How does ketamine elicit a rapid antidepressant response?

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Abstract

A single sub-psychotomimetic dose of ketamine, an ionotropic glutamatergic n-methyl-d-aspartate (NMDA) receptor antagonist, produces a fast-acting antidepressant response in patients suffering from major depressive disorder. Depressed patients report alleviation of core symptoms within two hours of a single low-dose intravenous infusion of ketamine with effects lasting up to two weeks. The rapidity of ketamine action implies that major symptoms of depression can be alleviated without substantial structural plasticity or circuit rewiring. Therefore, the ability of ketamine to exert a rapid effect provides a unique opportunity to elucidate the types of acute synaptic plasticity changes that can be recruited to counter depression symptoms.

Keywords

Introduction

In the last decade, clinical studies have demonstrated that intravenous administration of a low dose of ketamine triggers a rapid antidepressant response in patients with major depression [1–3] including treatment resistant depression [2,3] and bipolar depression [4,5]. These studies have bolstered the hope that patients that do not respond to traditional antidepressants, which target monoaminergic neurotransmission and typically take several weeks to show efficacy, can be treated rapidly with ketamine. Antidepressants with a rapid onset of action are particularly needed for patients at increased risk for suicide, as the long time frame required for the efficacy of classical antidepressants limits their use in emergency circumstances.

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Ketamine is a non-competitive glutamate N-methyl-D-aspartate (NMDA) receptor antagonist that binds to the open channel pore. Recent studies demonstrated that the antidepressant-like action of ketamine could be modeled in animals [6–8]. These studies also showed that similar to classical antidepressants, ketamine requires expression of brain-derived neurotrophic factor (BDNF) [6,9]. However, while ketamine triggered acute translation of BDNF protein was essential for its rapid antidepressant effects [6], ketamine action was not sensitive to inhibition of transcription and ketamine administration did not elicit an increase in transcription of BDNF mRNA arguing against the role of transcription dependent processes [6].

Classical antidepressants take several weeks to show efficacy. To explain their mechanism of action, there has been significant interest in long-term processes that rewire neuronal circuits. There is some evidence that such long-term circuit level reorganization may require neurogenesis and depend on transcriptional alterations as well as chromatin remodeling [10–12]. In contrast, ketamine exerts its action within hours, shortly after its clearance, thus pointing towards a fundamentally different mechanism that may nevertheless require BDNF signaling albeit in a much faster time frame. Therefore, the ability of ketamine to exert a rapid effect indicates that major symptoms of depression can be alleviated without any requirement of substantial circuit rewiring. This basic aspect of ketamine action provides a unique opportunity to elucidate the types of acute synaptic plasticity changes that can be recruited to counter depression symptoms. In addition, the NMDA receptor blocking action of ketamine is a biophysically well-characterized process, which makes it possible to identify specific signal transduction events that link NMDA receptor blockade by ketamine to subsequent elevation in BDNF levels.

How does blockade of NMDA receptors elicit plasticity?

Ketamine as well as other NMDA receptor antagonists produce rapid antidepressant-like effects in mouse behavioral models that are dependent on rapid protein synthesis of BDNF [6]. This study demonstrated that rapid synthesis of BDNF requires deactivation of eukaryotic elongation factor 2 (eEF2) kinase and decreased phosphorylation of eukaryotic elongation factor (eEF2). Experiments in animal models showed that ketamine-mediated blockade of NMDA receptors at rest deactivates eEF2 kinase, resulting in a reduction of eEF2 phosphorylation and desuppression of BDNF translation [6,13,14]. These effects were not mimicked by alterations in neuronal activity levels in vivo, suggesting that spontaneous glutamate release and subsequent NMDA receptor activation that occurs independent of action potentials comprise the primary target for low dose ketamine action [6]. In agreement with this premise, inhibitors of eEF2 kinase have been shown to trigger fast-acting antidepressant-like effects in mice, while ketamine does not produce an antidepressant effect in eEF2 kinase knockout mice [14]. These findings support the hypothesis that suppression of spontaneous neurotransmission mediated NMDA receptor activation is necessary and sufficient to trigger antidepressant-like responses [15,16]. A key role for BDNF in mediating antidepressant efficacy has previously been established by multiple studies [17]. Previous work has demonstrated that BDNF is required for behavioral responses to classical antidepressants [18]. BDNF expression in the hippocampus is increased by antidepressants [19] and BDNF deletion in the hippocampus attenuates antidepressant behavioral responses

