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DEPRESSION

Lasting restoration

> “the lasting antidepressant effects of ketamine may depend on newly formed spines”

Ketamine has rapid-onset and long-lasting antidepressant effects, but whether the same circuit-level mechanisms underlie its acute and more long-term effects is unknown. Now, Moda-Sava et al. demonstrate in mice that some of the sustained antidepressant effects of ketamine result from targeted increases in spine formation in the prefrontal cortex (PFC).

The authors used two-photon microscopy to track postsynaptic spines on the dendrites of PFC projection neurons in a model of depression in which mice were chronically exposed to corticosterone (CORT; a stress hormone) in their drinking water. CORT-treated mice showed increased immobility in the tail-suspension test (TST; an assay of motivated escape behaviour) and reduced sucrose preference (indicating anhedonia). CORT exposure drove spine elimination, and the sites of eliminated spines were more spatially clustered together on specific dendrites than would be expected by chance. Similar behavioural and spine-dynamic changes were observed in the repeated restraint stress model of depression, implying that these results may be generalizable.

The depression-like behaviours induced by chronic CORT exposure were abolished from 3 hours until at least 24 hours after a single dose of ketamine. Ketamine also increased the rate of spine formation in the PFC 12–24 hours after treatment, with newly formed spines also showing spatial clustering and branch specificity. Nearly half of the new spines formed less than 2 µm from where a spine was previously eliminated during the CORT treatment, suggesting that ketamine may induce partial restoration of CORT-eliminated spines.

Previous work has shown that nearly all newly formed spines that last 4 days or longer feature functional synapses. In this study, spines that formed at or close to a spine elimination site (restored spines) were more likely to last 4 days than spines formed de novo. Moreover, ketamine reversed the decrease in expression of postsynaptic density protein 95 (PSD95) induced by CORT. Therefore, ketamine-restored spines probably contain functional synapses.

Next, the authors used calcium imaging to investigate the effects of CORT and ketamine on PFC activity. PFC populations in naive mice showed synchronized calcium transient events. In animals chronically exposed to CORT, these events were less frequent and involved fewer neurons, but these changes were reversed by ketamine. In the TST, increases in calcium transients in the ventromedial PFC during bouts of immobility predicted the onset of a bout of struggling about a second later. CORT-exposed mice in the TST showed fewer calcium transients and longer bouts of immobility — effects all rapidly reversed by ketamine. Thus, ketamine reverses CORT-induced deficits in PFC function.

The rapid antidepressant effects of ketamine preceded changes in spine formation, prompting the authors to hypothesize that the lasting antidepressant effects of ketamine may depend on newly formed spines. To test this, the authors expressed activated-synapse-targeting photoactivatable RAC1 (AS-PaRAC1) in the medial PFC of mice that were subsequently exposed to CORT for 10 days and treated with ketamine on day 11. When photoactivated, AS-PaRAC1 selectively shrinks newly potentiated spines; here, the authors photo-activated AS-PaRAC1 either 3 or 24 hours after ketamine treatment, and assessed the lasting effects of ketamine 2 days after treatment, on day 13. AS-PaRAC1 activation 3 hours after ketamine treatment did not reduce the acute antidepressant effects in the TST. However, eliminating new spines formed 1 day after ketamine treatment blocked the lasting effects of ketamine on PFC calcium transients and behaviour in the TST. Notably, the same treatment did not reduce the sustained antidepressant effects of ketamine in the sucrose preference test, suggesting that PFC spine formation does not underlie the sustained effects of ketamine on anhedonia.

Together, these findings imply that the lasting (but not acute) antidepressant effects of ketamine on motivated escape behaviour depend on the restoration of dendritic spines on PFC projection neurons.

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ORIGINAL ARTICLE Moda-Sava, R. N. et al. Sustained rescue of prefrontal circuit dysfunction by antidepressant-induced spine formation. *Science* **364**, eaat8078 (2019)