Neurotoxicity Associated with Ketamine: An Antidepressant with Potential Risks

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Abstract. Ketamine is a traditional anesthetic, which has attracted much attention in recent years for its rapid antidepressant effect. It has performed particularly well in the treatment of patients with intractable depression, marking major breakthrough in the area of mental illness treatment. However, with further research, its potential neurotoxicity has gradually emerged, especially in the case of long-term or high-dose use. This article systematically reviews the multifaceted effects of ketamine on the nervous system, pointing out that while it exerts a rapid antidepressant effect through mechanisms such as NMDA receptor antagonism, it can also lead to nerve tissue damage, cognitive decline, mental health problems and addiction risk. The main challenge in this field is to ensure neurological safety while giving full play to its therapeutic benefits, especially when the dose control and monitoring strategies in long-term clinical applications are not yet perfect. Future research should further clarify the relationship between its dose and toxicity, and explore neuroprotective interventions. This review is mainly carried out from the following four aspects: the mechanism of nerve tissue damage, the manifestation of cognitive dysfunction, the impact on mental health and its possibility of addiction. It aims to comprehensively evaluate the neurotoxicity and clinical significance of ketamine, so as to provide a theoretical basis for its safe and reasonable application.

Keywords: antidepressant, ketamine, neurotoxicity, cognitive function impairment.

1. Introduction

Depression is a widespread mental disease that now affects millions of people globally, bringing major challenges to public health. Epidemiological studies show that depression is closely related to high disability rates, increased risk of suicide, and a huge burden on society. Patients usually experience persistent low mood, loss of pleasure, cognitive impairment and functional decline, which reduces the quality of life, and has negative effects on family and society. Although there are various antidepressant therapies to choose from, for example, selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), a large proportion of patients still do not have response to traditional drug treatment, which highlights the urgent need for more effective treatments.

Ketamine, an anesthetic that was mainly used in the surgical environment, has now become a promising fast-acting antidepressant. Its unique mechanism of action makes it different from

traditional monoamine antidepressants. The main pharmacological effect of ketamine is the non-competitive antagonism of N-methyl-D-aspartate receptor (NMDAR), which triggers a series of neuroplastic adaptation changes. In addition to blocking NMDAR, ketamine also interacts with a variety of other receptor systems and ion channels, including AMPA receptors, opioid receptors, GABA receptors, monoaminergic receptors, cholinergic receptors, hyperpolarized activated cyclonucleotide-gated (HCN) channels, and voltage-gated sodium channel and L-type voltage-dependent calcium channel. These interactions together contribute to its rapid antidepressant, analgesic and anesthesia effects. Ketamine has shown rapid and significant antidepressant effects, usually within a few hours, providing relief for the treatment of patients with treatment-resistant depression (TRD). This rapid onset of effect is a significant advantage compared with traditional antidepressants. However, the use of ketamine is not without risks. Its safety includes dose-dependent psychological and physiological side effects, such as dissociation, hallucinations, cardiovascular stimulation, and neurotoxicity that may exist in long-term or high-dose use. It is worth noting that long-term or high-dose deployment of ketamine is associated with changes in brain function structure, including decreased gray matter volume, impaired white matter integrity, and synaptic connection disorders [1]. In addition, the recreational use of ketamine is also associated with urinary system toxicity, cognitive disorders and the possibility of addiction. Therefore, ketamine also has a known potential for abuse and requires careful supervision in clinical practice. Although ketamine is a breakthrough in the treatment of depression, its application must be carefully managed to balance safety and efficacy and make sure that it becomes a useful tool.

2. Neurotoxic research on the usage of ketamine in medicine

Ketamine is a non-competitive N-methyl-D-aspartic acid (NMDA) receptor antagonist, which is globally used in anesthesia, sedation and analgesic treatment. Recently, it has attracted attention for its rapid antidepressant effect. However, there is more and more evidence to show that ketamine when used in long period or high doses, can cause severe neurotoxicity, thus causing structural and functional damage to the central nervous system (CNS). This chapter reviews the mechanism and manifestations of ketamine induced nerve tissue injury, and refers to the findings of neuroimaging studies from animal models, human stem cell-derived neurons and chronic users.

