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Understanding the opioid effects of ketamine: Where are we?

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Ketamine has been demonstrated to have rapid antidepressant effects, although the mechanism of action that underlies its rapid effects has been under debate for the last few years. The drug has been thought to exert its mood effects by blocking the NMDA receptor; however, binding to the receptor is micromolar, and attempts to develop other antidepressants with NMDA antagonism have yielded few effective follow-on compounds. A few years ago, we argued that the antidepressant effects involved mu-opioid agonist effects (1). We based this on several observations:

1) Ketamine's antinociception effects in rodents could be blocked by administration of a mu opioid antagonist.
2) Ketamine's rapid effects in refractory obsessive compulsive disorder (OCD) patients mirrored the rapid effects of morphine in another cohort of refractory OCD patients.
3) Ketamine has been reported to have micromolar binding to mu opioid receptors.
4) Other NMDA receptor antagonists (e.g., memantine) did not share similarly rapid antidepressant effects or any antidepressant effects.

Others pushed back in part because ketamine binds at micromolar affinity to mu opioid receptors (which is mild), but its binding to the putative NMDA receptor is similarly micromolar. We argued that the question of the importance of mu opioid activity in the antidepressant effect could be tested by twice treating major depressive patients in a crossover design, with ketamine (before or after having received a placebo or a mu opioid receptor antagonist).

We subsequently reported that naltrexone significantly reduced the antidepressant effects of ketamine in a cohort of depressed patients (2). Patients received two ketamine infusions spaced out by 2–9 weeks to ensure patients were depressed at both time points. These data unleashed a host of preclinical studies, and all but one demonstrated that the administration of naltrexone or another mu-opioid blocker blocked the behavioral (antidepressant or addictive) effects. Recently, our clinical study was replicated by Jelen et al in a larger cohort of depressed subjects (3).

Several brain areas have been studied to understand where the effects are occurring. These data were recently reviewed by Levinstein and colleagues (4). That review detailed the potential brain areas involved in the cross-talk between mu and NMDA. These include areas enriched for both receptors at large and those where neurons co-express both receptors. This evidence does point to ketamine acting via mu opioid activation, but there are a number of issues that arise in the data and that are worthy of further study.

When we noted that the antidepressant effects of ketamine in depressed patients were blocked by pretreating with the opioid antagonist, we argued that we could not disentangle ketamine's binding to mu opioid receptors from the drug's promoting release of beta endorphins. In a recent paper, Pittenger's group demonstrated in rodents that naltrexone blocked the behavioral effects of ketamine, but that the same behavioral responses were also blocked by pre-administering an antibody to beta endorphin (5). This suggests that ketamine's ability to release beta-endorphins is a key mechanism of action underlying its rapid effect. Further studies are needed to determine whether beta-endorphin release is necessary and sufficient for the antidepressant effects of ketamine, as clarifying this mechanism could inform development of more targeted rapid-acting antidepressants.

Another critical issue is which subregion(s) in the brain are specifically involved. There are data that injecting the antagonist in the prefrontal cortex blocks ketamine's effects, but as noted above, other areas are involved (e.g., amygdala). The opioid properties of ketamine and esketamine should be kept in mind when treating patients over time. Several groups have been concerned about the risk of becoming suicidal after stopping prolonged use of these drugs. An interesting observation in two preclinical and one clinical reports is that there are differential effects via the opioid blocking paradigms based on sex (6, 7). The antidepressant-like effects of ketamine appeared to be more easily blocked by the opioid antagonist in males. These findings may explain sex-related differences in prevalence and pathophysiology of depression, opening avenues for sex-tailored treatment approaches.

The finding that NMDA antagonists require opioid activation to exert rapid antidepressant effects suggests that screening for such activity may be essential in evaluating whether a candidate agent can produce rapid antidepressant responses. Understanding the opioid-mediated effects of ketamine provides a framework for accelerating development of novel rapid-acting antidepressants and optimizing their clinical application in patients with major depression.

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