In this Issue

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

Review: Addictive Drugs and Activation of Extracellular Signal-Regulated Kinases

Significant progress has been made in the effort to dissect the molecular changes associated with administration of addictive drugs in animal models. Addictive drugs activate the extracellular signal-regulated kinases 1 and 2 (ERK1/2) in the striatum, which control multiple substrates, some of which are critically involved in cocaine-mediated molecular and behavioral adaptations. Here, **Pascoli *et al.*** (pages 917–926) review recent knowledge on the implication of ERK in long-lasting neuronal adaptations underlying behavioral alterations induced by psychostimulants. They conclude that improved understanding of the molecular mechanisms underlying ERK1/2 activation by drugs of abuse may provide a new route for therapeutic treatment in addiction.

Actions of* N-*Methyl-D-Aspartate Receptor Antagonists

Ketamine exhibits rapid antidepressant effects, and the neural mechanisms underlying these therapeutic effects are being studied intensively. To this end, **Belujon and Grace** (pages 927–936) used the "learned helplessness" model of stress-induced depression to assess the relationship between ketamine effects on brain circuit function and behavior in rats. They report that ketamine has a therapeutic effect in this model in that it reduces helpless behavior in rats, normalizes the number of active dopamine neurons, and restores the capacity for long-term potentiation in the pathway from the ventral subiculum of the hippocampus to the nucleus accumbens. These findings suggest that the antidepressant effects of ketamine are expressed, in part, through circuits and mechanisms implicated in reward and motivation.

Troyano-Rodriguez *et al.* (pages 937–945) report on the identification of GABAergic neurons in the reticular nucleus of the thalamus as a cellular target for the action of *N*-methyl-D-aspartate (NMDA) receptor antagonists such as phencyclidine. Using electrophysiological techniques in rats, the authors show that phencyclidine markedly inhibits the activity of reticular GABAergic neurons, which provide feed-forward inhibition to the rest of the thalamus, therefore disinhibiting thalamo-cortical circuits, an effect likely involved in the cognitive and psychotomimetic effects of phencyclidine.

Dorsolateral Prefrontal Cortex Modifies Attentional Bias

Clarke *et al.* (pages 946–952) used transcranial direct current stimulation to target the dorsolateral prefrontal cortex, a region of the brain implicated in the control of attention, in order to evaluate its role in the modification of attention bias for threat. Compared with those who received sham stimulation, healthy volunteers who received active stimulation showed greater evidence of attention bias modification, which may hold implications for enhancing the therapeutic value of modifying such patterns of cognition.

Dose-Dependent Effects of Methylphenidate

Methylphenidate (MPH), commonly used to treat attention-deficit/hyperactivity disorder, exerts complex dose-dependent effects in the adolescent brain, but the underlying molecular mechanisms are not clear. In their study of adolescent rats, **Cheng *et al.*** (pages 953–962) found that administration of a clinically relevant low dose (0.5 mg/kg MPH) selectively potentiated NMDA glutamate receptor trafficking to the membrane and NMDA receptor function, facilitated recognition memory and attention, and diminished the detrimental effects of repeated stress. In contrast, a high dose (10 mg/kg MPH) suppressed glutamatergic signaling and induced hyperlocomotion. These data provide a potential basis for the dose-dependent dual actions of MPH.

White Matter Pathways for Successful Deep Brain Stimulation Response

Riva-Posse *et al.* (pages 963–969) used diffusion tensor imaging in patients with treatment-resistant depression to identify white matter connections that are involved in successful subcallosal cingulate deep brain stimulation. Whole-brain analysis revealed that 6-month and 2-year responders shared bilateral connections from activation volumes to three distinct areas: medial frontal cortex via forceps minor, rostral and dorsal cingulate cortex via the cingulum bundle, and subcortical nuclei. These findings suggest a novel strategy to optimize target and stimulation parameter selection for patients.

Randomized Controlled Trial of Intranasal Ketamine

Rapid antidepressant effects have been reported following a single dose of ketamine administered via an intravenous route. Here, **Lapidus *et al.*** (pages 970–976) report findings from a randomized, double-blind, crossover trial of intranasal ketamine in patients with treatment-resistant major depression. They report that, compared to placebo, a single intranasal dose of ketamine (50 mg) reduced depressive symptoms within 40 minutes and up to 48 hours. It was well-tolerated with minimal side effects, providing evidence that may lead to new approaches for the rapid treatment of depression.

Genome-Wide Methylation Analysis in Depression

There is mounting evidence to suggest that epigenetic mechanisms play a role in depression. **Dempster *et al.*** (pages 977–983) identified DNA methylation differences in a cohort of monozygotic twins discordant for adolescent depression. Using postmortem brain tissue from adults with major depressive disorder and matched controls, two of the depression-associated methylation differences were replicated. This identification of differentially methylated regions provides evidence for the role of epigenetic variation in depression and has the potential for use as a depression biomarker.

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