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# Potential involvement of serotonergic signaling in ketamine's antidepressant actions: A critical review

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ABSTRACT

A single *i.v.* infusion of ketamine, classified as an *N*-methyl-D-aspartate (NMDA) receptor antagonist, may alleviate depressive symptoms within hours of administration in treatment resistant depressed patients, and the antidepressant effect may last for several weeks. These unique therapeutic properties have prompted researchers to explore the mechanisms mediating the antidepressant effects of ketamine, but despite many efforts, no consensus on its antidepressant mechanism of action has been reached. Recent preclinical reports have associated the neurotransmitter serotonin (5-hydroxytryptamine; 5-HT) with the antidepressant-like action of ketamine. Here, we review the current evidence for a serotonergic role in ketamine's antidepressant effects.

The pharmacological profile of ketamine may include equipotent activity on several non-NMDA targets, and the current hypotheses for the mechanisms responsible for ketamine's antidepressant activity do not appear to preclude the possibility that non-glutamate neurotransmitters are involved in the antidepressant effects. At multiple levels, the serotonergic and glutamatergic systems interact, and such crosstalk could support the notion that changes in serotonergic neurotransmission may impact ketamine's antidepressant potential. In line with these prospects, ketamine may increase 5-HT levels in the prefrontal cortex of rats, plausibly via hippocampal NMDA receptor inhibition and activation of α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors. In addition, a number of preclinical studies suggest that the antidepressant-like effects of ketamine may depend on endogenous activation of 5-HT receptors. Recent imaging and behavioral data predominantly support a role for $5\text{-HT}_{1A}$ or $5\text{-HT}_{1B}$ receptors, but the full range of 5-HT receptors has currently not been systematically investigated in this context. Furthermore, the nature of any 5-HT dependent mechanism in ketamine's antidepressant effect is currently not understood, and therefore, more studies are warranted to confirm this hypothesis and explore the specific pathways that might implicate 5-HT.



**Contents**

1. Introduction . . . 28
2. Pharmacological targets of ketamine and its metabolites . . . 28
3. Current mechanistic hypotheses for ketamine's antidepressant activity . . . 29
4. Crosstalk between serotonergic and glutamatergic neurotransmission . . . 30
   4.1. Intracellular level . . . 30
   4.2. Synaptic level . . . 32
   4.3. Circuitry level . . . 32
5. Studies relevant for 5-HT signaling and the antidepressant potential of ketamine . . . 32
   5.1. Modulation of ketamine's antidepressant-like activity by 5-HT tone manipulations . . . 32
   5.2. Effect of ketamine on 5-HT reuptake and efflux as well as 5-HT related neuronal firing . . . 33
   5.3. 5-HT receptors associated with the antidepressant activity of ketamine . . . 34
      5.3.1. $5\text{-HT}_1$ receptors . . . 34

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5.3.2. 5-$HT_{2A}$ receptors . . . 34
5.3.3. 5-$HT_3$ receptors . . . 34
6. Conclusion . . . 35
Contributors . . . 35
Disclosure . . . 35
References . . . 35

## 1. Introduction

The role of the glutamatergic neurotransmitter system in major depressive disorder (MDD) has been subject to increasing interest during the last decade. This focus was precipitated by the observation that an *i.v.* infusion of ketamine, classified as a non-competitive *N*-methyl-D-aspartate (NMDA) receptor antagonist, at sub-anesthetic doses produced an antidepressant effect within hours of administration (Berman et al., 2000). This rate of therapeutic onset is particularly remarkable when compared to the delayed effects of current-first line antidepressants. Furthermore, ketamine has shown up to ~70% remission rate for patients that are resistant to current first-line treatment, and the symptom improvements caused by a single *i.v.* infusion may persist for more than a week (Niciu et al., 2014). Regrettably, ketamine can also cause serious psychotomimetic side effects as well as cognitive impairment and is consequently unsuited for widespread clinical use (Niciu et al., 2014). A similar rapid antidepressant response has not been observed with the selective serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitor (SSRI), citalopram, which is the only SSRI that is available as an *i.v.* formulation in some European countries (Kasper and Müller-Spahn, 2002). Therefore, the unique therapeutic properties of ketamine, has prompted researchers to explore the mechanisms mediating its antidepressant effects. However, despite many efforts, no consensus on its mechanisms has been reached. The vast majority of the studies has concentrated on ketamine's modifications of glutamatergic neurotransmission leading to neuroplastic changes (Kavalali and Monteggia, 2015; Li et al., 2010; Niciu et al., 2014) and, until recently, mostly disregarded any implication of other neurotransmitter systems in ketamine's antidepressant effects. Considering ketamine's complex pharmacological profile, which includes equipotent effects on several other mechanisms than NMDA receptor inhibition, some mechanisms may remain unrevealed using this approach. Additionally, modulation of neurotransmission across systems is an essential feature of neurobiology, and such crosstalk could potentially be important for ketamine's antidepressant activity. In support of this notion is the finding that the therapeutic effects of the multimodal antidepressant vortioxetine, which targets the serotonin transporter (SERT) and several 5-HT receptors, may at least partly depend on modifications in γ-aminobutyric acid (GABA) and glutamatergic neurotransmission (Sanchez et al., 2015). Thus, it appears relevant to consider multiple neurotransmitter systems when exploring mechanisms associated with antidepressant effects. For more than 40 years, MDD has been associated with decreased central serotonergic tone, and a large body of literature suggests that 5-HT is implicated in responsiveness to current first-line antidepressants (Charney, 1998; Heninger et al., 1996). A number of recent preclinical reports have found 5-HT-mediated modifications of ketamine's antidepressant-like activity (Fukumoto et al., 2014; Gigliucci et al., 2013; Kos et al., 2006; Owolabi et al., 2014). Moreover, ketamine has been found to modify multiple aspects of serotonergic neurotransmission that may be related to its antidepressant effect (Kapur and Seeman, 2002; Matusch et al., 2007; Nishitani et al., 2014; Waelbers et al., 2013; Yamanaka et al., 2014).

