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A ketoxime analogue of ketamine with distinct molecular actions on GABAA and NMDA receptors demonstrates superior antidepressant activity

Dissociative anesthetic ketamine can rapidly alleviate symptoms of psychiatric depression with prolonged duration of action. Despite the promise, untoward psycho-mimetic manifestations of ketamine have curbed its clinical application. In a search for a ketamine substitute with higher antidepressant activity and lower side effects, we synthesized several novel ketamine analogs and tested them *in vitro* and *in vivo*. A ketoxime analog, termed oximeamine, shows the following pharmacological properties compared to ketamine: First, oximeamine potentiates the activity of $GABA_A$ receptors, specifically that of cerebellar $\alpha_6\beta_2\delta$ subtype, with higher potency. Second, oximeamine blocks NMDA receptors with similar potency and efficacy yet associates with (on-rate) and dissociates from (off-rate) the NMDA receptors at a significantly faster rate. The relatively faster on- and off-rate of oximeamine appears most prominent at the NMDA NR1/NR2B receptor subtype. Third, neither oximeamine nor ketamine display any significant action on AMPA receptor subtypes. Finally, in forced swim test, oximeamine demonstrates a significantly greater antidepressant activity than ketamine. In conclusion, the differential yet lower intensity block of the NMDA receptor subtypes and the higher activity on the GABAA receptors, together with the more robust antidepressant activity herald the superiority of oximeamine over ketamine with higher antidepressant efficacy and lower side effects.

Recent Publications

1. Walters RJ, Hadley SH, Morris KDW, and Amin J: Benzodiazepines act upon $GABA_A$ receptors via two distinct and separable mechanisms. (2000) Nature Neuroscience; 3(12): 1274-1281.
2. Hevers W, Hadley SH, Lüddens H, Amin J: Ketamine, But Not Phencyclidine, Selectively Modulates Cerebellar $GABA_A$ Receptors Containing α_6 and δ Subunits. (2008) Journal of Neuroscience 28(20): 5383-5393.
3. Morris KW and Amin J: Insight into the mechanism of action of neuroactive steroids. (2004) Mol Pharmacol; 66:56-69.
4. Hadley SH & Amin J: Rat $\alpha_6\beta_2\delta$ $GABA_A$ receptors exhibit two distinct and separable agonist affinities. (2007) Journal of Physiology 581.3:1001-1018.
5. Amin J, Subbarayan MS. Orthosteric-versus allosteric-dependent activation of the GABAA receptor requires

numerically distinct subunit level rearrangements (2017). Scientific Reports 7 (1), 7770, 1-16.

Biography

J Amin laboratory has a primary interest in GABAA and NMDA receptor-channels. We have studied the structure/function relationship of subtypes of GABAA receptors to enhance our understanding of the molecular mechanism of action of sedative/hypnotic drugs. By co-expression of wild-type with anesthetic-sensitive subunits of GABAA receptors, we have determined the minimal number of subunits required for orthosteric- versus allosteric-dependent activation of GABAA receptor channels. The laboratory is also focused on drug discovery with particular interest in ketamine. In the last several years, we have synthesized a number of ketamine analogues and characterized their molecular actions on the NMDA and GABAA receptors. One oxime analogues of ketamine has shown great promise in terms of molecular signature on NMDA and GABAA receptors and in an animal model test for antidepressants.

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