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Review

Ketamine and suicidal ideation in depression: Jumping the gun?

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ABSTRACT

Depression and suicide are known to be intricately entwined but the neurobiological basis underlying this association is yet to be understood. Ketamine is an N-methyl D-aspartate (NMDA) receptor antagonist used for induction and maintenance of general anaesthesia but paradoxically its euphoric effects lead to its classification under drugs of abuse. The serendipitous finding of rapid-onset antidepressant action of subanaesthetic dosing with ketamine by intravenous infusion has sparked many preclinical and clinical investigations. A remarkable suppression of suicidal ideation was also reported in depressed patients. This review focuses on the clinical trials on ketamine that reported remedial effects in suicidal ideation in depression and addresses also the molecular mechanisms underlying the antidepressant and psychotomimetic actions of ketamine. The neuropsychiatric profile of subanaesthetic doses of ketamine encourages its use in the management of suicidal ideation that could avert emergent self-harm or suicide. Finally, the need for neuroimaging studies in suicidal patients to identify the brain region specific and temporal effects of ketamine, and the possibility of employing ketamine as an experimental tool in rodent-based studies to study the mechanisms underlying suicidal behaviour are highlighted.

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Abbreviations: Glu, glutamate; Gln, glutamine; HP, hippocampus; PFC, prefrontal cortex.

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1. Introduction

The latest edition of the Diagnostic and Statistical Manual of Mental Disorders, DSM-5, states that suicidal tendency is a common manifestation of many psychiatric conditions, especially depressive disorders [1], rendering patients susceptible to take inappropriate, but indeed, preventable fatal decisions [2,3]. For example, suicidal tendency is 20–30 times higher in patients with bipolar disorder than in the general population [4]. The delay in onset of clinical antidepressant efficacy observed with both pharmacotherapy and electroconvulsive therapy further increases the risk [5–7]. Suicide is not however an inevitable and integral component of depression but rather involves complex and poorly understood neurobiological mechanisms closely associated with, but likely separable from, depression. Curbing suicidal ideation would be the ideal strategy to avert the emergent self-harm responsible for the major proportion of deaths that are associated with depressive disorder. Here we draw attention to the potential for utilisation of ketamine, a dissociative anaesthetic and N-methyl D-aspartate (NMDA) receptor antagonist, which has attracted interest as a potential novel antidepressant strategy beyond the well accepted doctrine based on serotonin. A rapid-onset antidepressant effect was observed in patients with major depression who received intravenous infusion of subanaesthetic dose of ketamine over 40 min [8]. This unanticipated finding impelled many clinical investigations that reproduced the finding, as well as preclinical investigations that explored the underlying antidepressant mechanisms of ketamine especially in the past couple of years. More interestingly, rapid-onset antidepressant effects encompassed a remarkable suppression of suicidal ideation [8,9]. Further, one other group revealed reduction of suicidal ideation with ketamine even at lower doses when infused over a shorter duration [10,11]. The potential risks of ketamine and its association with liability for abuse may lead to reluctance to adopt ketamine for routine treatment of depression. However, in cases in which suicidal ideation threatens an imminent fatality, the delay in onset of clinical efficacy of conventional antidepressants may be life-threatening. Under such circumstances, evaluation of the potential risk-to-benefit ratio may justify a recourse to the more radical approach of using subanaesthetic dose intravenous ketamine. A number of recent reviews have explored the rapid-onset antidepressant effects of ketamine but its effect on suicidal ideation has received relatively little attention [12,13]. In this review, we showcase recent advances in neuropsychopharmacological investigations of ketamine in humans and rodents with an emphasis on the potential utility of ketamine in depressed patients with suicidal ideation.

