In this Issue

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

Cannabis: Consumption and Cognition

Chronic users of other drugs present with decreased dopamine receptors and low dopamine release in the striatum, but little is known about changes in chronic cannabis users. **Urban *et al.*** (pages 677–683) evaluated recently abstinent cannabis users with positron emission tomography compared to controls, and found no difference in dopamine D2 receptors at baseline or in dopamine release. However, earlier age of onset of cannabis use was associated with lower dopamine release in the associative striatum.

Cheetham *et al.* (pages 684–692) examined whether structural brain abnormalities are present prior to the onset of cannabis use in adolescence. They found that smaller orbitofrontal cortex volumes at age 12 predicted initiation of cannabis use by age 16, whereas the volumes of amygdala, hippocampus, and anterior cingulate cortex did not predict use. These findings suggest that structural abnormalities in the orbitofrontal cortex may contribute to risk for cannabis exposure.

Evidence indicates involvement of the endocannabinoid system in both the pathophysiology of schizophrenia and working memory function. Additionally, schizophrenia patients exhibit strong working memory deficits. Using functional magnetic resonance imaging (fMRI), **Bossong *et al.*** (pages 693–699) show that perturbation of the endocannabinoid system in healthy subjects with administration of Δ9-tetrahydrocannabinol (THC) induces reduced working memory task performance and abnormal brain activity patterns. Findings support the notion of endocannabinoid involvement in working memory, and suggest a role for this system in working memory deficits in schizophrenia.

Mechanisms of Substance Use and Stress

Peptide neurotransmitter systems are hypothesized to play an important role in the development of ethanol dependence. Using electrophysiology techniques, **Cruz *et al.*** (pages 666–676) investigated the interaction between nociceptin and corticotropin-releasing factor on gamma-aminobutyric acidergic transmission in naïve and ethanol dependent rats. Their results indicate that the nociceptin-corticotropin-releasing factor interaction on gamma-aminobutyric acid transmission in the central nucleus of the amygdala is upregulated in ethanol-dependent animals. Findings also suggest that the nociceptin receptor may serve as a therapeutic target for alcoholism.

A prior study found that cocaine hydrolase (CocH) acutely blocked cocaine-primed reinstatement in rats. To extend those findings, **Anker *et al.*** (pages 700–705) used a gene transfer paradigm to transduce CocH and report that cocaine-primed reinstatement of cocaine seeking was blocked for up to 6 months in rats that received CocH vector, but not in controls. In addition, amphetamine-primed reinstatement was unaffected, indicating that the CocH vector selectively suppresses reinstatement of cocaine seeking. Viral transfer of CocH may be useful for preventing relapse to cocaine addiction over extended periods of time.

Using an electrophysiological approach and behavioral assessment, **Ho *et al.*** (pages 706–713) report that protein kinase Mζ (PKMζ) activity is associated with cocaine-induced synaptic potentiation in the ventral tegmental area of rats. Their evidence also suggests that PKMζ expression is increased by a single or repeated cocaine exposure. These findings support the view that PKMζ inhibitors may abolish long-term, cocaine-induced synaptic potentiation.

Nguyen *et al.* (pages 714–724) examined the role of β-arrestin2 in cannabinoid type I receptor regulation following repeated THC administration in mice. Results show that β-arrestin2 regulates cannabinoid type I receptors in a brain region-dependent manner, and that this was associated with behavioral-specific tolerance to THC-mediated effects. These data suggest that cannabinoid ligands that do not recruit β-arrestin2 might have an enhanced therapeutic profile.

The extended amygdala is a brain region that has been shown to play a critical role in regulation of stress-related behaviors. **C. Li *et al.*** (pages 725–732) demonstrate that activation of the kappa opioid receptor, known to be involved in these behaviors, can regulate synaptic transmission in the extended amygdala. In addition, they provide evidence that these receptors can regulate long-range connections between subregions of this structure.

Substance Dependence and Antisocial Personality Disorder

Using a two-stage genetic association study of case-control and family-based cohorts, **D. Li *et al.*** (pages 733–740) found a single nucleotide polymorphism in the *COL25A1* gene that was significantly associated with antisocial personality disorder in both African Americans and European Americans, particularly in those with substance dependence. The findings were also replicated in an independent case-control cohort. Their findings suggest that *COL25A1*, which encodes the collagen-like Alzheimer amyloid plaque component precursor protein, may play an important role in the pathogenesis of antisocial personality disorder, especially in the context of substance dependence.

Neurocircuitry of Reward and Loss in Gambling

van Holst *et al.* (pages 741–748) used fMRI to investigate reward and loss expectancy during different probabilities of winning in problematic gamblers and healthy controls. Problematic gamblers showed higher activity in the reward system during reward expectation than healthy controls, but there was no difference between these groups during loss expectation. This provides evidence that problematic gamblers are characterized by abnormally increased reward expectancies, which may render them overoptimistic with regard to gambling outcomes.

Using fMRI, **Balodis *et al.*** (pages 749–757) report that individuals with pathological gambling demonstrate decreased activity in fronto-striatal neurocircuitry during anticipatory processing relative to a control group. Activity in the ventral striatum in the gambling group also correlated inversely with levels of impulsivity, consistent with prior findings in alcohol dependence. Altogether, these results suggest that impulsive tendencies may be reflected in diminished ventral striatal activations to reward anticipation and may represent targets for treatment development in addictions.

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