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Ketamine-Based Treatment of MDD: a Biologist's Perspective

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Abstract

Ketamine's potential as a fast-acting reagent to treat MDD, especially treatment-resistant depression has caught much attention recently. Although much has been learned about the biological mechanisms underlying ketamine's effect, there are a few critical issues remained to be resolved. This mini review will briefly discuss several controversial issues that warrant further studies, regarding the molecular, physiological, psychopharmacological, and behavioral effects of ketamine. Understand how ketamine works as an anti-depressant will open the door to better understanding of MDD and its treatment.

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Introduction

Despite current available antidepressants, major depressive disorder (MDD) presents as a major threat to public health, with a lifetime prevalence of 17% in the United States and 40-50% of patients unresponsive to treatment[1]. Moreover, the slow onset of therapeutic efficacy that usually takes 3 - 4 weeks is especially unhelpful for patients with suicidal ideation. Combined with treatment for resistant and accompanied comorbid anxiety disorders, a novel and rapidly acting antidepressant is highly desirable[2].

Ketamine is a low-affinity, activity-dependent, open channel blocker of NMDA subtype glutamate receptors (NMDARs). Ketamine has been shown to be effective in treating major depressive disorder (MDD), including treatment-resistant depression, with a rapid onset (on the order of hours) of efficacy and effective duration of days to weeks[3-5]. A few potential issues have been identified during the clinical testing of ketamine, which need to be resolved before ketamine or its derivatives/metabolites could be widely applied clinically. These improvements should come from a better understanding of biology of ketamine's efficacy. In this review, we will discuss the proposed biological mechanisms and critical unresolved issues related to ketamine's anti-depressant effects.

Clinical Effects and Potential Biological Mechanisms

After the serendipitous discovery of its antidepressant effects, ketamine has been successfully applied as a fast acting treatment of MDD in a clinical setting, especially for treatment-resistant MDD patients[3-5]. Its short-lasting and quick dissipating antidepressant properties requires repeated administration to keep its efficacy, while repetitive administration is severely limited by psychostimulant effects and addictive potentials[6]. It is in debate as whether these two side effects may be intricately connected to ketamine's antidepressant effects[7].

A few biological mechanisms have been proposed for ketamine's anti-depressant effect: (1) blockade of NMDARs on the GABAergic inhibitory neurons leads to reduced activation and enhanced excitation in the brain, the so called disinhibition hypothesis[8]; (2) blockade of NMDAR on the excitatory neurons at rest results in rapid protein synthesis of BDNF via reduced phosphorylated eEF2[9]; (3) increased mTOR signaling and increase in dendritic spine density in the excitatory neurons[10]; (4) reduced GSK-3 signaling[11]. The above mechanisms are likely to be connected or shared, rather independent of each other.

Critical Unresolved Questions for Moving Forward

Although ketamine has shown huge potentials to be a major breakthrough in treating MDD, especially treatment-resistant depression, there are a few critical unresolved issues. A better understanding of these issues will not only facilitate ketamine's approval for clinical use, but also provide important biological insights into the pathogenesis of MDD and its more effective treatment.

Is there anything special for ketamine as NMDAR antagonist In addition to ketamine, various NMDAR antagonists have been tested for their anti-depression efficacy, all with inferior efficacy than ketamine but some with better side-effect profiles12. A few things worthy of further considerations: (1) High-trapping vs. low-trapping (see below); (2) targeting NMDARs at rest. Some recent works have suggested that ketamine's effect is mediated via its inhibition of NMDAR at rest with physiological Mg2+ concentration. Interestingly, memantine does not target NMDARs at rest13 and also lacks anti-depressant effect14-15. (3) Subunit selectivity required? Clinical studies have shown that the efficacy of selective GluN2B antagonist in treating MDD does not occur until 5 days after

administration16-17. The possibility that selective antagonist affects less number of NMDARs than ketamine and hence takes longer to show effect needs to be tested. A few preclinical studies of GluN2B antagonists have also demonstrated anti-depression effect, with the absence of it in the GluN2B KO mice10, 18.

