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Short Commentary Open Access

New Role of Ketamine for Reversing the Unrelenting Treatment-Resistant Major Depression

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Short Commentary

Major depressive disorder (MDD) is a debilitating mental state that affects more than 300 million people at a global level according to recent World Health Organization report [1,2] and also anticipate to be a second leading cause of disease burden by the year 2020 [3]. Although a range of first class antidepressant medications primarily acted through a modulation of monoaminergic neurotransmitters are increasingly available, these drugs take at least three to eight weeks to actually produce a therapeutic effect [4,5]. Moreover, response and remission rates exhibited by these therapeutic interventions are inconsistent and significant amount of depressed patients found to be treatment-refractory to these conventional drugs [5]. That being said, there is a huge unmet medical need for people who are suffering from the treatment-resistant major depressive disorder (TRD). Serendipitously, infusion of ketamine at a lower dose displayed a robust and rapid antidepressant response in patients with TRD [6]; however, its widespread application has been highly regulated due to the serious untoward effects and addiction liability. Herein, the author has briefly described the successful journey of this miraculous club drug from its anaesthetic agent to more recent rapidly acting antidepressant drug and the underlying mechanisms for antidepressant effects displayed by ketamine and its major metabolite hydroxynorketamine (HNK).

Broadly, ketamine acts as a non-competitive voltage dependent antagonist of the glutamatergic N-methyl-D-aspartate (NMDA) receptor, which only blocks the receptor when the channel is open after activation [7]. It is used widely as an anaesthetic agent during surgery and in the management of pain in both animals and humans. In the past few years, a single intravenous infusion of racemic ketamine (0.5 mg/kg) reported to elicit a remarkable anti-depressant response within 100 min of injection and effects persisted up to 7 days [6,8-10]. Coyle and Laws [11] demonstrated a discrepancy in peak response time depending upon primary diagnosis including 24 h for the MDD and 7 days for bipolar depression. In this way, intravenous infusion of ketamine at a lower dose seems to be promising therapeutic options in the populations with TRD, bipolar depression and suicidal ideation [12,13]. Moreover, discovery of several other NMDA receptor antagonists are underway for the therapeutic indication of TRD [14].

The antidepressant-like effects of ketamine and associated underlying molecular mechanisms have been well studied in the preclinical animal models [15]. Acute injection of ketamine produced an antidepressant-like phenotype in the forced swim test (FST) [16] and therapeutic response reported to mediate *via* following crucial intracellular signaling pathways, i) the mammalian target of rapamycin, ii) the eukaryotic elongation factor 2 and iii) the glycogen synthase kinase-3 [17,18]. Additionally, the enhancement of GluA1 α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) activity and intracellular brain-derived neurotrophic factor signaling appears critical for the antidepressant effect of ketamine [16,19,20]. Collectively, it has been posited these post-synaptic intracellular signaling mechanisms triggered by ketamine induces synaptogenesis and glutamate transmission [21]. Interestingly, time taken for synaptic mechanisms have also been coincided with the behavioral outcomes i.e. acts within hours after a single ketamine administration and last longer up to 1 week [22,23].

Predominantly, ketamine is injected in the form of racemic mixture of equal parts of R (–) ketamine and S (+) ketamine, however, several publications precisely elucidated the therapeutic property of each of these enantiomers and associated underlying mechanisms [24]. S-ketamine has about a 4-fold better affinity for the NMDA receptor and greater anesthetic potency [25]. However, compared to S-ketamine, R-ketamine has been several times more efficient at reducing depression-like behaviours and yielded longer-lasting antidepressant-like effects in the FST [26]. These authors also extended their findings employing a major metabolite of ketamine called HNK and they observed promising antidepressant-like activity with acute HNK treatment. The antidepressant activity of HNK was associated with enhancement of neural activity by increasing synaptic levels of another neuronal receptor protein, AMPAR [20]. In addition to this, HNK showed fewer propensities towards the untoward effects and does not elicit several of the cognitive and motor side effects that have been linked to ketamine [27]. These findings revealed that production of a distinct metabolite of ketamine is necessary and sufficient to produce the ketamine antidepressant actions and open a new avenue for future ketamine research.

It has always been anticipated that ketamine generates the rapid and robust anti-depressant effect through other than NMDA receptor inhibition mechanisms, because even more potent NMDA receptor inhibitor, which binds to the same site as ketamine, fails to produce sustained antidepressant-like effects [27]. Thus, several lines of research is ongoing to differentiate the strong dissociative effects of ketamine from that of rapid, potent and long lasting antidepressant response at low dose even after acute administration [28,14]. Taken together, ketamine has demonstrated rapid and robust efficacy as an antidepressant by improving core depressive symptoms including depressed mood, anhedonia and suicidal thoughts in patients with treatment-refractory unipolar and bipolar depression when administered at sub-anaesthetic doses. The discovery of antidepressant activity of ketamine has been designated as "discovery of the decades" and it serving as a choice of antidepressant drug due to unbelievable effects in patients with unrelenting TRD. However, few burning questions are yet to be answered. Do men and women experience differences in the antidepressant effect of ketamine? Does ketamine

produce an immediate or sustained antidepressant effect *via* NMDA receptor inhibition? Will the antidepressant effects of ketamine sustained over time without a fear of addiction? Will repeat dosing become more successful in reducing depressive symptoms?

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