

Commentary

Brain-Derived Neurotrophic Factor and Vascular Endothelial Growth Factor: Siamese Twins in the Antidepressant Action

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More than two decades ago, Ron Duman's lab found that electroconvulsive shock and some antidepressants increased the expression of brain-derived neurotrophic factor (BDNF) in the rat brain, and this finding laid the foundation for the neurotrophic factor hypothesis of antidepressant drug action [1]. Subsequent research by several groups has largely confirmed this hypothesis. BDNF is the central regulator of neuronal plasticity and BDNF signaling through its receptor TRKB is both necessary and sufficient for the antidepressant action of most, if not all, antidepressants. More recently, Duman's lab searched for other factors that are activated by antidepressant treatments and found that vascular endothelial growth factor (VEGF) is activated by them and needed for their effects [2].

Through BDNF and VEGF signaling, antidepressants promote many forms of neuronal plasticity in many brain regions, including synaptogenesis, spine formation, branching of axons and dendrites as well as hippocampal neurogenesis [3]. By providing an opportunity for activity-dependent beneficial reorganization of neuronal networks underlying mood regulation, this antidepressant-induced plasticity may lead to the clinical antidepressant effect [3].

Plastic changes may take time, and this has been thought to produce the delay of days or weeks in the appearance in the clinical action of typical antidepressants, such as serotonin selective and tricyclic antidepressants. In contrast, ketamine has recently been shown to produce antidepressant effects that develop within minutes and last for several days, even if ketamine itself exits the body within hours [4]. Although the temporal profile of ketamine is very different from that of conventional antidepressants, it was soon shown that ketamine, too, activated BDNF signaling and required it for its antidepressant effects. Furthermore, VEGF is also required for the rapid effects of ketamine. In a series of experiments to pinpoint the mechanism and site of action of ketamine, Duman's lab has shown that signaling of BDNF or VEGF in the rodent median prefrontal cortex (mPFC), the region homologous to the mPFC in humans, is critical for ketamine-induced antidepressant-like effects [4, 5].

Clinical data supports the role of BDNF and VEGF in the pathophysiology of depression. The BDNF Val66Met polymorphism has been associated to human depression, at least in subgroups [6]. Similarly, a single-nucleotide polymorphism in the VEGF gene has been associated to an elevated risk to develop depression [7]. Also, an interaction between the VEGF-related SNP and a volume reduction of the subiculum, an anatomical part of the

hippocampal formation, in depressive patients has been suggested [8].

In a manuscript published in this issue, Deyama, Duman and coworkers investigate the interrelationship between BDNF and VEGF signaling in the prefrontal cortex [9]. Using three different tests for antidepressant-like behavior, they first replicate the findings of the critical role of the prefrontal cortex in the antidepressant effects of both BDNF and VEGF and then go on to demonstrate that a co-injection of an antibody that neutralizes the effects of VEGF together with BDNF into the mPFC blocks the beneficial effects of BDNF in these tests. They then confirmed and extended this finding by showing that a selective deletion of VEGF receptor fetal liver kinase-1 (FLK1) in pyramidal neurons in the mPFC prevents the antidepressant-like effects of BDNF administration, demonstrating that VEGF signaling is required for the antidepressant effects of BDNF. Unexpectedly, they find that co-injection of antibodies against BDNF into the mPFC blocks the antidepressant-like effects of VEGF, indicating an unusual mutual dependence of these two growth factors on each other. Experiments in cultured cortical neurons confirmed this mutual dependence: VEGF increased BDNF release in cultured neurons and pharmacological blockade of BDNF signaling prevented the growth-promoting effects of VEGF in cultured neurons. Conversely, BDNF increased VEGF release and drugs that block VEGF signaling prevented the neurotrophic effects of BDNF. Together these findings clearly demonstrate that the antidepressant and trophic effects of BDNF and VEGF depend on each other and are intertwined like Siamese twins.

How is this mutual dependence explained at cellular and molecular levels? Deyama et al. suggest a model where glutamate release from a presynaptic neuron in the PFC induces the release of both BDNF and VEGF from a postsynaptic pyramidal neuron, which leads to the activation of their receptors TRKB and FLK1, respectively, in the same neurons in an autocrine manner. However, both TRKB and FLK1 are receptor tyrosine kinases, and the signaling pathways known to be activated by them are very similar. Previous work has shown that VEGF, through FLK1, activates the phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt)/mechanistic target of rapamycin complex 1 (mTOR) pathway, which is also known to be activated by BDNF-TRKB signaling. Further, FLK1 activates phospholipase C γ (PLC γ), leading to the release of Ca $^{2+}$ from intracellular stores, and this pathway, too, is activated by TRKB. If the signaling pathways are shared, why is the activation of both receptors required? The authors did not perform dose-response studies, so it

is possible that a higher dose of either growth factor would make the other unnecessary. However, this is unlikely, since the dose of BDNF is already relatively high and intracortical injection produces a concentration gradient with high doses at the site of injection and lower further away, which produces a range of concentration in the tissue. There may be pathways less well characterized that are preferentially activated by only one of the factors, and a synergistic effect of these pathways may be necessary for the proper antidepressant effect.

