Anti-depressant fluoxetine reveals its therapeutic effect via astrocytes

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Astrocytes, the most abundant glial cells, have been focused on in the pathogenesis of depression recently. It is thought that antidepressants mediate their therapeutic effects by acting on neurons especially monoaminergic neurons, but they also act on glial cells including astrocytes. However, how astrocytes respond to antidepressants, and whether their responses are involved in therapeutic effects are poorly understood. The purpose of this study is to investigate the influence of fluoxetine (FLX), one of the most commonly prescribed drugs for the treatment of depression, on astrocytes.

Astrocytes are active regulators of brain functions by releasing so-called gliotransmitters such as ATP, and vesicular nucleotide transporter (VNUT)-dependent exocytosis is one of the pathways for ATP release. First, we revealed that FLX increased ATP exocytosis via VNUT in primary culture of hippocampal astrocytes, and FLX-evoked ATP release was inhibited in hippocampal astrocytes obtained from VNUT-knockout mice. We conducted in vivo ATP analysis and behavioral test in astrocyte-specific VNUT-knockout and overexpression mice after chronic administration of FLX. FLX-induced anti-depressive behavior was decreased in astrocyte-selective VNUT-knockout mice, but it was increased when astrocyte-selective VNUT was overexpressed in mice, correlating with ATP amounts in hippocampal tissues. This suggests that astrocytic ATP exocytosis via VNUT is required and sufficient to mediate the therapeutic effect of FLX.

Brain-derived neurotrophic factor (BDNF) is considered to have a major role in the therapeutic action of antidepressants. Using immunohistochemical analysis, we found chronic administration of FLX increased BDNF expression in hippocampal astrocytes, as well as neurons. Next, we investigated the mechanisms underlying the FLX-evoked increase in BDNF in hippocampal astrocytes, with a focus on extracellular ATP-mediated signals. The stimulation of ATP and its metabolite adenosine increased Bdnf mRNA and BDNF protein levels in a primary culture of hippocampal astrocytes. Moreover, based on our pharmacological analyses, we showed that ATP and adenosine act on P2Y₁₁ and adenosine A2b receptors, respectively, and upregulate BDNF via cAMP/PKA/pCREB-dependent pathways.

In conclusion, we demonstrated that the anti-depressant FLX acted on astrocytes and mediated its therapeutic effects by facilitating VNUT-dependent ATP exocytosis, causing an increase in BDNF in astrocytes.