

Ketamine for a Boost of Neural Plasticity: How, but Also When?

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Major depressive disorder affects millions of people and leads to debilitating symptoms. Although conventional antidepressants have been available and are often beneficial, they have several limitations, including a slow onset of action and an inadequate response for a substantial fraction of patients. Recently, ketamine—primarily a noncompetitive NMDA receptor antagonist, among other actions—was approved as a novel treatment for treatment-resistant depression and suicidal ideation. This was an exciting development because ketamine can relieve depressive symptoms rapidly and with sustained effect. What is the biological basis for ketamine's rapid antidepressant action? One framework gaining empirical support is that ketamine promotes neural plasticity. Specifically, ketamine appears to promote synaptogenesis in brain regions such as the medial frontal cortex and hippocampus, countering the dendritic atrophy and synapse loss associated with chronic stress and depression. This framework is supported by several studies showing that a single dose of ketamine increases the number of dendritic spines (1) by elevating their formation rate in the frontal cortex (2,3). Still unclear, though, is when and how the plasticity is boosted. Specifically, when does ketamine enhance the propensity for neural plasticity—so far, studies have looked only at synaptic connections, which is the final link in the chain of events. Moreover, how does ketamine enable neural plasticity? The full complement of molecular and cellular factors remains to be elucidated. Knowledge of both the timing and mechanisms underlying ketamine's plasticity-promoting potential will be key to harnessing fast-acting antidepressants. In the current issue of *Biological Psychiatry*, Wu *et al.* (4) present compelling data to define a time window for ketamine's plasticity potential and uncover dopamine as a crucial component of the mechanism.

Previous studies have provided clues into the time scale of ketamine's effect on neural plasticity. In one longitudinal two-photon imaging study, a single dose of ketamine increased dendritic spine density in the medial frontal cortex within a day (2). Another recent study indicated that ketamine begins to reverse stress-induced dendritic spine loss within 12 hours of drug administration but not before 6 hours (3). Intriguingly, blocking the plasticity actions of ketamine abolished its effect on motivated escape behavior in a mouse model, suggesting that sustained antidepressant actions require neural plasticity in the medial frontal cortex (3). Together, these previous studies underscored the importance of dendritic structural remodeling for ketamine's fast-acting antidepressant response. Still, a critical question remained: What is the time window in which ketamine engages neural plasticity to facilitate the behavioral improvements?

In the current study, Wu *et al.* (4) developed an innovative method to probe a neuron's likelihood to form new connections at the dendrites, termed plasticity potential, and applied it to investigate the timing of ketamine's plasticity actions. The approach relies on the knowledge that a local burst of glutamate efflux is sufficient to produce a new dendritic spine in a cortical pyramidal neuron (5). Briefly, the authors used two-photon imaging to visualize dendrites of a layer 5 pyramidal neuron from brain slices of the medial frontal cortex, then performed two-photon uncaging of glutamate over a small volume near a dendritic branch to evoke spinogenesis. Using this approach, Wu *et al.* (4) found that under control conditions new dendritic spines appeared 20% to 25% of the time. In the ketamine conditions, brain slices were collected at 2, 4, 12, 24, and 72 hours after administration. By the 2-hour time point, treatment significantly increased the probability of glutamate-evoked spinogenesis to ~50%. Notably, this time course corresponds to the time of a behavioral transition in ketamine-treated mice, where acute hyperlocomotor effects cease (6) and depressive-like behaviors begin to improve (3). The elevated plasticity potential was detected after 4 hours but dissipated by 12 hours, indicating a limited time window, which preceded the subsequent long-term increase in dendritic spine density. Figure 1 shows the time courses plotted in the context of behavioral timing reported by previous studies.

Alongside our growing understanding of the time scale of ketamine's effect, the underlying molecular and cellular mechanisms are also becoming more evident, including the role of dopamine. In one early study, subanesthetic ketamine increased the level of dopamine in the medial prefrontal cortex acutely for ~2 hours after drug injection (7). More recently, it was shown that photostimulation of neurons expressing the dopamine Drd1 receptor produced sustained antidepressant-like effects for up to 7 days, mimicking the effects of ketamine (8). By contrast, silencing Drd1-expressing neurons blocked the antidepressant action of ketamine (8). Overall, these results suggest that Drd1-expressing neurons could be relevant to the antidepressant effects of ketamine, but whether it was the cell type or if there was a more specific role for the dopamine receptor remained unclear.

In light of the above, Wu *et al.* (4) provide mechanistic insights into the link between dopamine signaling, specifically protein kinase A (PKA) signal transduction through Drd1 receptors, and the actions of ketamine. To dive into the mechanism of the Drd1 receptor, Wu *et al.* (4) started with three complementary experiments. First, they antagonized Drd1 receptors to block the increased spinogenesis evoked by ketamine, showing that Drd1 receptors are necessary for the drug's