[20]. Moreover, intraventricular or intrahippocampal BDNF infusion mimic antidepressant behavioral effects in rodents [21–23]. In addition to BDNF, experiments have shown that the rapid antidepressant effect of ketamine requires activation of BDNF's canonical receptor TrkB, indicating potential involvement of intracellular signaling cascades downstream of TrkB activation are required for the maintenance effects of ketamine [6]. For instance, BDNF is a potent endogenous activator of mTOR, which has also been suggested to underlie the antidepressant action of ketamine [7].

These studies have also shown that acute suppression of spontaneous NMDA receptor mediated neurotransmission potentiates synaptic responses in the CA1 regions of rat and mouse hippocampus that depend on eEF2 kinase function, BDNF expression, and increased surface AMPA receptors [14]. These findings demonstrated an unexpected dynamic impact of spontaneous glutamate release on synaptic efficacy. The key role for blockade of spontaneous NMDA receptor-mediated neurotransmission was validated by a recent set of experiments aimed to delineate the functional difference between ketamine and memantine [13]. Memantine is another noncompetitive NMDA receptor antagonist that has failed to mediate an antidepressant response in depressed patients in clinical trials [24–26]. Recent work has highlighted the essential role played by block of NMDA receptor responses at near resting membrane potentials in the presence of physiological levels of extracellular Mg^{2+} in the antidepressant action of ketamine. Experiments demonstrated that memantine, despite being a robust blocker of NMDA receptors when the pore is unoccupied with Mg^{2+}, which is more likely to occur during activity, was a poor blocker of resting NMDA currents activated by spontaneous release events [13]. The dichotomy between memantine and ketamine also extended to the downstream signaling pathways as memantine application *in vivo* did not elicit a significant decrease in signaling through eEF2 kinase and failed to trigger the increase in BDNF protein expression. This direct comparison of memantine and ketamine in preclinical models provided a critical validation of the "resting NMDA receptor block" hypothesis as it could explain a clinical finding that has been difficult to reconcile with global NMDA receptor blockade as the mechanism for antidepressant efficacy of ketamine.

Synaptic circuits that mediate the antidepressant action of ketamine

The increasing number of studies focused on elucidating ketamine's action on synaptic transmission present significant opportunities for conceptual advance by delineating the molecular basis of rapid antidepressant responses. In addition, clinical studies that assess the impact of alternative NMDA receptor blockers as well as other means of altering glutamatergic signaling on triggering antidepressant responses provide promising directions for new treatments [27–29]. However, the exact synaptic circuitry involved in mediating the rapid antidepressant responses of ketamine remains unclear. Recent studies have focused on hippocampus and prefrontal cortex as potential sites of action for ketamine [6,7]. Several lines of evidence point to a hippocampal localization. First, eEF2 dephosphorylation seen after ketamine administration is most prominent in hippocampal CA1 as well as dentate gyrus dendritic regions. Second, electrophysiological experiments uncovered robust potentiation of synaptic responses recorded in the CA1 region of ketamine application in vitro. Finally, administration of eEF2 inhibitors caused a decrease in eEF2 phosphorylation

and an upregulation of BDNF selectively in hippocampus [6]. The potential involvement of the hippocampal locus is consistent with earlier results that pinpointed hippocampus, in particular the dentate gyrus region, for the action of classical antidepressants [20]. Although, these data demonstrate the involvement of hippocampus with ketamine mediated antidepressant responses, there is also evidence that ketamine administration alters synaptogenesis in prefrontal cortex [7]. Future experiments are needed to selectively manipulate key signal transduction elements required for ketamine action in subregions of the hippocampus as well as other brain areas to uncover the synaptic circuitry, in particular where eEF2 kinase acts to mediate the rapid antidepressant action of NMDA receptor blockade. While it remains possible that ketamine may act more globally altering synaptic efficacy in a broad range of circuits to exert its antidepressants effects, it is important to bear in mind that the site of ketamine action may be distinct from other brain regions such as the lateral habenula or nucleus accumbens associated with the pathophysiology of depression [30,31].