Here, we discuss the pharmacological targets of ketamine's enantiomers and metabolites in relation to relevant antidepressant drug levels and summarize several hypothesized mechanisms of action for ketamine's antidepressant activity. Furthermore, we examine the interaction points between glutamatergic and serotonergic neurotransmission that potentially may be of relevance for ketamine's antidepressant effects and review the current evidence for implication of serotonergic neurotransmission in the antidepressant activity of ketamine.

## 2. Pharmacological targets of ketamine and its metabolites

Ketamine is a racemic mixture of *R*- and *S*-ketamine, where the *S*-isomer is a somewhat more potent NMDA receptor antagonist than the *R*-isomer (Table 1). Furthermore, ketamine is extensively metabolized into a large number of metabolites, including (*R*,*S*)-norketamine, (*R*,*S*)-dehydronorketamine, and a series of hydroxynorketamines (e.g., (2*S*,6*S*)-hydroxynorketamine and (2*R*,6*R*)-hydroxynorketamine) (Moaddel et al., 2013). (*R*,*S*)-norketamine is an NMDA receptor antagonist with a potency of the same order of magnitude as the parent compound and is therefore considered an active metabolite (Moaddel et al., 2013). The other metabolites do not have notable activity at the NMDA receptor. However, field and whole cell patch-clamp recordings have demonstrated that (2*R*,6*R*)-hydroxynorketamine potentiates α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor activation, although the mechanism responsible for these findings has not yet been established (Zanos et al., 2016). Moreover, in a recent study using patch-clamp techniques, (*R*,*S*)-dehydronorketamine was found to be a potent negative allosteric modulator (NAM) at the α7-nicotinic acetylcholine receptor (half maximal inhibitory concentration, $IC_{50}$ = 55 nM) (Moaddel et al., 2013). Similarly, (2*S*,6*S*)-hydroxynorketamine, (2*R*,6*R*)-hydroxynorketamine, and (*R*,*S*)-norketamine inhibited α7-nicotinic acetylcholine receptor function at concentrations <1 μM, whereas (*R*,*S*)-ketamine was inactive (Moaddel et al., 2013). Using the same techniques, (*R*,*S*)-ketamine and (*R*,*S*)-norketamine were effective inhibitors at α3β4-nicotinic acetylcholine receptors ($IC_{50}$ = 3.1 and 9.1 μM, respectively), whereas (*R*,*S*)-dehydronorketamine, (2*S*,6*S*)-hydroxynorketamine, and (2*R*,6*R*)-hydroxynorketamine were weak inhibitors ($IC_{50}$ > 100 μM) (Moaddel et al., 2013). The authors suggest that the inhibition of α7-nicotinic acetylcholine receptors by ketamine's metabolites may contribute to its antidepressant activity (Moaddel et al., 2013). However, the relevance of this mechanism for treatment of MDD still remains to be investigated in clinical trials. Inhibitors of selective α3β4-nicotinic acetylcholine receptors have in recent clinical trials failed to show efficacy and are therefore less likely to contribute to ketamine's antidepressant activity (Vieta et al., 2014).

Overall, the pharmacological mechanisms that mediate the antidepressant efficacy of ketamine and its metabolites are enigmatic and remain to be studied in further detail. However, except for data reported by Roth et al., 2013, which only showed notable activity at the NMDA receptor, it appears that the net effect of ketamine and its metabolites could involve NMDA, dopamine $D_2$, 5-$HT_2$, and α3β4- and α7-nicotinic acetylcholine receptors. The potencies for these targets are ≤ one order of magnitude relative to NMDA receptor potency, and the maximum plasma level of ketamine in patients infused *i.v.* with a subanesthetic dose (~0.5 mg/kg/h) is in the μM concentration range (i.e., approximately 200–250 ng/ml, which roughly corresponds to 1 μM) (Goldberg et al., 2010; Zarate et al., 2012). Similar inferences have