

Role of prefrontal VEGF signaling in the rapid antidepressant actions of ketamine

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Previous studies have shown that the NMDA receptor antagonist ketamine produces rapid and sustained antidepressant effects in treatment-resistant depressed patients, and that brain-derived neurotrophic factor (BDNF) signaling in the medial prefrontal cortex (mPFC) mediates the antidepressant actions of ketamine. Recently, we have found that the antidepressant-like effects of ketamine are blocked by forebrain excitatory neuron-specific deletion of either vascular endothelial growth factor (VEGF) or its receptor 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 behavioral actions, which are blocked by neuron-specific Flk-1 deletion. Moreover, inhibition of neuronal VEGF signaling blocks the neurotrophic/synaptogenic effects of ketamine. These findings indicate that neuronal VEGF-Flk-1 signaling in the mPFC plays a key role in the antidepressant actions of ketamine. We have also demonstrated that a heterologous interplay between BDNF and VEGF signaling in the mPFC is required to produce ketamine-like antidepressant responses to these neurotrophic factors. Together, these findings provide evidence for the neurotrophic mechanisms underlying the rapid and sustained antidepressant actions of ketamine, and pave the way for the development of rapid and more effective antidepressants with fewer side effects than ketamine.