenia-related symptoms in animal models and exhibits high specificity. Klimczak et al. [22] constructed a schizophrenia model by administering MK-801 to newborn mice. The regimen involved either chronic intraperitoneal injections of 0.1 mg/kg MK-801 from postnatal day 7 to 13 or a single perinatal injection of 1 mg/kg MK-801, followed by social isolation after weaning.

3. Dizocilpine（MK-801）

MK-801 is a highly selective non-competitive antagonist of the NMDA receptor and has attracted substantial interest in neuroscience research due to its unique chemical structure and pharmacological properties[23]. The core structure of MK-801 is 1-methyl-8-azabicyclo[3.2.1]octane, which is formed by the fusion of a nitrogen-containing octagonal ring with two phenyl rings, constituting the main molecular framework [24]. The 5S,10R isomer of Dizocilpine possesses a three-dimensional structure that enables it to precisely fit into the ion channel subunits of the NMDA receptor[25]. This stereochemistry allows the drug molecule to accurately embed into the receptor binding site, effectively blocking the opening of the ion channel. The nitrogen-containing bicyclic structure of this isomer can form stable van der Waals forces and hydrogen bonds with the inner wall of the NMDA receptor channel, further impeding the channel's opening[26]. When activated, the NMDA receptor is permeable to monovalent ions such as Na+ and K+, and also has high permeability to Ca2+. During the process of neural signal transmission, the ion channel of the NMDA receptor plays a critical role. When glutamate and glycine jointly activate the NMDA receptor, the ion channel opens, allowing calcium ions (Ca^{2+}) and sodium ions (Na^{+}) to flow into the cell. However, the 5S,10R-isomer of Dizocilpine can bind to specific sites within the ion channel through its stereostructure, thus preventing the opening of the ion channel. This blocking effect is non-competitive, meaning that the

drug molecules do not compete with glutamate or glycine for binding sites but act directly on the ion channel itself.[27].

In the synthetic research of Dizocilpine, the design of its synthetic pathway fully reflects the complexity and innovation of chemical synthesis. Typically, the synthesis process starts with benzylideneacetone as the raw material and undergoes five reaction steps to ultimately achieve the target product, with a total yield of about 28%[28]. In the synthesis process of Dizocilpine, the key chemical steps include a nitrogen-containing heterocyclization reaction, which constructs the core framework by introducing a nitrogen-containing heterocycle; hydrogenolysis, which is used to remove halogens or other protecting groups; and an intramolecular nucleophilic cyclization reaction facilitated by boron trifluoride-ether to form a bicyclic core structure. Additionally, the Grignard methylation reaction not only introduces a methyl group but also ensures the accuracy of stereochemistry, while the final desulfonation step removes unwanted functional groups to optimize the synthesis of the molecule. In each step, the optimization of reaction conditions plays a crucial role in the stereochemical purity and synthetic efficiency of the product28]. This efficient synthesis method not only provides high-purity samples of Dizocilpine for pharmacological research but also offers strong technical support for the development of NMDA receptor antagonists.

The neuroprotective effect of Dizocilpine may be due to its blocking action on NMDA receptors. NMDA receptors serve as key channels for calcium ion influx, and their excessive activation can lead to elevated intracellular calcium ion concentrations, triggering a series of pathological reactions such as the generation of reactive oxygen species (ROS), mitochondrial dysfunction, and apoptosis[29]. MK-801-mediated oxidative stress and membrane lipid changes can also affect the membrane potential, osmotic balance, and energy supply of nerve cells by disrupting ATPase. Neural activity consumes a large amount of ATP, and insufficient energy supply at synapses can impair synaptic transmission, ultimately leading to abnormalities in brain function and behavior[30]. In the cerebral ischemia model, MK801 demonstrated significant neuroprotective effects and effectively reduced neuron death caused by ischemia-reperfusion injury[31]. However, in clinical applications, MK801, as a potent NMDA receptor antagonist, may provoke a range of side effects, including cognitive dysfunction, psychiatric symptoms, and potential neurotoxicity.

