In This Issue

Volume 80, Number 6, September 15, 2016

A brief summary of the articles appearing in this issue of *Biological Psychiatry*.

Esketamine Clinical Trial

Singh *et al.* (pages 424–431) conducted a multicenter, double-blind, randomized, placebo-controlled trial to investigate intravenous esketamine for adults with treatment-resistant depression. Compared with placebo, the majority of patients (67%) who were treated with 0.20 or 0.40 mg/kg esketamine showed rapid and significant improvement in depressive symptoms. Adverse events, the most common of which were headache, nausea, and dissociation, were dose dependent. Symptom improvement did not differ between the doses, suggesting that the lower esketamine dose may be more tolerable for patients while maintaining efficacy.

Mechanisms of Depression Therapeutics

Using magnetic resonance spectroscopy, **Hone-Blanchet *et al.*** (pages 432–438) examined the neural effects associated with transcranial direct current stimulation (tDCS) of the dorsolateral prefrontal cortex in healthy adults. Compared with sham tDCS, active tDCS elevated levels of prefrontal *N*-acetylaspartate and striatal glutamate + glutamine during stimulation. Immediately following stimulation, no differences in metabolites were observed between active and sham tDCS, suggesting that the excitatory effects of tDCS are rapid, but short lived.

Creatine has been shown to enhance the efficacy of treatment with selective serotonin reuptake inhibitors, but the underlying mechanisms of these therapeutic effects are unclear. Using multimodal neuroimaging in a randomized clinical trial of female patients with major depressive disorder, **Yoon *et al.*** (pages 439–447) report that symptom improvement was greater in patients who received creatine augmentation, compared with placebo. The creatine group also showed increased prefrontal *N*-acetylaspartate levels and greater rich club connections. These improvements in depression-related metabolic and network dysfunction may underlie the ability of creatine to enhance antidepressant efficacy.

Sarkar and Kabbaj (pages 448–456) examined the effects of chronic isolation stress and ketamine in male and female rats. Male rats showed anhedonia and depression-like behavior, which correlated with decreases in spine density and synaptic proteins. Female rats showed a later onset of depression-like behavior and similar decreases in spine density and synaptic proteins, but no anhedonia. A single dose of ketamine reversed all changes in the male rats, but rescued only the depressive-like behavior in female rats. These data suggest that the mechanisms underlying ketamine's efficacy may differ between the sexes.

Depression is thought to involve functional deficits in the synaptic transmission of both gamma-aminobutyric acid (GABA) and glutamate. To elucidate the relationship between these phenotypes, **Ren *et al.*** (pages 457–468) assessed a mouse model of depression characterized by impaired GABAergic transmission. These mice showed reduced glutamate receptor expression and impaired glutamatergic synapses. A single dose of ketamine normalized these deficits. These data provide support for the interaction of these two neurotransmitter systems in the pathophysiology of depression, uniting the GABAergic and glutamatergic deficit hypotheses of depression.

The Role of BDNF in Chronic Stress

The mesolimbic dopamine circuit has been shown to mediate both reward and social aversion. In a model of chronic social stress in mice, **Koo *et al.*** (pages 469–478) examined the role of dopamine and brain-derived neurotrophic factor (BDNF) in this pathway using optogenetic stimulation and pharmacologic manipulations. They report that mesolimbic BDNF–tyrosine receptor kinase B signaling, but not dopamine signaling, is necessary for stress-induced depressive-like behaviors. These data provide insight into the differential actions of BDNF and dopamine observed between acute and chronic stress paradigms.

FGF2 and Anxiety

Fibroblast growth factor 2 (FGF2) has been linked to anxiety and depression. **Salmaso *et al.*** (pages 479–489) used a multimodal approach to show that FGF2 is required for the regulation of anxiety-like behavior in mice. They report that *Fgf2* knockout mice display increased anxiety, decreased hippocampal glucocorticoid receptor (GR) expression, and increased hypothalamic-pituitary-adrenal axis activity, all of which was rescued by FGF2 administration in adulthood. GR blockade prevented this therapeutic effect. These data indicate that FGF2 regulates anxiety behavior via modulation of GR transcription and hypothalamic-pituitary-adrenal axis activity.

Method: Amygdala Modulation to Regulate Emotion

The amygdala plays an essential role in emotion regulation. Regulating its activity could facilitate recovery from traumatic stress, but this was previously only possible via real-time functional magnetic resonance imaging. Here, **Keynan *et al.*** (pages 490–496) present the clinical potential of a novel imaging approach that allows for the monitoring of amygdala activity using electroencephalography. Their experiments show that this model reliably predicts amygdala-based activity and that using the technique with neurofeedback reduces amygdala reactivity and improves emotion regulation in participants.

ISSN: 0006-3223