Biological Psychiatry

Antidepressant Actions of Ketamine Versus Hydroxynorketamine

To the Editor:

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 *N*-methyl-D-aspartate receptor (NMDAR). They report that a racemic mixture of *R*- and *S*-ketamine is metabolized to (*2S,6S*)- and (*2R,6R*)-hydroxynorketamine (HNK), and that this metabolism is essential for the sustained antidepressant action of ketamine. They also show that (*2R,6R*)-HNK is the enantiomer of HNK that exerts behavioral, electroencephalographic, and cellular antidepressant-like effects in mice. Significantly, the effects of (*2R,6R*)-HNK are independent of NMDARs but somehow involve the activation of alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors. These findings challenge the widely held view that the rapid and sustained antidepressant actions of single ketamine administration are caused by its ability to inhibit the NMDAR (2) and consequently NMDAR-dependent synaptic plasticity (3).

We believe that it is premature to discard the NMDAR 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 humans have been a major problem in the development of therapeutics.

One tenet of the argument set forth by Zanos *et al.* is that they find that *R*-ketamine is more potent than *S*-ketamine in a range of mouse models of depression, and they contrast this with the finding that *R*-ketamine is less potent than *S*-ketamine as an NMDAR antagonist (by about two- to fourfold in vitro). However, there is considerable uncertainty of estimating the concentration of ketamine in the brain because ketamine is a fast-acting and distributing compound with extensive first-pass metabolism. In addition, in recent clinical trials [see (4)], it was found that intravenous *S*-ketamine was roughly twice as potent as racemic intravenous (*R,S*)-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 related to the difficulties in relating mouse models of depression to clinical depression in humans.

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, placebo-controlled clinical trial, it was found that the effects of *S*-ketamine were sustained for at least 2 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 humans. These observations in humans are, therefore, fully consistent with NMDAR block as the underlying mechanism of action of *S*-ketamine.

A third argument raised in the paper against the NMDAR 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. However, although MK-801 binds to the same site as ketamine (the "PCP" site), it does so with a different affinity and pharmacokinetic profile. It has already been shown that the therapeutic efficacy of these uncompetitive NMDAR antagonists depends on their affinity and voltage dependence. Specifically, memantine binds with low affinity to the NMDAR and shows efficacy in midstage Alzheimer's disease (but not in depression), whereas MK-801 binds with high affinity and is neurotoxic. A direct comparison of their actions shows a different effect on NMDAR-dependent synaptic plasticity (5). It is therefore not without precedent to suppose that the difference between ketamine and MK-801 relates to their 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, situations where rapid antidepressant effects have been demonstrated by other compounds unrelated to ketamine (where the metabolites are 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 NMDAR and has been shown to have sustained antidepressant-like effects in rodents and, more significantly, antidepressant effects lasting at least 1 week in humans (6). In addition, Mg^{2+}, which binds to a different site within the NMDAR, glycine-site NMDAR antagonists, and gaseous anesthetics with NMDAR antagonist action have all been shown to possess rapid antidepressant potential in animal models or in humans (7).

None of this, of course, excludes the possibility that HNK possesses rapid and persistent antidepressant action via an NMDAR-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 brain-derived neurotrophic factor signaling (1). In this case, it will be important to understand the underlying mechanisms. It is unclear whether clinically effective doses of ketamine could achieve the brain levels of HNK required for AMPA receptor activation. 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 NMDARs, is able to lead to rapid and sustained antidepressant action, which relates to the role of NMDARs in synaptic plasticity. NMDARs

SEE COMMENTARY ON PAGE e61

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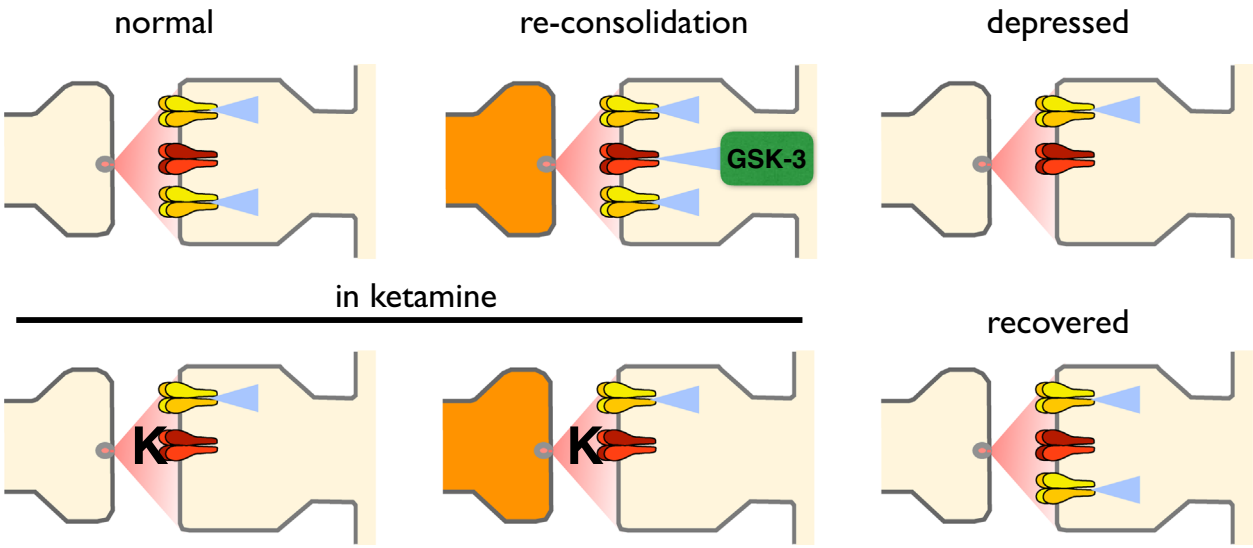

Figure 1. Ketamine and depression. A schematic of how ketamine (K) may result in antidepressant effects in humans by inhibiting *N*-methyl-D-aspartate receptors (NMDARs) and preventing reconsolidation of NMDAR-mediated synaptic plasticity at pathways that mediate emotional responses. (Red symbols, NMDARs; yellow symbols, alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors; blue triangles, activated receptor; orange presynaptic bouton, sufficiently active to engage NMDARs.) GSK-3, glycogen synthase kinase-3.

mediate the induction of long-term potentiation (LTP) and long-term depression (LTD) of AMPA receptor–mediated synaptic transmission at many synapses in the central nervous system (9). Mood is a form of plasticity that affects the emotional centers of the brain, where NMDAR-dependent LTP and LTD have been established to occur. It is not a 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 due to either 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 centers is the primary mechanism. However, this leads to the question as to how NMDAR antagonists that classically prevent the induction of synaptic plasticity can reverse a depressed synaptic state. 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 reconsolidation is known to be NMDAR dependent (10) and most likely involves plasticity at the same synapses that were initially modified. Mood could easily involve such repeated reconsolidation (i.e., reinforcement of the negative mood), therefore explaining its sensitivity to NMDAR antagonism.

The significance of this hypothesis is that if the underlying basis of clinical depression is LTD, there are many therapeutic opportunities downstream of the NMDAR itself. LTD involves complex, and incompletely established, signaling cascades, including molecules such as glycogen synthase kinase-3 (10). A schematic model for how ketamine may be having its rapid and sustained antidepressant effect is shown in Figure 1.

In conclusion, while several mechanisms have been proposed to account for the rapid and sustained antidepressant actions of ketamine (1), we firmly believe that the NMDAR hypothesis remains the strongest. We have elaborated upon this to propose that reconsolidation of NMDAR-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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Article Information

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