The NMDA receptor, which is intricately associated with glutamate, plays a pivotal role in the central nervous system as glutamate is a crucial excitatory neurotransmitter. MK-801 functions as a non-competitive antagonist of the NMDA receptor, primarily exerting its effects through receptor blockade[32]. Dizocilpine exerts its neuroprotective effects by binding to the ion channels of the NMDA receptor, effectively inhibiting the influx of Ca^{2+} and thereby attenuating glutamate-induced excitotoxicity. This mechanism confers upon Dizocilpine the potential to provide neuroprotection within the nervous system [33]. In summary, the excessive activation of NMDA receptors can lead to the onset of neurological diseases, causing an imbalance of ions inside and outside the cell membrane, activating neurotoxic signaling pathways, producing neurotoxic effects, and resulting in neuronal cell damage or death, thereby causing a series of neuronal functional disorders.

Tremblay et al. [34] demonstrated that MK-801 can effectively induce a tolerogenic phenotype in primary cultured cortical neurons by transiently blocking NMDA receptors, thereby significantly enhancing the neurons' long-term resistance to a wide range of damage signals. In specific experiments, cortical neurons were briefly exposed to MK-801 for 30 minutes and were subsequently stimulated with various cell death signals, including ischemia models and excitotoxicity-inducing conditions. The results revealed that neurons pretreated with MK-801 exhibited significant resistance to both apoptotic and non-apoptotic cell death. This finding provides compelling evidence supporting the exploration of NMDA receptor antagonists for neuroprotective applications.Given the bidirectional role of NMDA receptors in cognition, excessive inhibition of their activity can actually impair cognitive function. Therefore, how to balance the degree of NMDA receptor inhibition still requires careful consideration. The metabolites of Dizocilpine, including amines and phenolic compounds, are capable of participating in oxidative stress via electron transfer and the generation of

free radicals. Song et al. [35] have shown that the regulation of oxidative stress by Dizocilpine may be closely related to its neuroprotective role.

4. N-methyl-D-aspartate receptor

The NMDA receptor, which is a major excitatory amino - acid receptor in the central nervous system, is extensively dispersed throughout the brain. Among different brain regions, the highest concentration of this receptor is found in the hippocampus, cerebral cortex, striatum, and amygdala. This receptor functions as a cation channel, composed of various subunits, which permits the passage of primarily K^+ and Na^+ when activated, and also allows Ca^{2+} to pass through. The natural NMDA receptor can be voltage-dependently blocked by Mg^{2+}, rendering it an ideal component for molecular coherence detection. The NMDA receptor is mainly composed of three types of subunits, namely NR1, NR2, and NR3, which can produce various subunits through selective splicing of genes[36]. NR1 is the essential subunit of the NMDA receptor, serving as the functional subunit of the NMDA receptor complex, which is necessary for the ion channel function of this receptor, and NR1 forms the ion channel and is the most powerful neurotransmitter receptor in terms of regulation [37]. Through nucleic acid hybridization, immunohistochemistry, and Western blotting techniques, the expression of various subunits of the NMDA receptor has been studied and it was found that NR1 is widely distributed in various brain regions and the spinal cord. There is only one NR1 gene in the organism, named GRIN1, which contains three variable exons: exon 5, exon 21, and exon 22, which produce eight identical forms of the NR1 subfamily through alternative splicing [38]. The differences in NR1 are due to the number and types of these three exons (from N to C) it contains.NR2 is a multi-gene family that includes GRIN2A, GRIN2B, GRIN2C, and GRIN2D, which encode NR2A, NR2B, NR2C, and NR2D, respectively[39]. The distribution of the NR2 family shows distinct regional characteristics, with NR2A and NR2B being predominant in the forebrain and midbrain, NR2C primarily expressed in the cerebellum and various selection nuclei, and NR2D mainly expressed in the midbrain and mesencephalon, but none were found in peripheral tissues. The four NR2 subunits exhibit a certain degree of homology, with NR2A and NR2C showing 55% homology, NR2A and NR2B showing 70% homology, but the homology between NR2 subunits and NR1 subunits is less than 20%[40]. NR2 serves as a regulatory subunit of the NMDA receptors, and does not express independently, and its involvement modifies the functional characteristics of the entire receptor, enhancing the response of NR1 to excitatory amino acids (EAA)[41].

