Ketamine Metabolites: A Potential Treatment for Depression

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Abstract

Depression affects approximately 300 million people worldwide and causes 700 thousand suicides annually. Current depression medications are ineffective for approximately 30% of depression affected populations, thus new treatment options are needed. This review covers a brief history of ketamine, the neurochemical pathways it functions on, why it was considered an unacceptable antidepressant option, and examines how its metabolites may cause antidepressant effects. Ketamine is considered an unacceptable treatment option mostly due to its delirium side effects, with some studies also suggesting that chronic use of ketamine could have other negative health effects. However, research suggests that ketamine metabolites may have long lasting antidepressant effects and little to no delirium effects or confirmed health risks. This review argues that ketamine metabolites are a potential treatment option for both major depressive disorder and bipolar depression. To show the link between antidepressant effects and ketamine metabolites, two studies demonstrated that ketamine metabolites are formed in both human and mice subjects. In these studies, ketamine and specific ketamine metabolites were individually administered, and the results suggested long-lasting antidepressant effects and a lack of delirium upon administration of the strictly metabolite solution. Accordingly, specific ketamine metabolites might serve as the next best antidepressant medication. Indeed, these metabolites may represent an effective treatment option for both Major Depressive Disorder and Bipolar Depression, especially in patients for whom current medications have been ineffective.

Methods

- Data collected from: six review articles, 16 primary research articles, & two government data sets
- Summarized ketamine drug history, neurochemical pathways, and side effect limitations
- Reviewed ketamine metabolites and their potential as antidepressants
- Reviewed metabolite potential side effects and antidepressant effectiveness
- Discussed potential for effective antidepressant effects on two depression types.

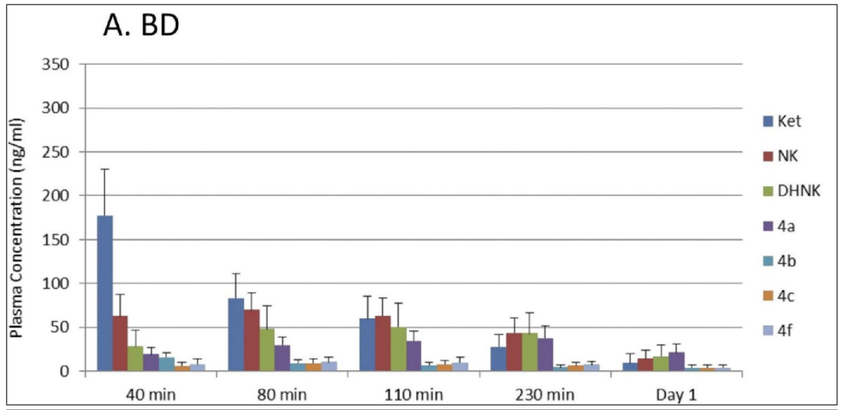

Figure 1: Plasma concentrations of ketamine and its metabolites over time in patients with treatment-resistant depression (bipolar depression [BD] patients **[A]** and major depressive disorder [MDD] patients **[B]**). (Ket) - Ketamine. (NK) - Norketamine. (DHNK) - Dehydronorketamine. (4a) - Hydronorketamine-4a. (4b) - Hydronorketamine-4b. (4c) - Hydronorketamine-4c. (4f) - Hydronorketamine-4f

Metabolite	BPRS Correlation & Significance	CADSS Correlation & Significance
DHNK	r = -.27 p = .04	N/A
HNK4c	N/A	r = -.29 p = .03
HNK4f	r = -.38 p = .003	r = -.35 p = .006

Figure 2: For all of these correlations, higher levels of the metabolite were associated with fewer dissociative symptoms and decreased symptom severity. r-value <1 refers to a negative correlation. Brief Psychiatric Rating Scale (BPRS). Clinician-Administered Dissociative States Scale (CADSS). (HNK4c) - Hydronorketamine-4c. (HNK4f) - Hydronorketamine-4f. (DHNK) - Dehydronorketamine.

