New Insights Into BDNF Signaling: Relevance to Major Depression and Antidepressant Action

Major depressive disorder is a serious multifactorial mental illness that is characterized by disruptions in multiple symptom domains, including affect, reward, suicidality, cognition, and homeostasis (1). According to the National Institute of Mental Health, it is the leading cause of disability for individuals 15–44 years old, affecting 18.4 million Americans (or 6.7% of the adult population) each year (2). Its prevalence is higher in women, who often report more severe symptoms and longer illness duration. Only 36.8% of patients achieve remission in response to first-line treatment, and a cumulative total of 67% achieve remission following multiple treatment trials that may take several months or years (3). Given its burden of disease, it is imperative that we improve our understanding of the pathophysiology of major depression, with the hope of developing more efficacious treatments.

Emerging evidence points to the impaired signaling of brain-derived neurotrophic factor (BDNF) as playing a key role in the pathophysiology of major depression. BDNF is one of a series of small proteins that the brain uses, first in its development and later in adulthood, to regulate nerve cell growth and function. Depressed patients exhibit low circulating levels of BDNF, which is a pattern that is reversed following treatment with antidepressants (4). Levels of *BDNF* and its receptor, *TRKB*, are also reported to be diminished, in a region-specific manner, in the postmortem brains of subjects with major depression (5–7). In addition, antidepressants in rodent models lead to increased brain BDNF protein levels (8), while intrahippocampal BDNF administration leads to diminished depressive-like behaviors (9,10). Recent work has also suggested that rapid antidepressant response following ketamine administration is mediated by BDNF signaling, a topic reviewed by Monteggia and Kavalali (11) in this issue of the *Journal*.

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Also in this issue, Tripp et al. (12) present a convergent state-of-the-art approach, combining analyses at the molecular and circuit levels of rodents and postmortem human subjects, which they used to investigate potential deficits in BDNF signaling in major depressive disorder. Animal models allow direct mechanistic studies, and human postmortem assays can determine indications of differences in these mechanisms in depressed individuals. Tripp et al. focused on the subgenual anterior cingulate cortex, a structure well known for its role in affective control. It provides top-down inhibition of the amygdala, and it is likely that the loss of this connectivity contributes to affective symptoms in major depression (13). The authors hypothesized that dysregulation of BDNF signaling with a downstream effect on GABA neurotransmission would occur in the depressed brain, and they tested this hypothesis using quantitative assays for gene expression.

Using transgenic mouse models, they first determined the degree of BDNF dependency of a set of GABA-related genes, which were chosen based on the results from their recent study of the amygdala (5). They used two rodent models of *Bdnf* knockdown, including mice with a constitutive heterozygous deletion of *Bdnf* ($Bdnf^{+/-}$) and those with a targeted disruption of exon IV ($Bdnf^{KIV}$), which leads to activity-dependent blockade of BDNF protein expression. *Bdnf* expression was decreased in both mouse lines, and converging evidence from both models revealed a set of genes with different levels of BDNF dependency within the cingulate cortex. Genes with a high level of BDNF dependency (i.e., those that showed robust decreases in expression in both mouse strains) were *Cort*, *Vgf*, *Sst*, *Tac1*, and *Npy*; those with intermediate BDNF dependency were *Snap25* and *Gad2* (*Gad65*); and those with little or no BDNF dependency were *Gad1* (*GAD67*), *Pvalb*, *Rgs4*, *Slc6a1*, *Calb2*, and *Gabra1*.

The authors then examined expression of these genes in postmortem brain tissue collected from 51 pairs of human subjects, with each pair consisting of one subject with major depressive disorder and one comparison subject with no psychiatric disorders, in order to determine whether disruption of the mechanisms they found in mice also exist in individuals with major depression. The pairs were matched for sex, with nearly identical group means for postmortem delay, brain pH, and RNA quality. The tissue samples were of high quality in terms of these three latter factors, all of which play critical roles in determining the validity of gene expression studies. The authors observed a 30% reduction in the expression of *TRKB*, but not *BDNF*, in the subgenual anterior cingulate cortex in depressed subjects. Significant decreases were also detected in the expression of genes with high (*CORT*, *VGF*, *SST*, and *NPY*), intermediate (*SNAP25* and *GAD2* [*GAD65*]), and low (*GAD1* [*GAD67*] and *PVALB* [*PV*]) levels of BDNF dependency. When the sample was segregated by sex, male subjects exhibited more robust differences in expression, which may have been related to sex-dependent expression differences in comparison subjects. The size of the cohort also allowed the authors to rule out potential confounds of medication, suicide, RNA quality, postmortem delay, age, and brain pH, thus increasing confidence in the validity of their findings.

When compared with the authors' previous findings in the amygdala, these data suggest several important brain region-specific and sex-dependent differences. In the amygdala, they detected a significant decrease in *BDNF*, but not *TRKB* (which is the opposite of their observation in the subgenual anterior cingulate cortex), along with a robust down-regulation of genes with high BDNF dependency, including *SST*, *CORT*, and *NPY* (5). The same genes were down-regulated in the subgenual anterior cingulate cortex, but their magnitude of change was greater in the amygdala in female subjects. These markers are expressed in a subset of inhibitory interneurons that provide inhibition of proximal dendrites. *GAD1* and *PVALB,* which were not BDNF dependent, were down-regulated in the subgenual anterior cingulate cortex but not in the amygdala; they are expressed in a separate class of interneurons that provide inhibition of the soma and the axon hillock. *CALB2*, which likewise was not BDNF dependent, is expressed in the third class of inhibitory interneurons and was down-regulated in the amygdala but not in the subgenual anterior cingulate cortex. Taken together, these data indicate dysregulation of the inhibitory microcircuitry, which is mediated by BDNF-dependent and BDNF-independent signaling in a brain region- and sex-dependent manner.

When interpreting these results, one needs to be mindful of several limitations. Most important among them is that the results are correlative. Thus, we cannot

know from these data whether disruption of BDNF signaling and related genes causes depressed mood in major depression or whether it is a mere correlate. Future mechanistic models in animal models may shed light on this issue. These findings need to be replicated in independent cohorts of postmortem brain tissue samples, and it is important to extend these analyses to potential changes in protein levels. Unfortunately, some of these may not be feasible given the current technical limitations, as exemplified by the unsuccessful attempts at quantifying levels of BDNF and TrkB proteins in the samples in this study.

The potential clinical importance of studying BDNF has increased because of new evidence that some of the actions of ketamine may involve BDNF synthesis. Monteggia and Kavalali (11) reviewed recent data demonstrating that rapid antidepressant action of ketamine is mediated by reduced elongation factor-2 phosphorylation, which in turn releases BDNF protein synthesis from its normal suppression. Their findings in mouse models indicate that this effect is mediated by the blockade of spontaneous, rather than evoked, *N*-methyl-D-aspartate-type glutamatergic neurotransmission. In conjunction with the findings reported by Tripp et al., this suggests that ketamine-evoked increase in BDNF signaling may affect the subgenual anterior cingulate cortex-amygdala circuit in a distinct fashion in male and female depressed patients, and thus separate classes of interneurons in each region are affected depending on sex.

Taken together, these data provide exciting new leads for elucidating the pathophysiology of major depressive disorder. This knowledge may facilitate development of treatments specifically tailored toward the relief of affective symptoms. These findings suggest that modulation of distinct molecular mechanisms within specific nodes of the brain limbic circuitry, as well as within local microcircuitry, may be required for both male and female sufferers of depression.

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