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Chapter

Emergence of Ketamine as a Rapid Acting Antidepressant: Mechanistic Insights and Future Directions

Atamjit Singh and Preet Mohinder Singh Bedi

Abstract

Ketamine is a phencyclidine derivative and N-methyl-D-aspartate receptor antagonist, widely popular as a dissociative anesthetic. Its use as an anesthetic in humans was progressively fallen out due to its associated adverse effects and the emergence of newer and safer anesthetics. In recent few decades, various reports related to its efficacy in the treatment of resistant depression with anti-suicidal potential draw significant attention from researchers around the globe. The rapid clinical effect of ketamine within hours as compared to traditional antidepressants that take several weeks makes it a hot topic in antidepressant research. Studies conducted in the recent past suggest its mechanism of action through glutamate modulation via receptors like NMDA, AMPA as well as downregulation of BDNF etc. This chapter will shed light on the various mechanisms of ketamine related to antidepressant activity. Along with that its pharmacokinetics, toxicology and ongoing clinical trials will also be discussed.

Keywords: ketamine, depression, antidepressant, NMDA, BDNF

1. Introduction

From last few decades with rapid development and modernization, significant improvements in the lifestyle of humans has been observed but with pros there are associated cons and so is major depressive disorder (MDD) which is affecting teenagers to adults and majorly observed in young working professionals. It is emerging as major contributor in global disease burden and reported as the second leading causes for disability [1]. According to the study conducted by mental health in Canada, MDD has lifetime prevalence of 11.3% [2]. Besides being a major challenge for healthcare system its pathophysiology is still not uncovered completely. One hypothesis based on monoamines suggest that it may resulted from functional deficiency of neurotransmitters named serotonin and/or noradrenaline which is widely utilized for categorization of antidepressant drugs [3]. But conflict is also standstill with the time frame of the effect and dose administration as clinical symptoms are observed after several weeks from the onset of therapy and only half are noted to have actual clinical response [4–7]. Apart from that one-third patients suffers from treatment resistant depression (TRD) that are nonresponsive to currently approved medications [8]. Non-responsiveness of currently available therapy especially for TRD arise the emergency need of more effective and safer antidepressant therapy.

Ketamine is a phencyclidine derivative and N-methyl-D-aspartate (NMDA) receptor antagonist, widely popular as a dissociative anesthetic. Ketamine was first reported for its efficacy in depression in year 2000, when sub-anesthetic intravenous dose of ketamine rapidly reduced the symptoms of MDD and effect continued up to 72 hours [9]. Taking lead from this, further clinical trials were conducted which showcase its efficacy in TRD patients with 60–70% response rate [10–14]. Onset of action was reported within 2–4 hours and last for 1 week with singe infusion while repeated infusions have effect up to 18–19 days. Clinical data also suggest the responsiveness of ketamine up to 44% on patients with comorbidities and ultra-resistant depression [15, 16]. In addition to this ketamine has been reported for its anti-suicidal and anti-anhedonic properties [14, 17, 18]. All this reports points toward the different mechanism of ketamine form traditional antidepressants.

2. Basic chemistry, pharmacology and pharmacokinetics of ketamine

Recently discovered antidepressant and anti-suicidal action of ketamine significantly attracted the researchers working in the field of psychiatry [9, 11, 19]. Ketamine is a phencyclidine derivative and a mixture of R(−) and S(+) enantiomers. Both R(−) and S(+) enantiomers has been explored widely and it was observed that S(+) enantiomer has higher potency than R(−) enantiomer (R-ketamine) for phencyclidine site on glutamate NMDA receptor along with stronger analgesic activity [20–24]. Inspired form these outputs, S(+) enantiomer also known as esketamine is now under investigations for antidepressant potential [25]. However

