In this Issue

Volume 73, Number 12, June 15, 2013

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

Rapid-Acting Antidepressants Special Issue

Pilc *et al.* (pages 1125–1132) review preclinical evidence that indicates the glutamatergic synapse contains multiple targets that may be exploited to develop novel antidepressants. *N*-methyl-D-aspartate (NMDA) antagonists like ketamine and traxoprodil provide target validation. They also discuss a structurally and functionally diverse group of compounds ranging from AMPA receptor potentiators to metabotropic glutamate receptor 5 antagonists that exhibit antidepressant-like properties in multiple models predictive of antidepressant activity in humans.

The observation that ketamine can produce meaningful clinical improvement of depressive symptoms within hours stimulated a new generation of basic antidepressant research that identified new neural signaling mechanisms in antidepressant response. These studies have provided a conceptual framework linking a group of novel antidepressant mechanisms. Here, **Krystal *et al.*** (pages 1133–1141) discuss the path that led to the testing of ketamine, consider its promise as an antidepressant, and review novel treatment mechanisms that are emerging from this line of research.

This review by **Zarate *et al.*** (pages 1142–1155) summarizes ongoing research exploring the identification of biomarkers involved in prevention, diagnosis, treatment response, severity, or prognosis of depression. Biomarkers of response for interventions with a rapid onset of action**,** including sleep deprivation and rapid-acting intravenous drugs (e.g., ketamine, scopolamine)**,** are highlighted. They also propose an alternative translation model for new treatments in psychiatry that would facilitate shorter studies, improve feasibility, and increase higher compound throughput testing for mood disorders.

The muscarinic receptors of the cholinergic neurotransmitter system were implicated in mood disorders decades ago, but only recently have been evaluated as a potential new target for antidepressant drugs. Here, **Drevets *et al.*** (pages 1156–1163) review a growing literature that demonstrates rapid and robust antidepressant effects of scopolamine, an agent that temporarily blocks cholinergic muscarinic receptors. The findings emphasize the potential for a new class of antidepressant drugs, but highlight the need for additional studies and replication of findings.

A significant subset of both major depressive and bipolar disorder patients rapidly and robustly improves with a chronotherapeutic intervention of one night of sleep deprivation therapy. **Bunney and Bunney** (pages 1164–1171) review this literature, where mood disorder patients are reported to have abnormal 24 hour rhythms including temperature, hormones, mood and sleep. These rhythms are controlled by clock genes. The dramatic effectiveness of sleep deprivation therapy suggests that abnormal clock gene machinery may represent a core pathophysiological defect in a subset of patients.

Sanacora and Banasr (pages 1172–1179) provide an overview of glial cell function and the postmortem and preclinical evidence suggesting glial cell abnormalities are associated with mood disorders. Examining the unique role of glial cells in regulating amino acid neurotransmitter function, they identify novel targets for drug development and provide a review of the preclinical and early phase clinical studies exploring the efficacy of drugs targeting glial cell function and glutamate neurotransmission in the treatment of mood disorders.

Recent evidence has suggested the glutamatergic system plays a primary role in psychiatric disorders. **Musazzi *et al.*** (pages 1180–1188) review clinical and preclinical studies that show structural and functional changes in brain areas where glutamate neurons and synapses are predominant. Interestingly, traditional monoaminergic-based antidepressants reduce glutamate release/transmission and prevent the acute stress-induced enhancement of glutamate release. Moreover, antidepressants may reverse the maladaptive changes observed in animal models of depression and regulate glutamate receptors. The use of NMDA receptor antagonists for experimental therapy has opened new avenues for glutamatergic rapid-acting antidepressants.

Dwyer and Duman (pages 1189–1198) review recent studies of the molecular and cellular mechanisms through which ketamine produces rapid antidepressant effects. Notably, this includes activation of the mammalian target of rapamycin and increased synaptogenesis in the prefrontal cortex, which allow rapid recovery from the neuronal atrophy and loss of synaptic connections caused by chronic stress. These findings have identified new targets for the development of novel rapid-acting antidepressants with fewer side effects.

In this review, **Monteggia *et al.*** (pages 1199–1203) discuss their recent work studying the molecular mechanisms underlying the rapid antidepressant effects of ketamine. They first showed that ketamine-mediated fast-acting antidepressant effects are dependent on a robust and rapid (within 30 minutes) increase of brain-derived neurotrophic factor at the translation level. They further identified eukaryotic elongation factor 2 (eEF2) kinase as a major molecular substrate that accounts for such rapid enhancement of local synaptic protein synthesis. They showed that ketamine-mediated blockade of NMDA spontaneous neurotransmission at rest inhibited the eEF2 kinase activity, which led to the reduction of eEF2 phosphorylation, and de-suppression of brain-derived neurotrophic factor translation. They discuss the potential role of eEF2 kinase as a new target for future development of fast-acting antidepressants.

Deep Brain Stimulation for Major Depressive Disorder

Schlaepfer *et al.* (pages 1204–1212) assessed the safety and efficacy of deep brain stimulation to the supero-lateral branch of the medial forebrain bundle in patients with treatment-resistant major depressive disorder. A rapid reduction in depression ratings was observed in 6 of 7 patients after 2 days of stimulation; 4 of 7 reached response criterion of a 50% reduction in depression scores after one week. At last observation (12 to 33 weeks), 6 of 7 patients were responders, with four classified as remitters. Oculomotor problems were the most prominent adverse events. These preliminary findings suggest that targeted bilateral stimulation may significantly reduce symptoms in treatment-resistant major depressive disorder.

0006-3223/$36.00
http://dx.doi.org/10.1016/j.biopsych.2013.05.002

Ketamine's Effects on Glucose Metabolism

Carlson *et al.* (pages 1213–1221) investigated glucose metabolism in depressed, unmedicated patients who received positron emission tomography scans before and two hours after ketamine infusion. Metabolism decreased in the habenula, insula, ventrolateral, and dorsolateral prefrontal cortices after ketamine versus baseline. Metabolism increased in the occipital, sensorimotor, parahippocampal, and inferior parietal cortices after ketamine. Improvement in depressive symptoms correlated with metabolic changes in the superior and middle temporal gyrus, and was inversely correlated in parahippocampal gyrus and temporoparietal cortex.