Synaptic mechanisms that may underlie long term antidepressant efficacy

Recent preclinical studies on ketamine action did not only address how ketamine may trigger an antidepressant effect but also provided clues on potential mechanisms that may maintain this effect in the long term. Ketamine mediated suppression of spontaneous NMDA receptor mediated neurotransmission results in a transient elevation in BDNF levels that returns to baseline within 24 hours after ketamine administration [6]. However, in patients as well as in animal models antidepressant responses remain detectable days to sometimes weeks beyond this initial time point [1,3,6,8]. This finding indicates that in future studies it will be critical to see whether specific changes in synaptic efficacy constitute the key end point in antidepressant action and if the increase in BDNF is only required as the initial triggering factor for this long term effect. According to this premise, triggering long term increases in synaptic efficacy may be sufficient to elicit antidepressant responses bypassing the need for BDNF. To address this question it will be important to test whether potentiation of synaptic responses detected after ketamine application is maintained throughout the time course of the antidepressant response. If synaptic potentiation is indeed sufficient to elicit antidepressant responses, it will be critical to better understand how this antidepressant driven plasticity overlaps with more traditional forms of Hebbian plasticity. For instance, a recent study demonstrated that acute serotonergic modulation could potentiate temporoammonic pathway input onto CA1 pyramidal neurons without altering Schaffer collateral synapses onto the same neurons [32]. However, this potentiation could be occluded by the canonical long-term potentiation elicited at the same synapse suggesting a shared mechanism [32]. Long term activity blockade or long term alterations in synaptic plasticity, similar to synaptic events elicited by ketamine, lead to homeostatic changes in synaptic strength by altering the prevalence of silent synapses [33]. There is also evidence that application of low doses of ketamine alters subsequent synaptic plasticity in hippocampal synapses [34]. Furthermore, recently reported metabotropic, Ca^{2+} influx independent, actions of NMDA receptors may also play a role in the maintenance of antidepressant effects as these putative metabotropic effects of NMDA receptors are spared by use-dependent channel blockers such as MK-801 or ketamine [35]. Taken together, these

recent findings on the synaptic plasticity events detected after antidepressant administration warrant further mechanistic scrutiny of the synaptic changes triggered by fast acting antidepressants to uncover the mechanism they share with canonical forms of synaptic plasticity identified at the same synapses.

The gradual reversibility of ketamine's antidepressant response also suggest that substantial permanent alterations in synapse numbers or connectivity are not likely involved in the antidepressant response but rather reversible functional alterations in synaptic plasticity are required. Purely functional increases in synaptic efficacy can be eventually reversed by activation of counteracting signaling pathways. Antidepressant response may eventually decline as homeostatic mechanisms that readjust synaptic gain in response to sustained changes in global levels of synaptic activity. Uncovering these counteracting mechanisms will be critical to assess the precise requirements for eliciting a reliable and sustainable antidepressant response with minimal clinical interventions [36].

Conclusion

Recent studies on rapid antidepressant action presented a productive merger of basic studies on synaptic transmission and plasticity with reverse translational approaches to uncover mechanisms of action for clinically validated rapid antidepressants. Identification of synaptic substrates that mediate an antidepressant response will offer new leads toward the development of robust, reliable fast acting antidepressants. The initial insight from this work suggests that acute alterations in synaptic efficacy may be sufficient to alleviate core depressive symptoms. Overall, information attained from these preclinical investigations will provide new insight to the molecular synaptic substrates that may be therapeutic targets and thus impact individuals with a number of neuropsychiatric disorders.

Acknowledgments

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Highlights

Ketamine triggers a rapid antidepressant response in patients with major depression

Ketamine elicits rapid translation of brain-derived neurotrophic factor (BDNF)

Rapid BDNF translation requires deactivation of eukaryotic elongation factor2 kinase

Ketamine, but not memantine, blocks resting NMDAR-mediated neurotransmission in Mg^{2+}

Block of resting NMDAR-mediated synaptic responses is essential for ketamine action