Go With the Flow: MOR(E) to Ketamine Than NMDA Receptor Antagonism

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Ketamine, originally developed in the 1960s as a dissociative anesthetic, has emerged as a rapid-acting alternative to traditional antidepressants, which typically take weeks to show effects (1). Ketamine's rapid-acting and sustained antidepressant effects have led to a paradigm shift in psychiatry, but precisely how ketamine produces these effects is a subject of intense debate. Unlike traditional antidepressants that target monoamines, ketamine primarily targets *N*-methyl-D-aspartate (NMDA) receptors by binding to the phencyclidine site deep inside the channel pore and preventing influx of Ca^{2+} and Na^{+} ions, leading to reduced activity of NMDA receptor–expressing cells. For this reason, ketamine is historically regarded as a noncompetitive NMDA receptor (NMDAR) antagonist, and consequently, its antidepressant mechanism of action has been attributed to its interaction with NMDA receptors (2). However, ketamine interacts with other pharmacological targets, including opioid receptors (3). Moreover, it is unlikely that NMDAR antagonism can solely explain ketamine's antidepressant effects, because more selective NMDAR antagonists do not produce robust therapeutic effects (4). This has prompted a reconsideration of ketamine's mechanism of action in depression, extending its actions to include opioid receptors and the opioid system (5–11).

In a recent randomized, double-blind, crossover study in 26 adults with treatment-resistant depression (TRD), Jelen et al. (12) replicated the seminal finding by Williams et al. (13) and reported that pretreatment with 50 mg oral naltrexone significantly attenuated the antidepressant effect of a 0.5 mg/kg intravenous ketamine infusion. In the same study (12), Jelen et al. showed that naltrexone attenuated ketamine-evoked increases in glutamatergic activity in the anterior cingulate cortex (ACC), a critical brain region involved in mood regulation and implicated in major depressive disorder (MDD).

In this issue of the *Journal*, Jelen and colleagues (14) present new results from the above-mentioned study, using three-dimensional pseudo-continuous arterial spin labeling MRI to examine whether naltrexone modulates ketamine's effects on regional cerebral blood flow (rCBF). rCBF reflects the amount of blood passing through specific, localized areas of the brain, acting as a surrogate marker for neuronal activity (15). The authors also correlated ketamine- and naltrexone-evoked rCBF changes with clinical symptom assessments and with receptor brain density maps using publicly available positron emission tomography (PET) datasets from studies performed in healthy human subjects.

Consistent with the authors' hypothesis, ketamine produced robust increases in rCBF across a specific brain network including the subgenual (sgACC), pregenual (pgACC), and dorsal ACC, and thalamus. However, contrary to their expectation, and perhaps unexpected given their prior findings (12), naltrexone pretreatment failed to reduce the ketamine-evoked rCBF increases. Instead, naltrexone by itself produced a global increase in rCBF across the sampled brain regions. Notably, ketamine-induced rCBF changes in the pgACC were associated with acute subjective effects, and those in the sgACC with antidepressant responses 24 hours later, whereas naltrexone pretreatment disrupted these associations. Ketamine-induced rCBF changes aligned with the brain distribution of the mu-opioid receptor (MOR) and metabotropic glutamate receptor 5 (mGluR5), whereas naltrexone modulation of ketamine's rCBF effects aligned with MOR and $GABA_A\alpha5$ receptor distributions. rCBF changes did not align meaningfully with the distribution of NMDAR, kappa-opioid receptors (KORs), or other $GABA_A$, dopamine, or serotonin receptors. Since the rCBF signatures aligned specifically with the regional distribution of MORs, but not KORs, the results substantiate the notion that ketamine's interaction with the opioid system primarily involves MORs.

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Jelen and colleagues' results broadly suggest that MORs and the opioid system act to exert a diffuse neuromodulatory effect on brain activity. Moreover, since naltrexone disrupted the biobehavioral coupling between ketamine-evoked rCBF

changes, subjective effects, and next-day symptoms, their results support a model whereby the MOR does not simply control the magnitude of ketamine's effects on regional brain activation but acts to modulate its evoked neural activity, subjective experience, and antidepressant response. Overall, their results support the interpretation that the MOR does not play an all-encompassing role in ketamine's acute physiological effects but may act to shape ketamine-evoked neuronal plasticity or circuit reconfiguration (5–7), influencing the transition from ketamine's acute physiological effects to its therapeutic outcomes and potentially explaining why its acute psychoactive effects do not reliably predict its sustained antidepressant efficacy.

Jelen and colleagues' findings resonate with emerging conceptual frameworks that reinterpret ketamine pharmacology through the lens of synergistic interactions between NMDAR, MOR, and potentially other neurochemical systems (3, 5–7). Integrating their findings with results from prior studies, the authors propose a speculative model where ketamine, via its combined actions on NMDARs and MORs on somatostatin-expressing GABAergic interneurons in cortical regions, inhibits these interneurons, leading to disinhibition of pyramidal neurons and increases in glutamate levels. While speculative, this model is consistent with the hypothesis that ketamine's rapid antidepressant effects coincide with glutamate activation (2) and suggests that glutamate increases alone are not sufficient to explain ketamine's rapid and sustained antidepressant efficacy, which may perhaps be better explained by how glutamate activation may interact with MOR and other modulatory systems to recruit downstream plasticity programs (5–7).

Ketamine is a game-changing medication for depression, but it produces reinforcement and has known misuse liability and abuse potential. Jelen and colleagues' findings also support recent frameworks proposing that bifunctional NMDA-MOR interactions may modulate not just ketamine's antidepressant effects but also its reinforcement, misuse liability, and potential for treatment of substance use disorders (7).

A major challenge in psychiatry is moving from observing drug effects to understanding their underlying mechanisms. Jelen and colleagues' integration of behavioral and neuroimaging data constitutes a prime example of combining multimodal datasets for offering a framework to clarify how ketamine works. However, the study's impact is limited by a relatively small size and the use of receptor maps derived from PET studies performed in healthy control subjects rather than patients with TRD. MDD with and without treatment resistance may involve distinct circuits and pathologies, with opioids showing more promise in TRD compared to MDD (5). Jelen and colleagues' findings in TRD are consistent with such observations, but future work should test the role of the opioid system in a study that contrasts TRD and MDD. Finally, the lack of a placebo infusion arm further limits the impact of these results, given that the opioid system is implicated in placebo and expectancy effects, and that ketamine's therapeutic profile may be shaped by such factors (16). Nevertheless, Jelen and colleagues' results are promising and support follow-up studies. Studies using larger sample sizes and incorporating placebo controls and multimodal approaches and biomarkers derived from healthy subjects and TRD and MDD patients would further clarify and strengthen our knowledge of specifically how NMDARs and MORs interact in the context of depression. Results from such studies may also be essential for guiding the development of next-generation rapid-acting antidepressants that preserve therapeutic efficacy while minimizing risks associated with MOR activation.

In sum, the big question that Jelen et al. attempt to answer is whether the opioid system meaningfully contributes to ketamine's antidepressant action. In their attempt to answer this, the authors provide new insights into how ketamine affects brain activity in the context of depression. Their findings show that MOR mediates ketamine-induced changes in rCBF and acts as a link between glutamate and GABAergic pathways, highlighting a critical synergistic NMDA-MOR-based mechanism for antidepressant efficacy. Their results support the premise that ketamine pharmacology should be expanded to include opioid system mechanisms, and lend further support to the notion that bifunctional NMDAR-MOR interactions may be involved in ketamine's therapeutic effects (5–7).

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