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EDITORIAL

Brain-derived neurotrophic factor-TrkB signaling and the mechanism of antidepressant activity by ketamine in mood disorders

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Brain-derived neurotrophic factor (BDNF) plays a key role in the pathophysiology of mood disorders such as major depressive disorder (MDD) and bipolar disorder (BD). According to the Biomarkers Definitions Working Group, BDNF is one of the most frequently investigated blood biomarkers in mood disorders. In this issue, Schröter et al. [1] investigated longitudinal multi-level biomarker analysis of BDNF in patients with MDD ($n=49$), BD ($n=37$) and healthy control subjects ($n=57$). The serum level of BDNF in patients with MDD was significantly lower than that in the healthy controls, but there was no difference between the serum levels of BDNF in the BD patients and healthy controls. Furthermore, methylation of *BDNF* exon I promoter in patients with MDD, but not BD patients, was significantly higher than that of healthy controls. However, there were no differences in serum BDNF levels and *BDNF* methylation between the samples from admission and discharge from the hospital. Furthermore, Engelmann et al. [2] reported that patients with MDD ($n=39$) who exhibited a normalization of memory dysfunction (i.e., delayed recall performance) had significantly higher plasma BDNF levels from baseline to day 56 than patients with persistent deficits ($n=43$), suggesting that BDNF influences the mechanisms underlying the normalization of memory dysfunction in MDD. However, the ELISA kit used in this study can recognize both BDNF (mature form) and its precursor proBDNF [3]. Given the opposite roles of BDNF (mature form) and proBDNF, further studies using ELISA kits that can specifically differentiate into mature BDNF and proBDNF are needed.

Patients with pain are more likely to be depressed compared with patients without pain, which is frequently followed by anhedonia (i.e., loss of ability to feel pleasure). In this issue, Fang et al. [4] investigated the role of BDNF and its receptor tropomyosin receptor kinase B (TrkB) in the development of neuropathic pain-induced anhedonia using a spared nerve injury (SNI) rat model. The SNI rats were divided into two groups based on the results of a sucrose preference test. Rats with the anhedonia-like phenotype exhibited a lower expression of BDNF in the medial prefrontal cortex (mPFC) than the rats without anhedonia-like phenotype and the sham-operated rats. Interestingly, a single injection of 7,8-dihydroxyflavone, a TrkB agonist, ameliorated the reduction in sucrose preference and reduction in BDNF-TrkB signaling in the mPFC of rats with anhedonia-like phenotype. This study suggests that BDNF-TrkB signaling in the mPFC plays a role in the mechanism of neuropathic pain-induced anhedonia [4]. Therefore, it is likely that TrkB agonists have a high potential for becoming therapeutic drugs for pain-related anhedonia. Furthermore, gut microbiota play a role in the mechanism of neuropathic pain-induced anhedonia in SNI rats with the anhedonia-like phenotype [5]. Interestingly, fecal microbiota transplantation from SNI rats with or without anhedonia could alter pain and depression- and anhedonia-like phenotypes in the mice treated with an antibiotic cocktail [5]. Collectively, it is likely that the brain–gut–microbiota axis might play a role in the mechanism of pain, as well as in the expression of depression-like phenotypes, including anhedonia, in rodents.

The discovery of the robust antidepressant actions of (*R,S*)-ketamine in treatment-resistant patients with MDD and BD is serendipitous in the field of depression research [6, 7]. BDNF-TrkB signaling is known to play a key role in the antidepressant effects of (*R,S*)-ketamine and its enantiomers [6, 7], but the precise molecular and cellular mechanisms underlying the antidepressant effects of (*R,S*)-ketamine and its enantiomers remain to be elucidated. In a double-blind, randomized, placebo-controlled study on healthy control subjects ($n=61$), Li et al. [8] reported that a decrease in functional connectivity (FC) between the posterior cingulate cortex (PCC) and dorsomedial prefrontal

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cortex (dmPFC) was shown at 24 h after infusion with (*R,S*)-ketamine (0.5 mg/kg over 40 min) and that the decrease in FC was correlated with the change in glutamatergic level in the perigenual anterior cingulate cortex at 24 h. This study suggests that (*R,S*)-ketamine produces a decrease in the FC of PCC-dmPFC at 24 h post-infusion in healthy control subjects, which is correlated with delayed changes in glutamatergic levels [8]. In contrast, it has been reported that (*R,S*)-ketamine infusion (0.5 mg/kg over 40 min) produces depressive symptoms (i.e., anhedonia) in healthy subjects [9]. Therefore, further studies of (*R,S*)-ketamine infusion in treatment-resistant patients with MDD or BD are needed.

On March 5, 2019, the United States Food Drug Administration approved the use of (*S*)-ketamine [(*S*)-enantiomer of (*R,S*)-ketamine] nasal spray for treatment-resistant depression. On December 19, 2019, (*S*)-ketamine nasal spray was approved in Europe. Because of a risk for serious adverse effects caused by (*S*)-ketamine nasal spray, it is only available in the hospital via a restricted distribution system under a Risk Evaluation and Mitigation Strategy. However, several important concerns about the efficacy of (*S*)-ketamine nasal spray have been pointed [10, 11]. An accumulation of preclinical data in rodent models of depression show that (*R*)-ketamine, another enantiomer of (*R,S*)-ketamine, has greater potency and much more long-lasting antidepressant effects than (*S*)-ketamine; the adverse effects of (*R*)-ketamine are less serious than (*S*)-ketamine [6, 7]. In this issue, Chang et al. [12] have reported that dopamine D_1 receptors may not influence the rapid and sustained antidepressant effects of (*R*)-ketamine, because the dopamine D_1 receptor antagonist did not block the antidepressant-like effects of (*R*)-ketamine in a chronic social defeat stress model of depression.

Clinical studies of (*R*)-ketamine in patients with MDD are currently being performed. We look forward to the results of studies analyzing (*R*)-ketamine infusion in patents with MDD and BD in the near future. In addition, investigating the role of BDNF-TrkB signaling in the antidepressant mechanisms of ketamine enantiomers in patients with MDD or BD is highly anticipated.

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Compliance with ethical standards

Conflict of interest Dr. Hashimoto is the inventor of filed patent applications on "The use of *R*-ketamine in the treatment of psychiatric diseases" and "(*S*)-norketamine and salt thereof as pharmaceutical" by the Chiba University.

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