SEE CORRESPONDING ARTICLE ON PAGE 1096

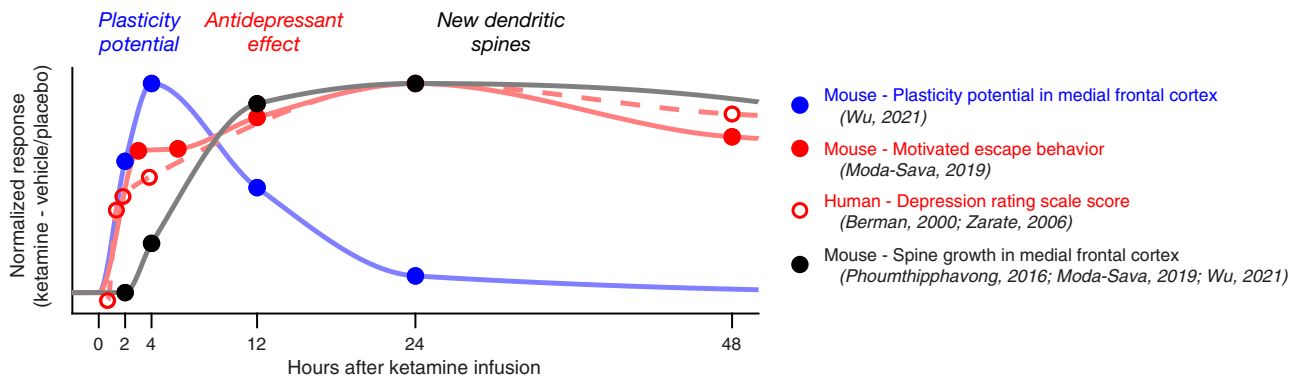


Figure 1. A schematic of the reported time courses of ketamine's neural and behavioral effects in mice and humans. Circles denote the response, normalized by subtracting effects of ketamine from vehicle or placebo, at specific time points as reported in the current and previous studies.

plasticity actions. Next, they used chemogenetic tools to inhibit dopaminergic neurons in the ventral tegmental area. Not surprisingly, the inhibition abolished the effect of ketamine on evoked spinogenesis as well as the delayed increase in spine density. Conditionally knocking out *Drd1* receptors in the medial prefrontal cortex similarly abolished ketamine's enhancement of evoked spinogenesis. Intriguingly, direct activation of *Drd1* receptors with the agonist SKF81297 mimicked ketamine's impact on evoked spinogenesis. Taken together, these results demonstrated that signaling via *Drd1* receptors mediates the increase in plasticity potential due to ketamine administration. Wu *et al.* (4) then sought to uncover the signal transduction pathways that may underlie *Drd1* receptor-dependent spinogenesis. One possibility is that the initiation of spinogenesis depends on glutamate but that further enhancement requires the stimulatory actions of PKA downstream of G_{α_s} -coupled *Drd1* receptors. Consistent with this hypothesis, Wu *et al.* (4) showed that bath application of the PKA suppressor H-89 or overexpression of endogenous PKA inhibitor blocked the expected increase in evoked spinogenesis by agonist activity at *Drd1* receptors. Overall, these experiments underscore the essential role of *Drd1*-PKA signaling for the plasticity actions of ketamine on frontal cortical pyramidal neurons.

While the above findings provided insights into neural mechanisms, a key question remained: Does *Drd1* receptor-dependent spinogenesis contribute to the antidepressant action of ketamine? To examine this possibility, Wu *et al.* (4) used a learned helplessness model of depressive-like pathophysiology in mice. This paradigm is based on the finding that rodents exposed to an acute stressor, in this case inescapable foot shocks, have lasting deficits in motivated escape behavior. In the current study, mice exposed to inescapable foot shocks were less likely to escape subsequent avoidable foot shocks and showed a concomitant reduction in glutamate-evoked spinogenesis. Conversely, ketamine was effective at correcting both the neural and behavioral deficits. Wu *et al.* (4) went on to show that the corrective effects of ketamine on behavior may depend on dopamine release in frontal cortex. On one hand, in the absence of ketamine, optogenetically or chemogenetically

evoked activity of dopaminergic axon terminals in the medial frontal cortex was sufficient to rescue motivated escape behavior following learned helplessness. On the other hand, when dopamine release in the medial prefrontal cortex was chemogenetically inhibited, the corrective effects of ketamine on behavior were abolished. Together, this exhaustive set of experiments implicate dopamine signaling in the antidepressant-like actions of ketamine.

The current study highlights dopaminergic transmission in the frontal cortex as a key ingredient in the plasticity actions of ketamine. Yet dopamine was studied in the context of glutamate-evoked spinogenesis, and additional glutamatergic mechanisms have been implicated in ketamine's action. For instance, ketamine antagonizes NMDA receptors in dendrite-targeting GABAergic interneurons to increase dendritic excitability of pyramidal neurons (6). This cortical microcircuit mechanism may underlie several of ketamine's puzzling effects on neural activity and behavior, including the enhancement of synaptic plasticity (9). On a longer time scale, synaptic strength is maintained and stabilized through compensatory mechanisms. Ketamine may act to shift homeostatic set points to influence neural plasticity (10). How these different molecular and microcircuit mechanisms come together with dopamine signaling to exert antidepressant actions remains to be resolved. To this end, more studies are needed to develop a complete picture of ketamine's efficacy and biological action.

To summarize, at the beginning of this commentary, we talked about finding out when and how ketamine promotes structural plasticity. For the when, Wu *et al.* (4) showed that the potential for glutamate-evoked spinogenesis rapidly increased 2 hours after ketamine administration. This effect curiously corresponds to the start of behavioral improvement and precedes the rise in dendritic spine density. For the how, dopamine, through *Drd1*-mediated activation of PKA, was shown to be instrumental to the plasticity actions of ketamine in the frontal cortex. Knowing when ketamine promotes structural plasticity, we may leverage or potentially extend the time window of spinogenesis using interventions that augment the plasticity actions. Knowing how ketamine enhances structural plasticity may help uncover novel targets for developing better, more precise rapid-acting antidepressants.

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Article Information

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