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Antidepressant Actions of Ketamine vs. Hydroxynorketamine

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In a recent issue of Nature, Zanos et al (1) show that metabolites of ketamine have rapid antidepressant-like actions in mice and that these are independent of the NMDA receptor. They report that racemic RS-ketamine is metabolized to (2S,6S;2R,6R)-hydroxynorketamine (HNK) and that this metabolism is essential for the sustained antidepressant action of ketamine. They further show that 2R,6R-HNK is the enantiomer of HNK that exerts behavioural, electroencephalographic and cellular antidepressant-like effects in mice. Significantly the effects of 2R,6R-HNK are independent of NMDA receptors but somehow involve the activation of AMPA receptors. These findings therefore challenge the widely held view that the rapid and sustained antidepressant actions of single ketamine administration are due its ability to inhibit the NMDA receptor (2) and consequently NMDA receptor-dependent synaptic plasticity (3).

We believe that it is premature to discard the NMDA receptor hypothesis for the rapid and sustained antidepressant actions of ketamine, for a variety of reasons. Foremost, the studies of Zanos et al were conducted using mice, and the difficulties of translating from rodents to man have been a major problem in the development of therapeutics.

One tenet of the Zanos argument is that they find that R-ketamine is more potent than S-ketamine in a range of mouse models of depression, and contrast this with the finding that R-ketamine is less potent than S-ketamine as an NMDA receptor antagonist (by about 2-4 fold *in vitro*). However, there is considerable uncertainty of estimating the brain concentration of ketamine, which is a fast acting and distributing compound with extensive first pass metabolism. Furthermore, in recent clinical trials (see e.g., 4), it was found that intravenous S-ketamine was roughly twice as potent as racemic intravenous RS-ketamine. These observations suggest that arguments based on small potency differences between enantiomers should be interpreted with caution. The differences in apparent enantiomer efficacy could be due to the difficulties in relating mouse models of depression to clinical depression in man.

A second argument was that the antidepressant-like effects of S-ketamine in mice are not sustained over 24 hours. However, in a recent double blind, randomized and placebo-controlled clinical trial, it was found that the effects of S-ketamine were sustained for at least two weeks (4). In addition, as Zanos et al (1) pointed out, S-ketamine is unlikely to be converted to the metabolite, 2R,6R-HNK and so this cannot be the explanation for the antidepressant effects of S-ketamine observed in man. These observations in humans are, therefore, fully consistent with NMDA receptor block as the underlying mechanism of action of S-ketamine.

A third argument raised in the paper against the NMDA receptor hypothesis is that Zanos et al. found, in agreement with earlier reports, that MK-801 did not exert sustained antidepressant

effects in their mouse models. But although MK-801 binds to the same site (the “PCP” site) as ketamine, it does so with a very different affinity and pharmacokinetic profile. It has already been shown that the therapeutic efficacy of these uncompetitive NMDA receptor antagonists, depends on their affinity and voltage-dependence. Specifically, memantine binds with low affinity to the NMDA receptor and shows efficacy in mid-stage Alzheimer’s disease (but not in depression), whereas MK-801 binds with very high affinity and is neurotoxic. A direct comparison of their actions shows a very different effect on NMDA receptor-dependent synaptic plasticity (5). It is therefore not without precedent to suppose that the difference between ketamine and MK-801 relates to their very differing abilities to interact at the PCP site. Therefore, a negative finding, as with MK-801, could have a variety of explanations, including the mode of action of the compound, its pharmacokinetic properties and its ability to engage its target.

Much more difficult to refute are positive effects, for example those situations where rapid antidepressant effects have been demonstrated by other compounds, unrelated to ketamine (where the metabolites will be very different). In this respect, it is significant that rapid and persistent clinical antidepressant effects have been reported for CP-101,606. This compound is a selective negative allosteric inhibitor of the GluN2B subunit of the NMDA receptor and has been shown to have sustained antidepressant-like effects in rodents and, more significantly, antidepressant effects lasting at least one week in humans (6). In addition, Mg^{2+}, which binds to a different site within the NMDA receptor, glycine-site NMDA receptor antagonists and gaseous anaesthetics, with NMDA receptor antagonist action, all have been shown to possess rapid antidepressant potential in animal models and/or in humans (7).

None of this, of course, excludes the possibility that HNK possesses rapid and persistent antidepressant action via an NMDA receptor independent mechanism, as Zanos et al (1) claim. Given the reported lack of side-effects that are associated with ketamine, it will be interesting to see how these findings translate in the clinic. The observation that, like ketamine, the rapid antidepressant actions of HNK require intact AMPA receptor mediated synaptic transmission (1) suggests that the actions of ketamine and HNK may converge at some point, possibly at the level of eEF2 phosphorylation and BDNF signalling (1). In which case, it will be important to understand the underlying mechanisms. Presently, it is unclear whether clinically effective doses of ketamine could achieve the brain levels of HNK required for the AMPA receptor activation. Indeed peak levels of plasma HNK are approximately 0.1 μM in humans treated for depression (8) whereas Zanos et al report 100 fold higher concentrations of HNK for effects on AMPA transmission *in vitro*, and for efficacy in their mouse model *in vivo*.