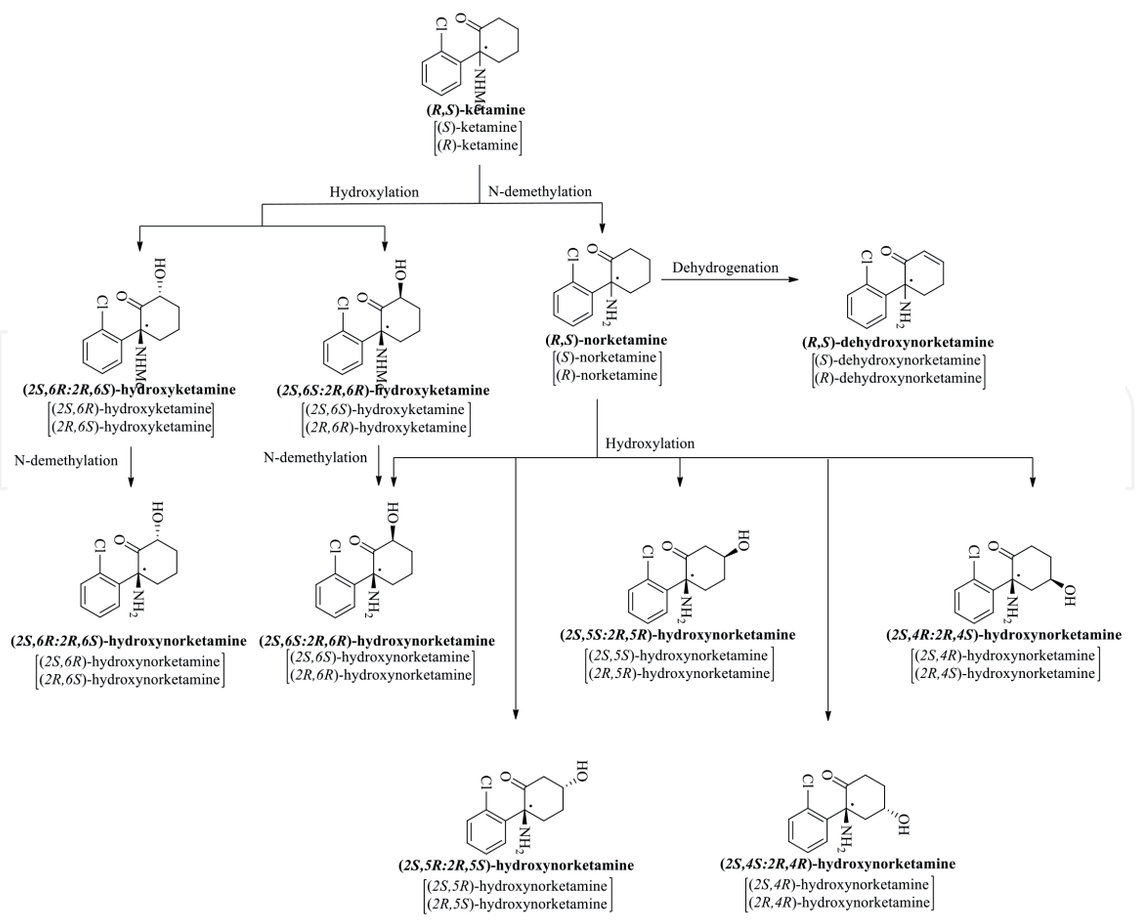

Figure 1.
General layout of metabolic pathway of ketamine showcasing stereoseletive metabolism through various cytochrome P450 enzymes.

conflict between these two is also exist with the side effects profile of both enantiomers related to dissociation, psychoses and cognition [26]. Reports suggest the rapid onset of antidepressant effects with R-ketamine but higher side effects than esketamine [27–34]. Ketamine undergo metabolism through CYP2B6- and CYP3A4-mediated N-demethylation resulting norketamine which further catabolized into hydroxynorketamines (HNKs) and dehyronorketamine (**Figure 1**). Investigations was also carried out on metabolites of ketamine. 2R,6R-HNK has been observed to have antidepressant like efficacy with nil side effects on rat models while several contradictory reports are also available [35–43]. Specifically, metabolite of esketamine i.e. S-norketamine showed antidepressant like properties with lesser side effects as with esketamine [44]. When talk about bioavailability, ketamine has varying bioavailability profile with different routes i.e. 100% with intravenous, 45% with intranasal, 30% with sublingual, 20% with oral, 93% with intramuscular while 30% with rectal route [24, 30, 44].

