MOOD DISORDERS

Targeting protein synthesis for fast antidepressant action

Ketamine, an injectable drug that is used to induce anaesthesia in surgery, also has a rapid and sustained antidepressant effect. However, its psychotomimetic and cognitive effects preclude its long-term use. As currently available antidepressants commonly take weeks to reach efficacy, understanding the fast mechanism of action of ketamine could aid the development of much-needed treatment options for patients with major depressive disorders. Now, Monteggia and colleagues show that the rapid synthesis of brain-derived neurotrophic factor (BDNF) that results from the ketamine-mediated blockade of *N*-methyl-D-aspartate receptors (NMDARs) is responsible for the fast-acting antidepressant effects of the drug in mice.

First, the authors determined the time course of behavioural antidepressant effects in wild-type mice, by carrying out antidepressant-predictive tasks such as the forced swim test (FST), and in a mouse model of depression, following the administration of a single low dose (3 mg per kg) of ketamine. In agreement with previous findings, an antidepressant-like response was observed after 30 minutes and lasted for 1 week. Similarly, acute treatment with conventional antidepressants (such as the selective serotonin reuptake inhibitor fluoxetine or the tricyclic antidepressant imipramine) did not produce these antidepressant-like responses.

Ketamine blocks NMDARs at the phencyclidine site within the ionotropic channel, but little is known about the downstream signalling events that lead to its antidepressant effects. In this study, the authors investigated whether BDNF, which is involved in the pathophysiology of mood-related disorders, could be mediating the antidepressant effects of ketamine. Interestingly, ketamine did not have an antidepressant effect in BDNF-knockout mice or in mice in which the BDNF receptor TRKB had been conditionally knocked out. Furthermore, they found that ketamine triggers a rapid but transient increase in BDNF protein translation in the hippocampus, which is required for the fast-acting and long-lasting antidepressant response.

NMDAR blockade in the absence of neuronal activity has been shown to trigger protein synthesis by dephosphorylating and activating eukaryotic elongation factor 2 (EEF2), which is a key mediator of ribosomal translocation. Here, the authors show that in ketamine-treated neurons there is a decrease in EEF2 phosphorylation, which allows for an increase in BDNF translation. Treatment of wild-type

mice with EEF2 kinase (EEF2K) inhibitors also led to a decrease in EEF2 phosphorylation and an increase in levels of BDNF protein in the hippocampus. Importantly, these inhibitors exerted antidepressant-like effects in the FST after 30 minutes, a timescale that is comparable to ketamine. No such responses were observed in the BDNF-knockout mice, which indicates that BDNF expression following EEF2K inhibition is required for producing antidepressant-like responses. This study suggests that EEF2K might be a novel target for the development of fast-acting antidepressants.

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