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Neurobiological mechanisms of Antidepressant effects of ketamine

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Abstract. The primary component of the drug ketamine, ketamine is a white powder derivative of phenylcyclohexylpiperidine that is widely used as an analgesic and dissociative anesthetic. Ketamine is an N-methyl-d-aspartate (NMDA) receptor antagonist that comes in levo- and dextro-conformations. It acts on the NMDA receptor and can quickly relieve depression symptoms; its effects last for a few days to a couple of weeks. Its antidepressant qualities have been established during the last 20 years, and ketamine research has made significant strides and discoveries lately. From a neurobiological perspective, this paper presents the primary molecular pathways via which ketamine considerably reduces depressed symptoms. It also summarizes and looks ahead to future directions for ketamine and depression research. It also gives us a deeper understanding of the antidepressant mechanism of ketamine and offers a theoretical framework for the creation of novel antidepressant medications. In the meantime, the quick antidepressant action of ketamine offers fresh perspectives on how to treat depression, which is anticipated to encourage innovation in the field. It also offers new ideas for treating other mental illnesses, like bipolar disorder and anxiety disorders.

Keywords: neurobiology, ketamine, depression.

1. Introduction

Throughout the world, depression affects hundreds of millions of individuals, negatively affecting their social functioning and quality of life. While there are many different antidepressant drugs on the market, the majority of them don't work for many patients and take several weeks to start working. As a result, researchers are focusing a lot of their efforts on finding new, fast-acting antidepressant therapies. It has recently been discovered that ketamine, an unusual anesthetic, provides strong, quick antidepressant effects. In 1985, ketamine was added to the World Health Organization's List of Essential Medicines, despite its initial synthesis in 1962. In the medical setting, ketamine is typically administered as a general anesthetic due to its ability to cause dissociative anesthesia. It is currently listed in China as a Schedule I restricted substance. Clinical investigations conducted in 2000 revealed that sub-anesthetic ketamine dosages have immediate and sustained antidepressant effects on depression [1]. 2019 saw the official approval of esketamine nasal spray as a standard medication for depression by the US Food and Drug Administration. The S-enantiomer of ketamine is the primary ingredient in esketamine, yet there are still some unwanted effects. Although its antidepressant mechanisms are not entirely known, ketamine's most remarkable qualities are its lengthy duration of action and quick therapeutic efficacy in treating depression. This article presents the neurobiological ideas behind the numerous widely accepted

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pathways by which ketamine significantly improves depression. This work offers a thorough investigation of the neurobiological underpinnings of ketamine's antidepressant effects, which is highly significant both theoretically and clinically. It also offers a valuable theoretical framework and useful recommendations for the creation of new antidepressant medications and the management of depression. From a theoretical perspective, it guarantees the safe and efficient use of ketamine in the treatment of depression and offers additional scientific guidelines for its practical application. Ketamine's rapid onset of action offers patients with depression a new therapeutic option, particularly for those with refractory depression and a high risk of suicide. Its antidepressant mechanism of action also serves as a valuable guide for the development of new antidepressant medications, which can aid in the creation of medications with less side effects and longer duration of action.

2. Current research

2.1. Increasing the number and function of dendritic spines on Layer V Pyramidal Neurons

A single dose of ketamine has been demonstrated to improve the quantity and functionality of dendritic spines on layer V pyramidal neurons in the mPFC by electrophysiological and morphological studies. This includes a rise in the number of large-diameter mushroom spines with high levels of synaptic effectiveness, as well as an increase in the frequency and amplitude of excitatory postsynaptic currents caused by serotonin and hypothalamic secretion [2]. Studies have revealed that mice displaying depressive-like behavior have lower dendritic spine density, fewer phosphorylated CREB levels, and lower amounts of the proteins NRBP1 and BDNF in the mPFC. R-ketamine administered intraperitoneally has an antidepressant effect via stimulating the production of dendritic spines and the expression of the proteins BDNF and NRBP1 [3]. Furthermore, R-ketamine's antidepressant effects may be facilitated by CREB-BDNF signaling in mPFC microglia (Figure 1).

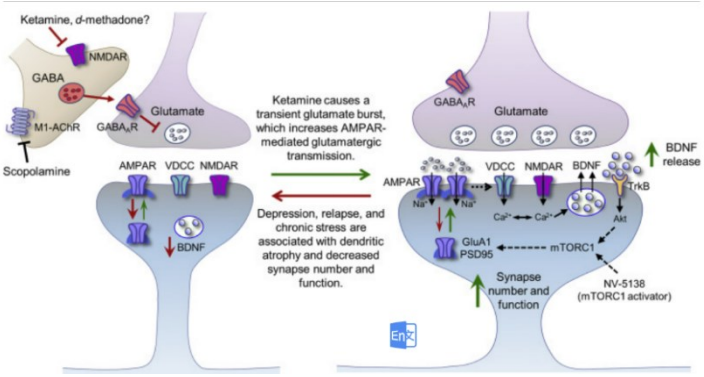

Figure 1. The stimulation of AMPAR activity, BDNF release, and the mTORC1 signaling pathway underlie the rapid and sustained antidepressant effects of ketamine [4]

The mTOR complex 1 (mTORC1) pathway is a crucial downstream signaling route that regulates neuronal activity, neurotrophic factor signaling, amino acid levels, and energy consumption. It is responsible for the protein synthesis-dependent synaptic plasticity. Increased levels of the phosphorylated and activated versions of mTOR, eukaryotic initiation factor 4E-binding protein 1 (4E-BP1), and p70 ribosomal S6 kinase (p70S6K) in the mPFC are indicative of the rapid activation of mTORC1 signaling by low-dose ketamine [3].