3. Overview of the status of clinical trials with ketamine and its enantiomers

Report on antidepressant efficacy of ketamine by Berman group in 2000 [9] initiated series of studies related to antidepressant activity of ketamine all around the globe. Multiple meta-analysis now established the candidature of ketamine against major depressive episodes in both bipolar as well as unipolar depression while efficacy was higher in unipolar as compared to bipolar depression [45–50]. In addition to this, numerous studies reported its effect last up to a week only for unipolar while it is up to 3–4 days in case of bipolar depression [46, 47, 49]. Randomized Controlled trials (RCT) exist in which effect of repeated infusions of ketamine for depression is studied but there is still lack of long term trial [51–53]. Studies on different routes of administration were also conducted that majorly include intranasal, sublingual and intramuscular [54–57]. In fact intranasal esketaminerecently got FDA clearance for TRD which was based on three acute-phase and two maintenance phase studies. These acute studies were conducted on severely depressed patients [58]. Maintenance trials were conducted up to 88 weeks where patient was administered esketamine weekly or every second week showcase reduced after relapse risk and also assured safety up to a year [59, 60]. A phase three trial consisted of 200 patients suggest the significant improvements in depression with ketamine adjuvant to an antidepressant [61]. There is another 5 year ongoing trial by Janssen for safety [62]. Keeping in view the antidepressant efficacy if R-ketamine, a phase I trial was started by Perception Pharmaceuticals but results are not processed yet [28].

4. Mechanistic insight into the antidepressant activity of ketamine

4.1 AMPA, BDNF and mTOR

Glutamate is one of the major excitatory neurotransmitters in central nervous system of human body that mainly acts on NMDA, ionotropic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors (co-localized with NMDA) and metabotropic glutamate receptors. Glutamate activates AMPA receptors at synaptic cleft, which permit the entry of sodium ions into postsynaptic membrane. Entry of sodium ions results in depolarization of postsynaptic membrane that cause removal of NMDA receptor channel voltage-dependent magnesium ion block that activate NMDA receptor which allow the entry of

sodium as well as calcium ions. Ketamine is a well-established non-competitive type NMDA receptor antagonist. Brain-derived neurotrophic factor (BDNF) and mTOR are two major proteins that are suspected to be involved in mechanistic window of ketamine. BDNF is a growth factor protein in central nervous system that promote neurogenesis and synaptogenesis along with support in survival of existing neurons. On the other hand, mTOR is suggested to have major role in neuronal development and circuit formation. mTOR further made two sub complexes known as mTOR complex 1 (mTORC1) and mTOR, from which mTORC1 is a target of ketamine [63, 64].

It has been observe that glutamatergic neurotransmission is deregulated in MDD and enhanced levels of glutamate levels in serum and plasma were observed in patient's dealing with MDD that why plasma glutamate levels are directly correlated with severity of depression [65–68]. Enhanced glutamate cause by loss of glial cells in MDD increases extra synaptic glutamate levels that suppressglutamatergic neurotransmission via activation of metabotropic glutamate receptor 2 (mGluR2) autoreceptors. A study suggest that change in depression symptoms by non-ketamine NMDA receptor antagonists like traxoprodil, lanicemine and rapastinel was much lower ass compared to ketamine [34, 69–71]. Ketamine good antagonistic activity for NMDA receptors present on γ-aminobutyric acid (GABA) that prevent activation of GABA interneurons resulting in downstream disinhibition of glutamatergic neurons that cause glutamate surge. Elevated levels of glutamate initiates activation of postsynaptic AMPA receptors that potentiate BDNF andmTORC1 signaling pathways. Ketamine demonstrated activate glutamate release and transmission in rat prefrontal cortex (RPC) [72]. Ketamine was also observed to enhance AMPA-evoked electrophysiological responses in the rat hippocampus and medial PFC pointing toward the involvement of ketamine in AMPA receptor transmission [73–77]. In a mouse model, ketamine was observed to increase the expression levels of two subunits of AMPA receptor known as GluA1 and GluA2 [34, 78].

