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Research Highlight

Blocking NMDA receptor at rest: a possible alleviation of depression

Wei LU

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Depression is a common but serious illness, which is described as a state of low mood or mood disorder that involves feelings of sadness lasting for two weeks or longer[1]. Depressed people may suffer from a spectrum of syndromes, including change of sleep habitation or pattern, dramatic weight loss, cognitive impairments or even suicide. One conventional antidepressant medication is selective serotonin re-uptake inhibitor[2, 3]. However, the weeks delay of its efficacy constitutes the major drawback of this treatment[3]. Therefore, fast-acting antidepressants are urgently needed for clinical treatment of depression. Autry *et al* reported in a recent issue of *Nature* that *N*-methyl-*D*-aspartate receptor (NMDAR) antagonists could be such candidates by triggering rapid behavioural antidepressant responses[4].

It was previously observed that patients with major depressive disorder symptoms could be relieved shortly after a single low-dose intravenous infusion of ketamine, a non-competitive NMDAR antagonist, with the effects lasting up to two weeks[5, 6]. This exciting observation inspires the authors to investigate the underlying cellular mechanisms. The authors first found that non-competitive NMDAR antagonists ketamine, CPP and MK-801 reduced immobility of wiled-type C57BL/6 mice in notable behavioural responses, such as the forced swim test (FST) and novelty-suppressed feeding (NSF), and the antidepressant-like behavioural effects of ketamine and CPP emerged as early as 30 min after the administration and persisted for at least 24 h. Because NMDAR antagonists applied acutely *in vivo* are eliminated within hours, it is more likely that the long-lasting antidepressant effects come from synaptic plasticity caused by the acute blockade of NMDAR. Brain-derived neurotrophic factor (BDNF) has been proved to be involved in both synaptic plasticity and antidepressant action[7, 8]. This study further demonstrated that fast-acting antidepressant responses required rapid increase in the translation of BDNF protein and TrkB activation, which might in turn initiated synaptic plasticity. Many forms of activity-dependent plasticity require NMDAR activation[9]. Thus, blockade of NMDAR does not seem to be in favor of triggering plasticity that might underlie the fast-acting antidepressant responses.

It has been found that the spontaneous and evoked forms of glutamatergic activity may utilize distinct signaling pathway[10, 11]. It is possible that NMDAR blockade would initiate a different signaling pathway that depends on spontaneous activity. Eukaryotic elongation factor 2 (eEF2) is a critical catalytic factor for ribosomal translation during protein synthesis. It has been proposed that NMDAR activity at rest would affect eEF2 phosphorylation and subsequent translation of target transcripts[12]. The authors demonstrated that ketamine at rest inhibited spontaneous mEPSCs and dose-dependently de-phosphorylated eEF2, allowing translation of target proteins. These results demonstrated that ketamine's rapid antidepressant effect results from inhibition of NMDAR-mediated spontaneous synaptic responses, leading to decreased eEF2K activity and subsequent attenuated eEF2 phosphorylation, which in turn rapidly increases BDNF translation.

The authors elegantly elucidate the cellular mechanisms underlying fast-antidepressant responses of a single, low-dose intravenous infusion of ketamine under clinical treatment and provides the first evidence that tonic resting glutamatergic neurotransmission is involved in behavior. Moreover, this study shed new light on the potential of therapeutic approaches on translational machinery. eEF2 is proposed to be the key molecule involved in synaptic BDNF translation that act downstream of NMDAR blockade and could be novel therapeutic targets for the development of faster-acting antidepressants.

Future challenge will be to examine the possible involvement of extrasynaptic NMDAR blockade in the fast-acting antidepressant responses. Ambient

Department of Neurobiology, Nanjing Medical University, Nanjing, 210029, China
Correspondence: Prof Wei LU
(luweishmu2@yahoo.com.cn)

tonic NMDAR activation by extracellular glutamate has been detected under basal condition[13]. Ketamine can abolish both spontaneous synaptic and extrasynaptic NMDAR responses. Recent evidence suggests that activation of extrasynaptic NMDAR induces neuronal death in pathological conditions, whereas synaptic NMDAR promotes neuronal survival in physiological conditions[14, 15]. Blockade of spontaneous activity of the extrasynaptic NMDARs might be able to trigger a distinct signaling pathway involving eEF2. In addition, previous studies support the involvement of cortical mTOR signaling in ketamine-mediated antidepressant responses and the blockade of the responses by rapamycin[16]. These findings are obviously inconsistent with the results of this study. More works are needed to resolve the discrepancies. Moreover, considering the fundamental roles of NMDAR in neuronal functions, possible side effects should be also mindful if the period of clinical ketamine treatment needs to be prolonged.

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