In This Issue

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

Novel Glutamatergic Targets to Treat Addiction

Cocaine reduces glutamate in the nucleus accumbens core, which in turn affects synaptic plasticity and vulnerability to relapse. Here, **Scofield *et al.*** (pages 441–451) showed that activation of Gq-DREADD in nucleus accumbens core astrocytes enhances glial glutamate release in rodents. They also found that glial Gq-DREADD activation is sufficient to inhibit cue-induced reinstatement of cocaine, but not sucrose, seeking, an effect that is mediated by group II metabotropic glutamate receptors (mGluRs 2 and 3). These data suggest that selective stimulation of mGluR2/3 may serve as a promising pharmacogenetic therapy to prevent cocaine relapse.

Group II mGluRs have been identified as targets for addiction treatment, but compounds developed to date have had important limitations. Here, **Justinova *et al.*** (pages 452–462) demonstrated that AZD8529, a highly selective mGluR2 positive allosteric modulator, decreases nicotine self-administration and relapse to nicotine seeking in monkeys with a history of nicotine self-administration. AZD8529 did not affect food self-administration in the monkeys and also decreased nicotine-induced dopamine release in rats. These findings suggest that AZD8529 and related mGluR2 positive allosteric modulators may be considered in the treatment of nicotine addiction.

Cue-induced drug craving increases after prolonged forced abstinence, a phenomenon termed 'incubation of drug craving'. In this article, **Caprioli *et al.*** (pages 463–473) present a choice-based model in rats in which incubation of methamphetamine craving also occurs after prolonged voluntary abstinence. They also report that administration of AZD8529 decreases this incubation in both the forced and voluntary abstinence models. This novel animal model may better simulate the human addiction cycle of voluntary abstinence/treatment followed by relapse.

Genetic Mapping: Examinations of Opioid Addiction and Social Recognition

Opioid receptor gene variants have yet to be definitively associated with the risk for opiate addiction. **Hancock *et al.*** (pages 474–484) used cis-expression quantitative trait loci mapping to identify variants associated with mu opioid receptor (*OPRM1*) gene expression in human brain. The authors then tested the variants for association with heroin addiction in one discovery and two independent replication cohorts. They identified significant and replicable associations between some common variants in *OPRM1*, rs3778150 in particular, and heroin addiction. They also found that these variants may explain previously reported inconsistent associations for a long-studied functional variant in *OPRM1*.

The identification of genes that mediate social and object recognition may reveal mechanisms underlying cognitive and behavioral functioning. **Bruining *et al.*** (pages 485–495) performed genetic mapping of social recognition, followed by functional characterization in a knockout mouse model of the identified candidate, *Pcdh9*, a gene previously associated with autism spectrum disorder. They found that *Pcdh9*-deficient mice display deficits in long-term social and object recognition and impairments in sensorimotor development, along with structural changes in sensory cortex.

Hippocampal Activity as a Predictor of Cocaine Relapse

Adinoff *et al.* (pages 496–504) explored regional cerebral blood flow as a predictor of relapse in abstinent patients with cocaine use disorder. Compared with controls, patients who relapsed within 30 days showed increased regional cerebral blood flow in the posterior hippocampus. In addition, resting state functional connectivity was increased between the posterior hippocampus and posterior cingulate cortex in relapsed patients relative to patients who did not relapse. These findings may reflect a propensity for heightened reactivity to cocaine contextual cues and ruminations among patients at the highest risk of relapse.

Role of the Insula in Disgust Processing

The insula is implicated in disgust processing, but it has been unclear whether it is required for the recognition and regulation of disgust. In a voxel-based morphometry study of patients with neurodegenerative disease, **Woolley *et al.*** (pages 505–514) found that the development of new disgusting behaviors and deficits in recognizing disgust in others are associated with distinct but partially overlapping patterns of gray matter loss in the insula. These findings suggest that the insula is required for normal disgust processing in humans.

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