Increased levels of BDNF and mTOR in rat hippocampus were observed within 30 minutes of treatment with ketamine [73, 79, 80]. Important to mention here that analgesic tramadol enhanced the effect of ketamine on force swim test along with upregulation of mTOR in the PFC and hippocampus of rat [81]. It is interesting to observe that increased BDNF and mTOR levels in hippocampal and RFC are controlled by AMPA because in a study treatment with AMPA receptor antagonist increased forced-swim test immobility time with reduced levels of BDNF and mTOR while with agonist immobility time reduced along with increased levels of both BDNF and mTOR [82]. Reports were also observed that suggest the nullification of antidepressant activity of ketamine with pre-treatment of rapamycin an mTORC1 inhibitor [83].

Numerous reports are present in the literature suggesting the possibility of ketamine's antidepressant activity via BDNF. No antidepressant activity was observed on treatment of ketamine in genetically modified mice lacking BDNF [73]. It is proposed that antagonism of NMDA through ketamine deactivates the eukaryotic elongation of factor 2 (eEF2) kinase that de-supress the translation of BDNF. Mice having Val66Met single-nucleotide polymorphism in BDNF gene showed impairment in BDNF release and mRNA trafficking. Administration of ketamine in these mice showed reduced antidepressant activity [84]. Reversal of anhedonicbehaviour with ketamine was observed in rats with chronic mild stress along with complete restoration of dendritic atrophy and dendritiv BDNF mRNA trafficking [85]. In social defeat stress model of mice, ketamine lessen reduction in BDNF, spine density of dendrites, synaptogenesis markers (GluA1 and PSD-95) in PFC, CA3 and dentate gyrus region of hippocampus at 8th day of treatment [86]. Elevated levels of BDNF were supposed to be associated with the lower severity