In term of physiological functions, NMDA receptors play multiple roles in the central nervous system. First, during the development of the nervous system, NMDA receptors are involved in neuronal survival, differentiation, and synaptic plasticity by regulating calcium inward flow. Second, NMDA receptors are critical for the formation of higher cognitive functions such as learning memory, and their unique voltage-dependent and ligand-gated properties make them a central molecule in the regulation of synaptic plasticity. Of particular note, NMDA receptors are highly permeable to Ca2+, a property that enables them to mediate intracellular calcium signaling, which in turn regulates multiple downstream signaling pathways. However, aberrant NMDA receptor function has been closely associated with a variety of neurological disorders, including depression, schizophrenia, Parkinson's disease, and Alzheimer's disease, making NMDA receptors an important target for the treatment of neurological disorders.

The mechanism of action of Dizocilpine (MK-801), a non-competitive antagonist of NMDA receptors, is of unique research value. Unlike competitive antagonists, Dizocilpine does not directly compete with the agonist binding site of the NMDA receptors, but exerts its inhibitory effect by binding to sites within the receptor. This mode of action is clearly voltage-dependent, and its inhibitory effect is closely related to cell membrane potential. Electrophysiological experiments show that Dizocilpine displays different inhibitory effects on the two main NMDA receptor subtypes, GluN1/GluN2A and GluN1/GluN2B. Compound 6f showed high relative inhibition (~90% for GluN1/GluN2A), while compound 3l showed moderate inhibition (~50%)[7]..

From a neuroprotective point of view, Dizocilpine showed significant neuroprotective effects in NMDA-induced neurodegeneration models. The mechanism of action mainly involves blocking the inward flow of excess calcium ions, thereby preventing neuronal damage from excitotoxicity. Moreover, Dizocilpine and its derivatives exhibit favorable blood–brain barrier permeability, a crucial attribute for their application as central nervous system agents. Regarding safety, research has demonstrated that Dizocilpine derivatives are well-tolerated within an appropriate dosing range and do not induce significant motor dysfunction or cognitive deficits. These characteristics render Dizocilpine an important pharmacological tool for investigating NMDA receptor function and for the development of therapies targeting related disorders[7].

5. The value of Dizocilpine as a potential therapeutic drug.

MK-801 exerts a potent inhibitory effect on NMDA receptors, characterized by its high affinity and specificity. This has positioned it as a frequently employed agent in modeling schizophrenia through NMDA receptor hypofunction. However, the robust and long-lasting binding properties of MK-801 have also been associated with several adverse effects, such as psychotic-like behavior and cognitive dysfunction, which have limited its clinical application. Studies have shown that MK-801, whether administered systemically or locally within the brain, can induce behavioral and neurological alterations that closely resemble those observed in schizophrenia[42]. Zhao et al found through RNA sequencing that the gene expression in the frontal cortex of mice treated with MK-801 changes, which subsequently affects stress responses and components such as synapses and mitochondrial respiratory chains in the frontal cortex[43]. MK-801 may also regulate the expression of synapse-related proteins by modulating miRNA, which can inhibit translation and/or promote mRNA degradation by binding to the 3'-untranslated region (3' UTR), thereby suppressing protein expression[44]. The levels of iRNA in different regions of the brain of MK-801 treated mice can be upregulated or downregulated. Dysregulated miRNAs target genes associated with GABAergic, dopaminergic, and cholinergic synapses, indicating that these miRNAs are involved in the regulation of these pathways. Additionally, MK-801 also downregulates gene expression in the Wnt/β-catenin signaling pathway, inducing positive symptoms by affecting dopamine transmission. Furthermore, both genetic and epigenetic factors play crucial roles in brain development. Therefore, besides genetic changes, epigenetic alterations are also involved in the pathogenesis of schizophrenia, where the methylation of genes involved in the formation of dopamine, GABA, and acetylcholine can directly impact the onset of the disease[44]. Moreover, MK-801 has been shown to exert potential effects on cognitive function.Li et al. found that in adolescent rats, administration of MK-801 resulted in cognitive deficits and impairments in synaptic growth of hippocampal neurons, findings that are reminiscent of those observed in patients with schizophrenia.[45]. These findings further substantiate the capacity of MK-801 to replicate cognitive deficits characteristic of schizophrenia, thereby offering a crucial experimental model for elucidating the pathogenesis of this disorder.