2.1. Nervous tissue injury

Human-induced pluripotent stem cells (hiPSC)-derived striatoid GABA cell projection neurons (SPN),the ketamine exposure has been proven to promote the growth cones, synaptic formation and dendrite development. Ketamine destroys the cytoskeleton dynamics through the activation of glycogen synthase kinase-3β (GSK-3β) and the prohibition of histone deacetylase 6 (HDAC6), resulting in a decrease in neurite length, dendritic density and synaptic connection [2]. These changes, accompanied by the dissociation of the presynaptic part and changes in calcium activity, indicate a functional defect in the neural network, which will lead to serious health problems. In newborn rats, the repeated use of ketamine will downregulate the Notch1 signaling pathway, which is crucial to the differentiation of neural stem cells (NSC). Ketamine reduces the expression of Jagged1, Notch1, NICD1 and Hes1 in the hippocampal dentate gyrus, resulting in impaired proliferation of neural stem cells, impaired differentiation of astrocytes and long-term cognitive dysfunction [3]. Activation of Notch1 by overexpression of Jagged1 or NICD1 can reverse these effects, highlighting the role of this pathway in ketamine-induced developmental neurotoxicity [4]. Long-term use of ketamine is associated with a significant decrease in the volume of gray matter in

the brain, especially in the frontal and parietal regions [5]. Compared with the control group, the volume of gray matter in the upper left and right frontal gyrus of ketamine users was smaller, and the degree of reduction in the volume of gray matter was related to the duration of use of ketamine and the total amount of use. Similar results were also observed in areas, for example, the orbital frontal cortex, medial prefrontal cortex and hippocampus, it plays an important part in executive function and memory. Diffusion tensor imaging (DTI) studies show that the fractional anisotropy (FA) of the frontal lobe and temporal vertex of people who use ketamine for a long time is reduced, indicating that the integrity of the white matter is damaged, and the axial diffusion rate of the right hemisphere is reduced, suggesting axon damage and demyelinating. These changes may be the potential causes of cognitive and mental symptoms frequently reported by long-term users [6]. Resting functional magnetic resonance imaging (fMRI) study shows that thalamocortical and corticocortical connections of ketamine users is disordered. The functional connection in the thalamus, motor area, posterior parietal lobe and prefrontal cortex is weakened, which is related to craving score. In addition, the change in the connection of the default mode network and the enhancement of the anterior cingulate cortex-prefrontal cortex connection are related to the depressive symptoms of long-term users. In short, ketamine exposure, especially in the context of development or long-term high-dose use, can cause serious damage to nerve tissue through a variety of pathways, including GSK-3β/HDAC6 signaling pathway, Notch1 inhibition and glutamic acid-mediated excitotoxicity. These mechanisms can lead to structural defects, such as decrease in gray matter and white matter, functional disconnection of key neural networks, and long-term cognitive and behavioral disorders. Further research is needed to clarify the dose-reaction relationship and determine the protective strategy against ketamine-induced neurotoxicity.

2.2. Cognitive function impairment

The dose of ketamine in sub-anesthesia can cause significant and repeatable damage to core cognitive function, which mainly affects working memory and spatial memory. The structural and functional brain changes described above are related to measurable cognitive defects. Patients with long-term use of ketamine show damage in spatial ability to memorize, executive function and episodic memory, which is related to hippocampal and prefrontal lobe atrophy. In newborn rats, ketamine-induced neural stem cell disorders lead to persistent defects in spatial learning in adulthood, which was confirmed by the Morris Water Maze Test [7]. In the lateral prefrontal cortex (LPFC) of primates, an area that is crucial for advanced cognition. Ketamine selectively destroys working memory performance in natural tasks, while retaining perception and motor ability. This behavior defect is caused by the fundamental disturbance of microcircuit function, which is characterized by the differential regulation of neuronal subtypes: ketamine inhibits the activity of fast-spiking inhibitory interneurons, while increasing the activity of broad-spiking excitatory neurons [8]. This destruction of the excitation-inhibition balance reduces the spatial tuning of the memory position of individual neurons and reduces the information content encoded by the neuron group, which ultimately impairs the network's ability to maintain stable working memory characterization. In addition, in the neural circuit between the medial entorhinal cortex (MEC) and the hippocampus - in the neural infrastructure that is crucial to spatial navigation and memory - ketamine can lead to the serious disintegration of spatial characterization. It significantly increases the discharge frequency of MEC excitatory neurons, destroys the time discharge frequency relationship between cell pairs (which is a necessary condition for stable spatial coding), and inhibits the activity of hippocampal place cells. This leads to a serious loss of spatial information, making it impossible for animals to accurately navigate or remember the spatial position. This finding is also

confirmed by the significant reduction in the accuracy of the group decoder that predicts the position of animals [9]. After this acute "spatial decoherence" stage, the system will undergo a long-term reorganization, manifested as a continuous remapping of the MEC spatial discharge mode. In general, the research results of these cross-species and specific brain circuits show that the damage of ketamine to cognitive function is a direct consequence of its destruction of the subtle NMDA receptor-mediated balance in the microcircuit, which leads to the collapse of the tuning of individual neurons and the coding mechanism at the group level, and these mechanisms System is necessary for memory and navigation.