The results of Deyama et al. do not rule out a contribution of additional cell types. The experiments presented by the authors establish the localization of the FLK1 receptor into pyramidal neurons, but BDNF and VEGF are both secreted molecules that can diffuse some distant from their release site and therefore activate also other cells than the direct pre- and postsynaptic neurons. In fact, parvalbumin-containing (PV) interneurons have been implicated in the action of ketamine, and although these cells do not express BDNF, they abundantly express TRKB receptors and VEGF. Therefore, activity-dependent release of BDNF might activate TRKB receptors in PV cells, which could stimulate VEGF release and FLK1 activation in pyramidal neurons (Figure 1). Alternatively, since PV neurons are known to be powerful regulators of plasticity of ensembles of pyramidal neurons, VEGF-induced FLK1 signaling might release BDNF from pyramidal neurons that through TrkB activation in PV interneurons might set the stage for pyramidal cell plasticity and synaptogenesis, which would then be necessary for the antidepressant action. The latter scenario is consistent with the notion that disinhibition through a reduction in PV cell activity is involved in the antidepressant effects of ketamine. Both of these arrangements would place BDNF and VEGF signaling into a serial as opposed to a parallel pathway, and interruption of a serial pathway at any step would be expected to disrupt the function of the entire pathway. Further experiments examining the cellular location of the release and action of BDNF and VEGF would shed more light into these hypothetical scenarios.

Local injection of BDNF into PFC produces antidepressant-like effects and injection of BDNF antibody into the PFC blocks the effects of systemic administration of ketamine, suggesting that the mPFC is a critical region in the brain network mediating antidepressant-like behavior. However, previous studies show that injection of BDNF into hippocampus or midbrain regions also produces antidepressant-like effects [3], and these effects are unlikely due to diffusion of BDNF into the mPFC after injection, because BDNF is very sticky and does not diffuse easily. These studies suggest that the network mediating antidepressant-like behavior is distributed and activation of it by BDNF, and perhaps also by VEGF, at several nodes produces similar effects.

Are the interdependent effects of BDNF and VEGF specific for ketamine or are they required for the actions of other antidepressants as well? Deyama et al. suggest that the difference between rapid acting and typical antidepressants is that both increase the levels of BDNF and VEGF, but only ketamine induces their release. However, behavioral effects of typical antidepressants require BDNF and VEGF signaling [2, 10], and they acutely increase BDNF signaling [10], which suggests that typical antidepressants do increase BDNF release. Therefore, despite of the very different temporal profiles,

ketamine and typical antidepressants activate very similar kind of biological processes.

The intertwined effects of BDNF and VEGF revealed by Deyama et al. [9] suggest that our understanding of antidepressant effects is still rudimentary. The processes that ultimately differentiate the effects of ketamine from typical antidepressants are unclear and why the effects of typical antidepressants take so long to develop remains a mystery. Neuroplastic processes have been linked to depression and the antidepressant action, however, from a clinical perspective, the exact meaning of these processes in both the development of depression and their treatment remains unclear. It is likely that several signaling pathways, cell types, networks and brain areas need to be brought together for an antidepressant response to develop, and even more comprehensive process is likely needed for a long-term remission.

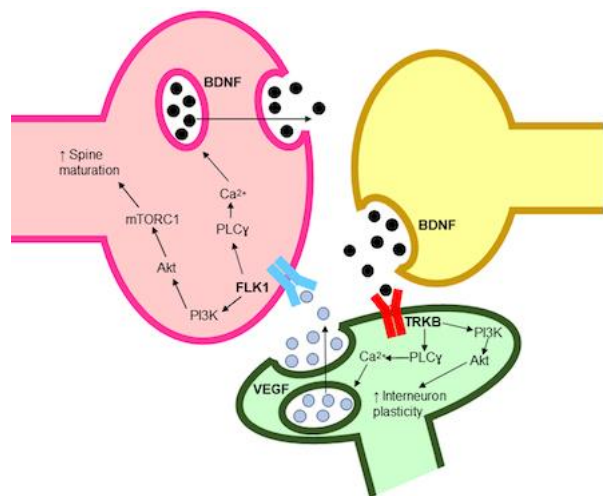


Figure 1: A model for a serial action of BDNF and VEGF in the ketamine action. Akt: protein kinase B; BDNF: brain-derived neurotrophic factor; Ca^{2+} : calcium ion; FLK1: fetal liver kinase 1; mTORC1: mechanistic target of rapamycin complex 1; PI3K: phosphoinositide 3-kinase; PLC γ : phospholipase C γ ; TRKB: tropomyosin-related kinase B; VEGF: vascular endothelial growth factor.

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Article Information

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