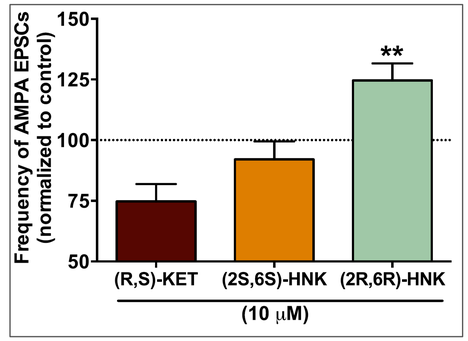

Figure 3: Comparative graph of frequency of excitatory postsynaptic currents (sEPSCs) mediated via AMPA receptors 20 min following (R,S)-KET, (2S,6S)-HNK, and (2R,6R)-(HNK) administration. **p<0.01

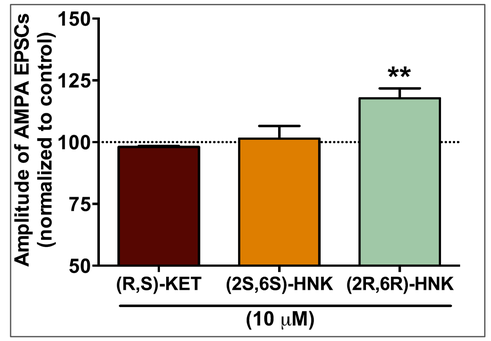

Figure 4: Comparative graph of amplitude of excitatory postsynaptic currents (sEPSCs) mediated via AMPA receptors 20 min following (R,S)-KET, (2S,6S)-HNK, and (2R,6R)-(HNK) administration. **p<0.01

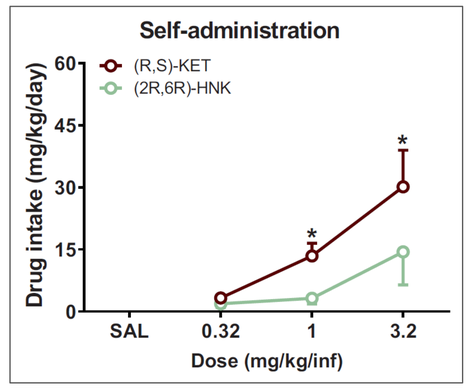

Figure 5: Unlike ketamine, (2R,6R)-HNK did not alter drug intake in the self-administration task in mice. *p<0.05 SAL, saline.

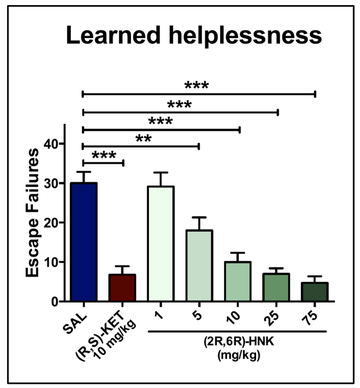

Figure 6: Dosage dependent comparison, of acute and sustained antidepressant and anti-anhedonic effects, of (2R,6R)-HNK and (R,S)-KET. *p<0.05, **p<0.01, ***p<0.001. SAL, saline.

Conclusions

- BP & MDD patients create differing levels of ketamine metabolites
- DHNK, HNK4c, & HNK4f metabolites negatively correlated with dissociative and depression symptoms
- (2R,6R)-HNK activates AMPA receptor more frequently and with higher EPSC amplitude compared to Ketamine
- (2R,6R)-HNK does not show abuse potential
- (2R,6R)-HNK shows acute and long lasting antidepressant and anti-anhedonic effects

Next Steps

- Verify potential side effects of Chronic AMPAR activation
- Verify various metabolites effects on both BD and MDD patients
- Verify efficacy of metabolite antidepressant/anti-anhedonic effects on population unaffected by current drugs