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NMDA受容体拮抗薬ケタミンの即効性抗うつ作用における“神経栄養因子”VEGFの役割

Role of "a neurotrophic factor" VEGF in the rapid antidepressant actions of the NMDA receptor antagonist ketamine

○出山 諭司[1]
○Satoshi Deyama[1]

1. 金沢大院医薬保
1. Inst Med Pharm Health Sci, Kanazawa Univ

Ketamine, an NMDA receptor antagonist, produces rapid and sustained antidepressant actions in patients with treatment-resistant depression. Previous studies have shown that depression is associated with reduced levels of neurotrophic factors including brain-derived neurotrophic factor (BDNF) and vascular endothelial growth factor (VEGF), contributing to neuronal atrophy in the medial prefrontal cortex (mPFC) and hippocampus, and that activity-dependent BDNF release in the mPFC is essential for the rapid antidepressant actions of ketamine. VEGF is a pleiotropic growth factor expressed by neurons and astrocytes, as well as endothelial cells, in the brain and exerts potent neurotrophic effects primarily via a high-affinity tyrosine kinase receptor Flk-1. Although VEGF has been implicated in the effects of conventional monoaminergic antidepressants, the role of VEGF in the antidepressant actions of ketamine has remained unclear. Recently, we have demonstrated that the rapid antidepressant actions of ketamine are blocked by forebrain excitatory neuron-specific deletion of either VEGF or Flk-1, intra-mPFC infusion of a VEGF neutralizing antibody, or local knockdown of Flk-1 in mPFC excitatory neurons. Intra-mPFC infusion of VEGF is sufficient to produce ketamine-like antidepressant effects via neuronal Flk-1. Moreover, ketamine increases spine density in the apical tuft of mPFC layer V pyramidal neurons, and this neurotrophic/synaptogenic effect is blocked in mice with excitatory neuron-specific VEGF deletion in the forebrain. These findings indicate that neuronal VEGF signaling in the mPFC plays a key role in the rapid antidepressant actions of ketamine.

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