2.3. Mental health damage

Long-term non-medical use of ketamine is associated with serious mental health impairment, which is characterized by a high incidence of insanity and depressive symptoms. In a cross-sectional study of individuals with ketamine use disorder, more than 70% of patients had symptoms such as some forms of hallucinations and delusions, while 64% of patients reported comorbid depressive symptoms [10]. The severity of these clinical manifestations is also closely related to potential neuroanatomical changes, because the reduction in the thickness of the left lower and left superior temporal gyrus is negatively correlated with the severity of negative symptoms, while the thinning of the cortex in the left central anterior is combined with a higher depression score. The concentrated manifestation of this mental symptom and the extensive thinning of the cortex (especially in the frontal and parietal areas) highlight the serious mental health burden caused by the long-term use of ketamine and highlight its overlap with the symptoms observed in primary mental illnesses such as schizophrenia. In addition, the study also revealed a dose-dependent relationship. That is, the greater the use of ketamine, the more serious the thinning of the cortex of the right lower parietal lobe and the right anterior midfrontal lobe, which indicates that the greater the use, the more obvious the abnormal manifestation of the brain structure [10]. These findings show that ketamine abuse can not only cause acute psychological disorders, but also lead to persistent changes in brain structure, which are the basis of persistent mental health disorders and provide an important model for understanding substance-induced mental and emotional disorders.

2.4. Addiction

Because ketamine has a hallucinogenic effect, its abuse has become a major public health problem. It can lead to impaired cognitive and sensory function, and also cause long-term brain damage. This study gives key perspective into how chronic use of ketamine can change the dopamine system of the brain, which is the core of the reward and motivation pathway. Researchers found that repeated use can lead to dose-dependent and different changes in dopamine neuron populations and their long-range projections. Specifically, they observed a decrease in the number of tyrosine hydroxylase-positive (TH+) neurons in the midbrain region related to behavioral states (such as the dorsal raphe [DR], which regulates social behavior, and the posterior raphe [RR], which can cause fear). At the same time, the number of TH+ neurons in similar areas of the hypothalamus (such as the arcuate nucleus [ARH]) increased. These extensive structural changes are accompanied by changes in innervation in key areas; the projection of the prefrontal lobe region (such as the cingulate cortex, which is related to reward processing and decision-making) is increased, while the projection of the sensory area (such as the auditory and visual cortex) is reduced. This non-uniform plasticity is facilitated by a group of TH mRNA+ neurons in a state of translation inhibition, which can achieve rapid adaptation. This mechanism may be the reason for the significant reorganization

of neural networks, which in turn leads to long-term cognitive and behavioral changes associated with ketamine addiction.

3. Conclusion

Current evidence shows that although ketamine is a fast-acting antidepressant, it has a significant risk of neurotoxicity, especially in the case of long-term or high-dose use. Comprehensive research results show that ketamine can cause extensive structural and functional damage to the central nervous system. These damages include direct nerve tissue damage, manifested as disorders in the process of synaptic generation and dendritic maturation in human neurons, and neurodevelopmental disorders caused by the Notch1 signaling pathway in animal models. Neuroimaging studies of long-term users have also confirmed these findings, showing a decrease in gray matter volume, impaired white matter integrity, and interruption of connections in cognitive and emotional networks. In addition, the use of ketamine can also lead to serious cognitive defects, mainly by destroying the excitation-inhibition balance in microcircuits, which is crucial for working memory and spatial characterization. The association between long-term use and severe mental health disorders, including psychosis and depression, is associated with the thinning of the cortex, which highlights its huge mental health burden. Crucially, the addictive potential of ketamine is supported by evidence of different morphological remodeling of the brain's dopamine system, which changes the neuronal group and their projection in the reward and behavioral state loop. This non-uniform plasticity may be a potential cause of long-term behavioral changes associated with addiction. Therefore, although ketamine provides a novel therapeutic mechanism, its application must be strictly managed. The balance between its rapid antidepressant effect and potential neurotoxicity, cognitive impairment and addiction requires careful dose control, monitoring of treatment duration, and further research on protective strategies to mitigate these adverse effects and ensure its safe use in clinical practice.

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