2. Antidepressant mechanisms of ketamine

The NMDA antagonism following administration of subanaesthetic doses of ketamine has both remedial (antidepressant) and adverse (psychotomimetic) consequences in humans and rodents [14–21]. Interestingly, lanicemine (AZD6765), an NMDA channel blocker with lower propensity to cause psychomimetic effects than ketamine, showed rapid-onset and sustained antidepressant effects [22]. The antidepressant mechanisms of ketamine involving various neurotransmitters, signalling pathways and neurotrophic factors that lead to synaptogenesis and plasticity effects have been extensively reviewed in the recent past [23–32]. A simplified version of the proposed mechanism that underlies the rapid-onset antidepressant action of ketamine is presented here based on preclinical investigations, which report that NMDA antagonism modulates downstream pathways in rodent brain, especially in prefrontal cortex and hippocampus (Fig. 1). Recent reports demonstrated some common neurochemical and molecular changes in hippocampus and prefrontal cortex that perhaps underlie the antidepressant effect of ketamine. They are, inhibition of glycogen synthase kinase-3 (GSK-3) an enzyme involved in mTOR pathway [33], upregulation of glutamate levels, downregulation of Neuregulin 1 (NRG1)-ErbB4 signalling in a subset of pyramidal neurons, parvalbumin, 67-kDA isoform of glutamic acid decarboxylase (GAD67) and gamma-aminobutyric acid (GABA) [34,35], and reduction in the expression of interleukin (IL)-1β and IL-6 [36]. Other studies looked into the neurochemical changes in either of the structures separately. In the prefrontal cortex, antagonism of excitatory NMDA receptors by ketamine predominantly affects inhibitory interneurons resulting in increases in alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor-mediated neurotransmission that activates a downstream pathway involving the mammalian target of rapamycin (mTOR) leading to increased synaptic signalling protein expression, spine density and synaptic activity via pp70S6K (a serine threonine kinase) and inhibitory 4E binding proteins (4E-BP) [15,37,38] (Fig. 1). A recent study proposed that increased protein synthesis via mTOR is mediated by antagonism of GluN2B-containing NMDARs in the PFC [39]. Further, an Akt-mediated phosphorylation of GSK-3β was reported to underlie the rapid-onset antidepressant effects of ketamine [40]. In the hippocampus, NMDA antagonism causes dephosphorylation of eukaryotic elongation factor 2 (eEF2K) leading to brain-derived neurotrophic factor (BDNF) upregulation and a consequent activation of its cognate tropomyosin-related kinase B (TrkB) receptor [41,42]. Phosphorylation of adenosine monophosphate-activated protein kinase (AMPK) partly contributes to the BDNF upregulation [43]. Further, a downregulation of microRNA-206, a modulator of BDNF, due to ketamine treatment is reported to upregulate BDNF [44]. Upregulation of BDNF by one of these mechanisms, if not all, leads to synaptogenesis and remodelling by multiple downstream cascades, including the Ras-mitogen-activated protein kinase (Ras-MAPK) pathway [45], transient receptor potential cation channel subfamily C (TRPC) activation [46], augmented actin [47] and tubulin [48] polymerisation, and via intracellular mTOR activation [49]. To date, detailed investigations of these two mechanisms, AMPA neurotransmission-mediated modulation of m-TOR and BDNF-mediated modulation of multiple of pathways including m-TOR, have largely been reported separately in the prefrontal cortex and hippocampus, respectively (Fig. 1). However, ketamine (10 mg/kg) increased the levels of both BDNF and mTOR in prefrontal cortex and hippocampus [50]. Chronic doses of a combination of ketamine and AMPA, at dose levels which were ineffective when given alone, displayed antidepressant effects that were associated with upregulation of BDNF, synapsin and mTOR in hippocampus [51]. Further studies are required to investigate the implication that the same AMPA–BDNF–mTOR antidepressant molecular mechanisms occur in both prefrontal cortex and hippocampus. Acute ketamine treatment (5–10 mg/kg) elevated the expression of ribosomal protein S6 (rpS6P), a signalling protein downstream of mTOR and p70S6K activation, in prelimbic and infralimbic prefrontal cortex, basolateral amygdala and nucleus accumbens core of rat [52]. A recent report suggested that the loss of parvalbumin interneurons in the prefrontal cortex contributes to the antidepressant-like (and propyschotic-like) effects of ketamine [53]. Isomers of ketamine are known to have differential antidepressant effects in animal models of depression. In juvenile mice exposed to neonatal dexamethasone, single dose of R-ketamine showed rapid-onset and long-lasting antidepressant effects compared to S-ketamine [54]. Despite the lack of direct evidence, the results of this preclinical study, which is in line with a clinical case report [55], tempts us to speculate that R-isoform may contribute to the rapid and long-standing antidepressant effects, while the S-isoform may mediate the psychotomimetic effects.