Ketamine can suppress spontaneous glutamate release-induced postsynaptic NMDA receptor (NMDAR) activity by directly acting on glutamatergic pyramidal neurons in the mPFC and hippocampus. This initiates the intracellular signaling cascade necessary for quick and long-lasting antidepressant responses. As a result of eukaryotic elongation factor 2 kinase (eEF2K or CaMKIII) being inactivated by ketamine's blocking of resting NMDARs, eEF2 phosphorylation is reduced, BDNF is translated and released, and pyramidal neurons in the hippocampus CA1 synaptically are enhanced [5].

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2.2. Regulation of GABAergic and Glutamatergic Neurotransmission

Abnormalities in neurotransmission and neuronal plasticity may result in aberrant connection patterns within large-scale brain networks in individuals with major depressive disorder (MDD) and bipolar disorder (BD) [6]. Studies on humans and animal models of depression have shown that network dysfunctions are linked to changes in brain glutamate and gamma-aminobutyric acid (GABA) levels [7]. Together, glutamatergic neurons and GABAergic inhibitory interneurons, two diverse neuronal populations found in the neocortex and hippocampus, preserve the equilibrium between excitation and inhibition. Research has shown that whereas subanesthetic dosages of ketamine encourage excitation, anesthetic concentrations block the excitability of both cell types. The selective blocking of NMDARs on GABAergic interneurons by subanesthetic dosages of ketamine is demonstrated by in vivo electrophysiological recordings and two-photon calcium imaging in rodents [8]. This results in an indirect disinhibition of glutamate neurotransmission.

2.3. Ketamine Inhibits Burst Firing of the Lateral Habenula (LHb)

The lateral habenula (LHb) is involved in depression and the negative reward mechanism. It also controls the dopaminergic and serotonergic systems. Behavioral despondency and anhedonia are brought on by LHb neurons firing suddenly. Experimental pharmacology and modeling suggest that NMDARs and low-voltage-sensitive T-type calcium channels (T-VSCCs) are necessary for LHb burst firing. It is sufficient to locally block T-VSCCs or NMDARs in the LHb to produce fast antidepressant effects. Ketamine suppresses downstream monoaminergic reward regions and quickly improves mood by preventing LHb neurons' NMDAR-dependent burst activity [9].

Ionotropic glutamate receptors, or NMDARs, are important mediators of synaptic plasticity because they permit cation flow. NMDARs are heterotetrametric complexes made up of four subunits: two GluN1 subunits, which are required, coupled with either $GluN_3$ (GluN3A and B) or GluN2 (GluN2A, B, C, D) subunits. Complex receptor characteristics, including as glutamate binding, channel conductance, inactivation, and calcium permeability, are determined by the subunit makeup [10]. An important relationship exists between NMDARs and AMPA receptors (AMPARs). Ketamine can enter and block NMDAR channels by opening them and removing Mg^{2+} blockage from the channel pores by AMPAR-mediated postsynaptic membrane depolarization.

Ketamine is an NMDAR channel blocker that is activity-dependent. For up to 24 hours in mice and about a week in humans, ketamine can block NMDARs and prevent burst firing in the LHb. Ketamine's long-lasting suppression of NMDARs is activity-dependent rather than the result of endocytosis. The antidepressant effects of ketamine treatment can be shortened or prolonged depending on when the LH-LHb circuit is activated. According to research, ketamine's long-lasting antidepressant effects within a day are mediated by long-term blockage of NMDARs in the LHb area [11].

2.4. Ketamine Influences the Expression of Inflammatory Mediators and Pathways in Microglial Cells

Ketamine can change how signal transducers and transcription factor activators bind, which can have an impact on the transcriptional control of genes that have STAT3 binding sites in their promoter regions later on [12]. In the presence of ketamine, genes that were tested using chromatin immunoprecipitation assays exhibited a substantial increase in STAT3 occupancy. Similar gene expression profiles are produced in microglial cells by exposure to ketamine and its two active metabolites, where STAT3 regulates the Type I interferon pathway. The control of downstream gene expression is linked to the alteration of STAT3 intracellular location caused by ketamine or its metabolites [13]. Important signaling pathways including AKT/PI3K/mTOR and the Type I interferon pathway are regulated by STAT3, a transcription factor and signaling mediator for a range of pro-inflammatory cytokines (such IL6 and IL10) [14]. These molecular pathways are complex since ketamine affects neurotransmission, neuroinflammation, and intracellular signaling. Furthermore, via its interaction with EEF2, STAT3 mediates a portion of the antidepressant effects of ketamine. Memory consolidation, synaptic plasticity, and protein translation are all correlated with EEF2 [15].