In contrast, it is possible to propose a readily testable framework for how ketamine, acting via NMDA receptors, is able to lead to rapid and sustained antidepressant action, which relates to the role of NMDA receptors in synaptic plasticity. NMDA receptors mediate the induction of LTP and LTD of AMPA receptor-mediated synaptic transmission at many synapses in the CNS (9). Mood is a form of plasticity that affects the emotional centres of the brain, where NMDA receptor dependent LTP and LTD have been established to occur. It is not a far stretch of the imagination to propose, therefore, that the underlying mechanism for mood is a change in LTP and LTD in these brain regions. In terms of depression, this would be either due to LTP of some form of anhedonia or LTD of a hedonic state. Given the effectiveness of GluN2B-selective antagonists, which have been shown to selectively block LTD (9), it would be most probable that LTD of pleasure centres is the primary mechanism. But, this leads to the question as to how NMDA receptor antagonists that classically prevent the induction of synaptic plasticity can reverse a depressed synaptic state. Here, the answer may be reconsolidation. It is now well established that when memories are recalled, they revert to a labile state where they need to be

relearned, and can be modified. This re-consolidation is known to be NMDA receptor dependent (10) and most likely involves plasticity at the same synapses that were initially modified. Mood could very easily involve such repeated reconsolidation (i.e., reinforcement of the negative mood), thus explaining its sensitivity to NMDA receptor antagonism.

The significance of this hypothesis is that if the underlying basis of clinical depression is long-term synaptic depression (LTD) then there are many therapeutic opportunities downstream of the NMDA receptor itself. LTD involves complex, and incompletely established, signalling cascades, including molecules such as GSK-3 (10). A schematic model for how ketamine may be having its rapid and sustained antidepressant effect is presented in Fig. 1.

In conclusion, whilst several mechanisms have been proposed to account for the rapid and sustained antidepressant actions of ketamine (1), we firmly believe that the NMDA receptor hypothesis remains the strongest. Here we have elaborated upon this to propose that re-consolidation of NMDA receptor-dependent LTD at reward pathways in the brain may be the principal target of ketamine and other rapidly acting antidepressant drugs.

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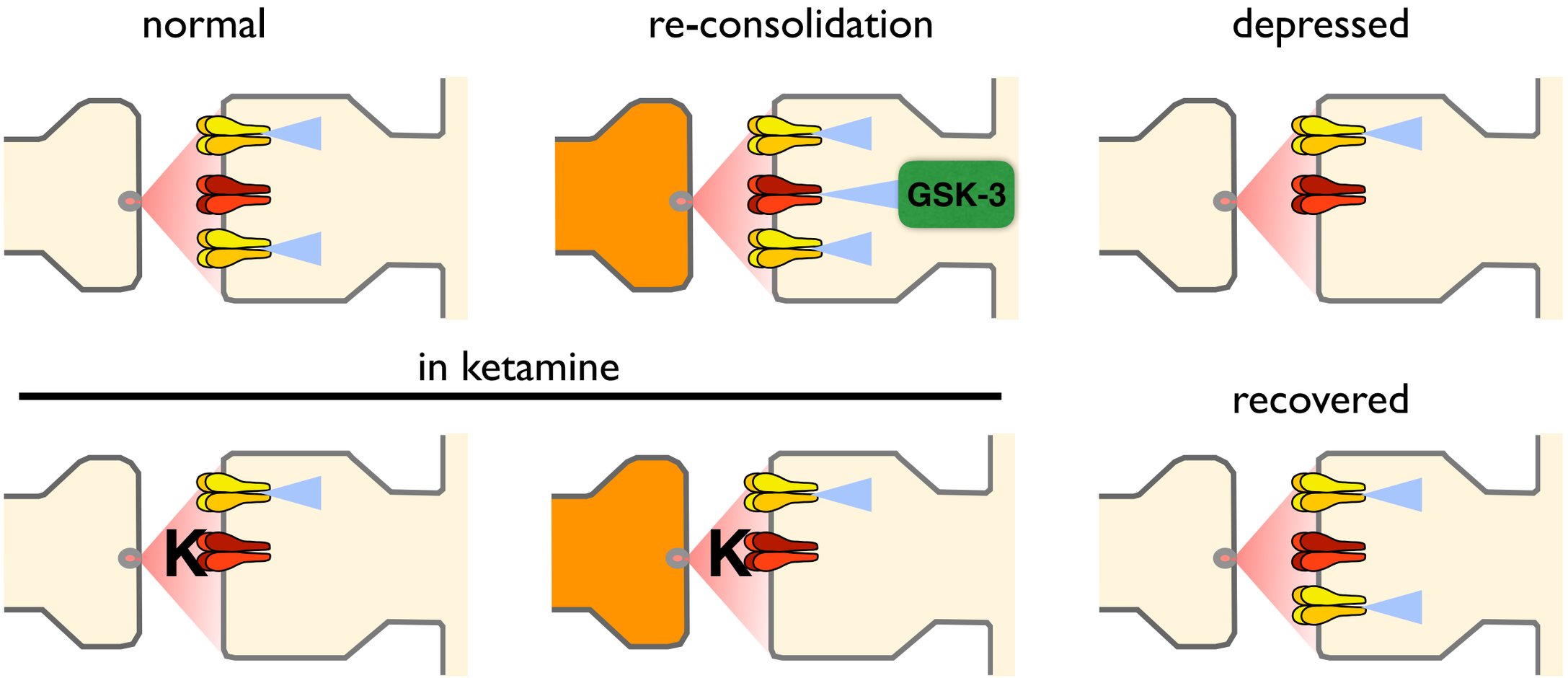
Fig. 1. Ketamine and depression. A schematic of how ketamine (K) may result in antidepressant effects in humans by inhibiting NMDA receptors and preventing reconsolidation of NMDA receptor-mediated synaptic plasticity at pathways that mediate emotional responses. (Red symbols, NMDA receptors; Yellow symbols, AMPA receptors; Blue triangles, activated receptor; Orange presynaptic bouton, sufficiently active to engage NMDA receptors). GSK-3: Glycogen Synthase Kinase-3.

Figure 1


normal
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