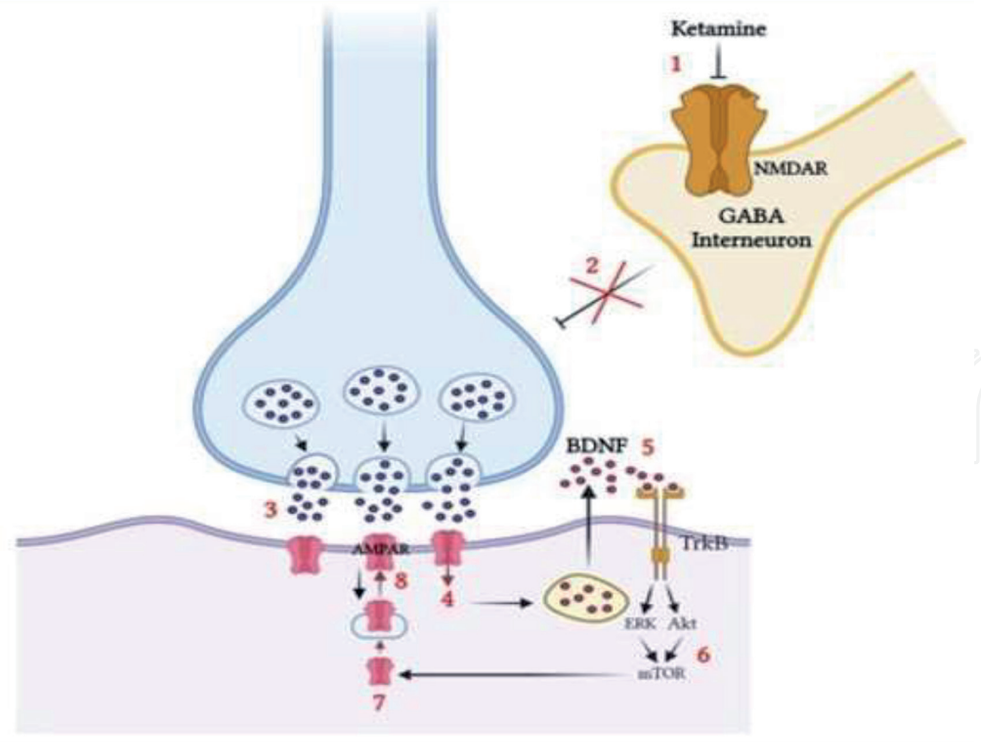

Figure 2.
Flow diagram of antidepressant activity of ketamine. (1) ketamine binds with N-methyl-d-aspartate receptors (NMDARs) and reduce excitability of γ-aminobutyric acid (GABA) ergic interneurons that results, (2) non-inhibition of glutamatergic neurons, (3) that further increase glutamate release which binds with α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptors resulting inflow of sodium and calcium into cell, (4) cause activation of voltage gated calcium channels, (5) that further triggers the release of brain-derived neurotrophic factor (BDNF) into glutamate synapse. (6) BDNF from synapse binds with tropomyosin receptor kinase B (TrkB) resulting activation of MEK–ERK and PI3K-Akt signaling cascades that converge on to mTOR lead to (7) increased synaptic protein translation. (8) increased proteins in synapse lead to increased AMPAR-mediated synaptic transmission causing elevated synaptogenesis. All these events are hypothesized to restore disrupted connectivity between key brain regions and can be the possible reason of rapid and sustained antidepressant action of ketamine.

of depression like symptoms on rating scale [87, 88]. A study carried out on three depressed patients, suggest their response to ketamine and have increased levels of plasma mTOR expression and eEF2 phosphorylaton [89]. It is worth to note that in a trial conducted on 20 patients, pre-treatment with rapamycin tripled the response rate after 2 weeks from treatment thus may be due to targeting of rapamycin on neuroinflammation through its immunisupressant activity or may be due to promotion of haemostatsis of synaptic density (**Figure 2**) [90].

4.2 D-serine

D-serine is a potential co-agonist at NMDA receptor which is a possible biomarker in depression. Numerous studies highlighted the abnormality of D-serine levels in depression highlighting the antidepressant properties of D-serine [91–95]. Ketamine was found to inhibitor the transport of D-serine while ketamine metabolites were observed to decrease intracellular (PC-12 cells) concentrations of D-serine thus increasing plasma D-serine levels which is possible prediction related to its to antidepressant action [96–99].

4.3 Opioid system

Ketamine also have capability to bind with opioid receptors (mu, delta and kappa), monoaminergic receptors and transporters, and muscarinic and

nicotinic cholinergic receptors [100]. Proposition is made that anti-suicidal as well as antidepressant actions of ketamine is related to the opioid system which is confirmed from the pre-treatment of naltrexone after that antidepressant effect was attenuated in patients [100, 101]. However many discrepancies are also exist along with [102, 103] because buprenorphine and methadone both are agonists to the opioid receptors and does not have any effect on antidepressant properties of ketamine [103]. These results rebels the role of opioid system in ketamine's antidepressant effects. Thus role of opioid in ketamine's antidepressant effects is yet unclear and controversial.

5. Future trends

With unique mechanism of action as compared to traditional antidepressants along with anti-suicidal properties, ketamine successfully attracted the researchers and physiologists toward itself in last two decades. However large mechanism of actions are still need to uncover thus it will be continue to be a hot topic and active area of research in psychiatry. There if a dire need to investigate the appropriate safety to efficacy ration of ketamine in depression therapy along with establishment of appropriate regimens for maintenance of therapy and discontinuation too. Reliable biomarkers are also needed to properly predict the response and adverse effects of ketamine. Numerous reports are also present in literature that caution the utilization of ketamine as an antidepressant in clinical practice [76, 104–108]. Keeping these thing apart, currently ketamine is emerging as a promising approach for treatment of patients suffering from TRD. Ketamine and its related neurochemical biomarkers can act as leads for development of future antidepressants.

6. Conclusion

Rapid antidepressant effect of ketamine depression therapy and important discovery in depression research. Its efficacy against TRD and anti-suicidal potential is a boon in depression research but at the same time its negative side effects and potential for being abuse is not to be neglected. However pathways like BDNF, mTOR, AMPA along D-serine and opioid receptors provided sufficient understanding but large portion of its mechanisms are still need to uncover. Even some studies create conflict to each other which is needed to be resolved. Overall analysis suggest that there is an important need to discover all aspects of ketamine in depression therapy to efficient use of this drug as an antidepressant in clinical practice. Moreover, ketamine can act as a lead for the development of new class of rapidly acting future antidepressant agents.

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Conflict of interest

The authors declare no conflict of interest.

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