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2.5. Ketamine and hypothalamic-pituitary-adrenal (HPA) axis regulation

An important part of the neuroendocrine network, the HPA axis is a neuroendocrine system that regulates immune response, mood and emotions, digestion, and energy consumption and storage, among other physiological activities. From the simplest invertebrates to humans, many species have an HPA axis. It controls glucocorticoid levels by coordinating the actions of glands and utilizing feedforward and feedback loops. Because of the different times at which glucocorticoids are released during the circadian rhythm, the paraventricular nucleus of the hypothalamus is extremely responsive to external physiological cues, such as the light/dark cycle. The sympathetic autonomic nervous system can quickly release glucocorticoids from the adrenal glands, which are normally linked to acute stress [16]. Glucocorticoids mediate the body's reaction to stress.

Birnie et al. found that after subanesthetic dosages of ketamine were infused, repeated blood sampling in undisturbed, freely acting rats showed considerable corticosterone release. The results confirm that the HPA axis activity, not the effects of the sympathetic nervous system on adrenal activity, is directly responsible for this reaction. The time of ketamine treatment may be important for HPA axis activity; when glucocorticoids do not frequently bind to receptors, corticosterone levels rise dramatically when ketamine is delivered at equal dosages during periods of inactivity [17]. The effects of subanesthetic doses of ketamine on sympathetic nervous system activity and their impact on HPA axis function warrant further investigation.

2.6. Ketamine influences brain functional connectivity and brain network activity

Current research indicates that ketamine has a variety of impacts on brain connections, but its importance cannot be understated. Hallucinations and dissociation are two of the many negative effects of ketamine that are linked to these effects as well. Through its representational hub, the posterior cingulate cortex (PCC), ketamine reduces the functional connectivity of the Default Mode Network (DMN) to the dorsal nexus (DN), the pregenital anterior cingulate cortex (pgACC), and the medioprefrontal cortex (mPFC). Furthermore, by 24 hours after infusion, ketamine had broken the connection between the pgACC, mPFC, and contralateral dorsomedial prefrontal cortex (dmPFC) [18]. While thalamo-cortical connection is largely unchanged, there is a substantial correlation between increased sedation levels (awake, light, and heavy) and reduced connectivity between the mPFC and the DMN as well as between the left executive control network (ECN) and the right ECN [19].

Additionally, ketamine has a major impact on hippocampal connection. Research has revealed that ketamine causes hippocampus networks that are prone to emotional and cognitive disorders to become more hyperconnected. Ketamine decreases connectivity in the auditory and somatosensory networks associated with the physical and emotional processing of pain, such as the ACC, insula, and amygdala, according to research using resting-state fMRI (rsfMRI) [20].

Prefrontal cortex (PFC) and left hippocampal hyperconnectivity is caused by acute ketamine treatment. Ketamine reduces functional connectivity in the frontotemporal and temporoparietal regions and increases hippocampal Glx (glutamate + glutamine—an indicator of enhanced excitatory neurotransmission). This points to a possible connection between higher Glx levels and changes in connectivity. These results suggest that changes in resting-state networks and elevated glutamatergic transmission in the hippocampus may result from NMDA receptor hypofunction [21]. Additionally, ketamine reduces the connection between the frontal and parietal lobes mediated by NMDA and AMPA receptors. Ketamine's blockage of the NMDA receptor increases the activity of the AMPA receptor, which in turn increases the activity of the mTOR pathway, triggering the manufacture of synaptic proteins including synapsin and Arc [22]. These studies underscore the complex and multifaceted impacts of ketamine on brain network connectivity, highlighting both its therapeutic potential and associated challenges.

3. Conclusion

Presently, depression stands as the most prevalent mental illness, impacting more than 2 billion individuals globally and contributing to around 800,000 suicide deaths annually. Common side effects

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of mainstream antidepressants include significant non-response rates and delayed onset of action. Examples of these include selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs). In individuals with severe depression and bipolar disorder, ketamine exhibits strong and quick antidepressant effects that peak 24 hours after a single intravenous infusion, beginning as early as 40 minutes after the infusion. However, 1-2 weeks after administration, the effect on depression diminishes. Fewer trials have demonstrated the effectiveness of ketamine in treating depression longer than one week, and even fewer beyond two weeks.

The limited data in favor of ketamine may be explained by variations in patient etiology and subtypes, ketamine dosage, delivery route, and pharmacokinetics [23]. Designing antidepressant medications with a rapid onset and an extended half-life is therefore crucial. Ketamine's quick antidepressant effects have spurred a surge of basic, translational, and clinical research, but these developments have not yet resulted in clear-cut molecular frameworks or innovative therapeutic strategies. Although slow-acting antidepressants have well-defined receptor targets, compared to commonly used chronic antidepressants, finding comparable effective drugs with receptor targets or other parts of ketamine's mechanism similar to ketamine's has been generally unsuccessful.

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