Addictive potential: As one of the popular recreational drugs, Ketamine's psychostimulant effects are also deemed to induce addictive behaviors19. It is still in debate as whether ketamine directly impacts the reward system (the dopaminergic projections from the ventral tegmental area (VTA) to the nucleus accumbens (NAc)), or only strengthens the associations between drug related contextual stimuli and drug intaking, which drives ketamine usage at certain conditions as a maladaptive memory. In other words, whether ketamine itself encompasses positive and negative reinforcing potency and elicits compulsive drug intake still need to be clarified20.

Dissociative thoughts: Originally used as an anesthetic and analgesic drug due to it dissociative effects and distinct from other canonical anesthetic drugs, ketamine induces psychotropic effects ranging from dissociation to schizophrenia-like symptoms (positive, negative, and cognitive deficits)21. NMDAR antagonism is likely a trigger of the persistent psychosis since another NMDAR antagonist, PCP, also induces persistent psychosis22. Interestingly, memantine, a drug approved for treating Alzheimer's disease, did not induce dissociative thoughts or psychosis14-15. Some studies have suggested these differences are caused by their different trapping characters, the off rate where high off rate (low trapping) was deemed to easily leave the channel as it closes and thus the channel function recovers. Ketamine showed an 86% trapping while mematine showed 50-70% trapping23. Most patients felt dissociation-like psychotomimesis at ketamine concentration of 50-100 ng/ml, well below the concentration required for antidepressant effect (150-200 ng/ml). Another low-trapping NMDAR antagonist AZD6765 did not induce dissociative symptoms but also exhibited limited anti-depressant effect24. This also applies to other NMADR antagonists tested on MDD patients25. In various preclinical animal models of depression, R-ketamine has been shown to have superior anti-depressant efficacy and longer-lasting effect than S-ketamine. More impressively, it has also been shown that R-ketamine is effective in a depression model refractory to the current medication for MDD patients 26-27. Interestingly, it has also been shown that R-ket does not produce the undesirable psychotomimetic effects in animals28.

Can AMPAR potentiators be an alternative and perhaps a better option? A recent study by Zanos and colleagues demonstrated that one of the main metabolites of ketamine, 6-hydroxy norketamine ((2R,6R)-HNK), is the main mediator of ketamine's anti-depressant effect29. Most importantly (2R,6R)-HNK is not a NMDAR antagonist, but rather an AMPAR potentiator. This raises a very important question about whether NMDAR antagonism is required for ketamine's efficacy, and furthermore, whether AMPAR potentiator could be a better alternative due its lack of additive potential in triggering dissociative thoughts. Positive allosteric modulators that enhance AMPAR activity (such as the CX series Ampakines) has shown significant benefits in various preclinical tests30, but ultimate did not proceed in clinical trials due to potential pathological concerns.

Is synaptic plasticity required? The fact that repetitive infusion of ketamine is required to prevent relapse of depressive symptoms suggests that no lasting changes have occurred with ketamine administration and hence unlikely plasticity is required for its efficacy. Furthermore, although preclinical studies have shown increased density of dendritic spines and increased number of AMPARs9-10, no study has demonstrated a

clear increase of synaptic connections in an input-specific manner. If new connections are formed, where do the presynaptic inputs come from? Are they branching off the existing ones or converting silent synapse into functioning ones? A possible mechanism is that ketamine induces metaplasticity to alter the subsequent generation of plasticity. Preliminary report showed ketamine may exert antidepressant effects via modulation of metaplasticity31.

What major brain regions are involved? Two likely regions are hippocampus and PFC, and it will be quite informative to compare ketamine and its metabolite, or other NMDAR antagonists, or AMPAR potentiators, to understand whether they activate distinction brain regions.

Summary and Future Directions

Ketamine offers a golden opportunity, to both serve as an anti-depressant drug and to our better understanding of the pathology of MDD. One of the critical questions is whether NMDAR antagonism is required for ketamine's fast action. Once we are sure of this, the path forward is straighter.

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