Consequently, MK-801 and its structurally analogous NMDA antagonists have attracted considerable interest in the realm of Alzheimer's disease treatment research. Song et al.[46] have shown that derivatives of Dizocilpine can effectively inhibit NMDA receptors without inducing the psychomimetic side effects typically associated with the parent compound, Dizocilpine. These derivatives have also been found to mitigate hippocampal damage in models of NMDA-induced neurodegeneration, thereby underscoring their neuroprotective potential.

Almeida et al.[8] investigated the proteomic alterations elicited by the NMDA receptor antagonist

Dizocilpine exhibits potential value in antidepressant therapy. Animal studies have demonstrated that Dizocilpine possesses antidepressant effects across a range of behavioral models. For instance, a low dose of Dizocilpine significantly decreased the immobility time of experimental animals in both the forced swimming test (FST) and the tail-suspension test (TST), indicative of its potential antidepressant properties[47]. Additionally, Dizocilpine was observed to increase the frequency and duration of animals' entries into the open arms in the elevated plus maze (EPM) test. However, its

anxiolytic effect did not reach statistical significance.[48]. These findings indicate that the antidepressant efficacy of Dizocilpine may be modulated by dosage and experimental conditions.

Dizocilpine exerts an inhibitory effect on the excitatory action of glutamate by non-competitively antagonizing NMDA receptors, thereby modulating the equilibrium between excitation and inhibition within the nervous system. This mechanism holds potential for alleviating depressive symptoms, given that individuals with depression frequently exhibit dysfunction of the glutamatergic system. Additionally, Dizocilpine may enhance neuroplasticity by upregulating the expression of brain-derived neurotrophic factor (BDNF), which is crucial for neuronal survival and synapse formation. However, adverse effects such as hallucinations and psychosis have significantly restricted its broad clinical application, confining its use primarily to basic research endeavors.In schizophrenia models, Dizocilpine has demonstrated some amelioration of certain positive symptoms. Wang et al. utilized a phenylcyclohexylpiperidine (PCP)-induced animal model of schizophrenia and observed that Dizocilpine significantly alleviated stereotyped behaviors and normalized aberrant activity levels. This effect is likely due to its mechanism as an NMDA receptor antagonist [49]. However, the impact of Dizocilpine on negative symptoms and cognitive functions appears to be more intricate.

Dizocilpine has shown potential for neuroprotection in neurodegenerative conditions, including Alzheimer's disease (AD), which is marked by neuronal loss and synaptic degeneration [50]. Excitotoxicity, frequently set off by excessive activation of NMDA receptors, plays a crucial role in these pathological processes. Dizocilpine can reduce excitotoxicity and safeguard neurons by blocking NMDA receptors and decreasing calcium influx [51]. Additionally, Dizocilpine might decelerate cognitive decline by modulating synaptic plasticity and maintaining synaptic structure and function.

6. Summary and prospect

This review seeks to thoroughly investigate the potential applications of MK-801 as an NMDA receptor antagonist in the field of psychiatric disorders. It meticulously explores how MK-801 exerts neuroprotective effects and modulates synaptic plasticity by selectively blocking NMDA receptor ion channels. In addition, the review examines the therapeutic potential of MK-801 in treating depression, anxiety, and schizophrenia. It also critically evaluates the rapid antidepressant effects and cognitive improvements demonstrated by MK-801 in various experimental studies. However, it is crucial to address the limitations of MK-801, particularly its neurotoxicity and potential side effects. The review summaries the future prospects of developing safer and more efficient NMDA receptor antagonists, using MK-801 as a prototype, to provide a solid theoretical basis for innovative therapeutic strategies targeting psychiatric disorders.

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