

Novel mode of antidepressant action based on exercise-induced beneficial effects

Makoto Kondo, Shoichi Shimada

Dept. Neurosci & Cell Biol., Grad. Sch. Med., Osaka Univ.

Major depression is a highly prevalent mental disorder affecting many people worldwide. Although selective serotonin reuptake inhibitors (SSRIs) are the most widely used antidepressants, a significant proportion of depressed patients do not achieve remission after initial treatment. It has been known that physical exercise provides neurogenic and antidepressant effects, and we recently demonstrated that the serotonin type 3 (5HT₃) receptor is essential for exercise-induced hippocampal neurogenesis and antidepressant effects. In this study, we examined the 5HT₃ receptor-mediated mechanism underlying hippocampal neurogenesis and antidepressant effects, and tried to establish novel prevention and treatment for depression, which is based on mechanisms of exercise-induced beneficial effects. Here, we showed that treatment with a 5HT₃ receptor agonist induces antidepressant effects and increases hippocampal neurogenesis, in a fluoxetine-independent manner. In addition, histological analyses revealed that the 5HT₃ receptor and insulin-like growth factor 1 (IGF1) are expressed in the same neurons in the hippocampal dentate gyrus. Furthermore, *in vivo* microdialysis and drug microinjection analyses showed that 5HT₃ receptor agonist treatment increases extracellular IGF1 levels in the hippocampus, and that IGF1 signaling is required for the 5HT₃ receptor-dependent hippocampal neurogenesis. Our findings suggest a novel 5HT₃ receptor-IGF1 mechanism that is distinct from fluoxetine-induced responses. A novel mode of antidepressant action could provide a new therapeutic target for depression, especially bringing significant benefits for SSRI-resistant depressed patients.