Biological Psychiatry: Celebrating 50 Years

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

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More than 2 decades ago, Ronald Duman's laboratory 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 neurotrophic receptor tyrosine kinase 2 (TrkB) is both necessary and sufficient for the antidepressant action of most, if not all, antidepressants. More recently, Duman's laboratory 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).

Antidepressants promote many forms of neuronal plasticity in many brain regions through BDNF and VEGF signaling, including synaptogenesis, spine formation, branching of axons and dendrites, and 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 reuptake inhibitors 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 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 *et al.* (4) and Deyama *et al.* (5) have shown that signaling of BDNF or VEGF in the rodent medial prefrontal cortex (mPFC), the region homologous to the mPFC in humans, is critical for ketamine-induced antidepressant-like effects.

Clinical data support the role of BDNF and VEGF in the pathophysiology of depression. The BDNF Val66Met polymorphism has been associated with human depression, at least in subgroups (6). Similarly, a single nucleotide polymorphism in the VEGF gene has been associated with an elevated risk of developing depression (7). Also, an interaction between the VEGF-related single nucleotide polymorphism and a volume reduction of the subiculum—an anatomical part of the hippocampal formation—has been suggested in patients with depression (8).

In this issue of *Biological Psychiatry*, Deyama *et al.* (9) investigate the interrelationship between BDNF and VEGF signaling in the PFC. Using three different tests for antidepressant-like behavior in rodents, Deyama *et al.* (9) first replicate the findings of the critical role of the PFC in the antidepressant effects of both BDNF and VEGF and then go on to show that a coinjection of an antibody that neutralizes the effects of VEGF together with BDNF into the mPFC blocks the beneficial effects of BDNF in these tests. Deyama *et al.* (9) 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 coinjection 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. These findings clearly show 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.* (9) 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 similar. Previous work has shown that VEGF, through FLK1, activates the phosphoinositide 3-kinase/protein kinase B/mechanistic target of rapamycin complex 1 pathway, which is also known to be activated by BDNF-TrkB signaling. In addition, FLK1 activates phospholipase Cγ, leading to the release of Ca^{2+} from intracellular stores; this pathway, too, is activated by TrkB. If the signaling pathways are shared, why is the activation of both receptors required? Deyama *et al.* (9) did not perform dose-response studies, so it

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is possible that a higher dose of either growth factor would make the other unnecessary. This is unlikely, however, because 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 farther away, which produces a range of concentration in the tissue. There may be pathways that are less well characterized and 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 presented by Deyama *et al.* (9) do not rule out a contribution of additional cell types. The experiments presented in their study establish the localization of the FLK1 receptor into pyramidal neurons, but both BDNF and VEGF are secreted molecules that can diffuse some distance from their release site and therefore also activate cells other than the direct presynaptic 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, given that 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 have shown that injection of BDNF into the hippocampus or midbrain regions also produces antidepressant-like effects (3), and these effects are unlikely to be caused by the diffusion of BDNF into the mPFC after injection because BDNF is sticky and does not diffuse easily. These studies suggest that the network mediating antidepressant-like behavior is distributed and that activation of it at several nodes by BDNF, and perhaps also by VEGF, produces similar effects.

Are the interdependent effects of BDNF and VEGF specific for ketamine or are they required for the actions of other antidepressants? Deyama *et al.* (9) 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, the behavioral effects of typical antidepressants require BDNF and VEGF signaling (2,10), and they acutely increase BDNF signaling (10), which suggests that

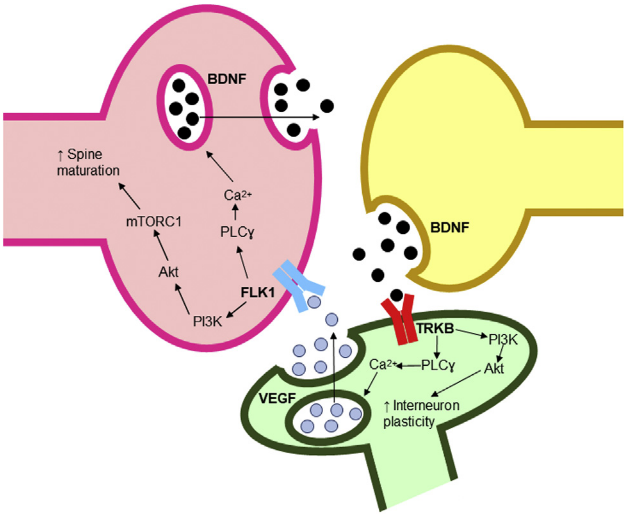

Figure 1. A model for a serial action of brain-derived neurotrophic factor (BDNF) and vascular endothelial growth factor (VEGF) in the action of ketamine. Akt, protein kinase B; Ca^{2+}, calcium ion; FLK1, fetal liver kinase 1; mTORC1, mechanistic target of rapamycin complex 1; PI3K, phosphoinositide 3-kinase; PLCγ, phospholipase Cγ; TrkB, neurotrophic receptor tyrosine kinase 2.

typical antidepressants do increase BDNF release. Therefore, despite the different temporal profiles, ketamine and typical antidepressants activate similar types 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 that an even more comprehensive process is likely needed for long-term remission.

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