In this Issue

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

Examining Potential Therapies for Substance Dependence

Mann *et al.* (pages 706–713) investigated the use of as-needed nalmefene, an opioid system modulator, in alcohol-dependent patients over 24 weeks. They found that nalmefene was significantly better than placebo in reducing alcohol consumption and improving clinical status and liver enzymes. Nalmefene was generally well-tolerated. These findings suggest that nalmefene constitutes a potential new pharmacological treatment paradigm for alcohol dependence.

Li *et al.* (pages 714–720) examined cue craving in nicotine-dependent volunteers randomized to receive one session of either high frequency or sham repetitive transcranial magnetic stimulation applied over the dorsolateral prefrontal cortex. Craving induced by smoking cues was reduced among participants who received real stimulation. This finding suggests that the use of brain stimulation techniques should be further explored for smoking cessation treatment.

Success in active vaccination against methamphetamine abuse has lagged behind advances in immunopharmacotherapy for cocaine and nicotine. **Miller *et al.*** (pages 721–728) report that vaccination with an anti-methamphetamine hapten attenuates thermoregulatory disruption and locomotor effects of methamphetamine in rats. This study supports efforts to develop vaccines against methamphetamine that would be suitable for human therapy.

Receptor Involvement in Drug Reward and Relapse

Toll-like receptor 4 (TLR4), an innate immune system receptor, has previously been linked to the acute rewarding effects of opioid drugs. Here, **Theberge *et al.*** (pages 729–737) report that chronic delivery of the TLR4 antagonist (+)-naltrexone in rats prevented the development of incubation of heroin, but not methamphetamine, craving. These findings provide evidence for a role of TLR4 in cue-induced drug seeking in a rat model of drug relapse, and support the notion that mechanisms of cue-induced relapse to opioid and psychostimulant drugs may not be identical.

Nicotine and alcohol may share some common effects on brain circuits. Using mouse models, **Liu *et al.*** (pages 738–746) provide data showing that alcohol can modulate activity of ventral tegmental area dopaminergic neurons in the brain's reward circuitry via $\alpha 4$ subunit-containing nicotinic acetylcholine receptors. As these receptors have been previously identified as critical for nicotine reward, they may represent potential therapeutic targets to reduce both smoking and alcohol consumption.

Neurochemical Systems: Role in Behavior

Wassum *et al.* (pages 747–755) used fast-scan cyclic voltammetry in rats to monitor mesolimbic dopamine signaling during a task to assess the effects of a reward-paired cue on an independently-trained reward-seeking action. They found that both the frequency and amplitude of phasic dopamine release events, as well as slower nontransient dopamine levels in the nucleus accumbens, were increased during reward cue presentation. These findings provide evidence for a relationship between phasic mesolimbic dopamine release and incentive motivation.

Dysfunction in neurochemical systems is associated with impaired goal-directed behaviors, but the effects of natural neurochemical variation on differences in individual behavior have been unclear. In a study of non-human primates, **Groman *et al.*** (pages 756–762) provide evidence that the interaction between dopamine in the putamen and serotonin in the orbitofrontal cortex accounts for a significant proportion of natural variation in inhibitory control abilities. These findings indicate that monoaminergic systems across different brain regions functionally interact to modify aspects of behavioral control, providing insight into the neural mechanisms underlying risk for impulsivity-related psychiatric disorders.

Mechanisms of Alcohol Consumption

Moonat *et al.* (pages 763–773) investigated the epigenetic basis for the genetic predisposition to anxiety and alcoholism. They showed that alcohol-preferring (P) rats display heightened anxiety and higher expression of histone deacetylase 2 (HDAC2) in the amygdala compared to non-preferring rats. Both acute ethanol exposure and knockdown of HDAC2 in the central amygdala resulted in increased global and gene specific histone acetylation and produced anxiolytic effects in P rats. HDAC2 knockdown also attenuated the alcohol drinking behavior of P rats. These data demonstrate a direct role for HDAC2-mediated epigenetic mechanisms in anxiety and alcoholism.

Alcohol-preferring rats are a widely used genetic model of elevated alcohol consumption, but the specific genetic factors underlying this behavior remain unknown. **Schank *et al.*** (pages 774–781) show that alcohol self-administration in P rats is selectively sensitive to blockade of neurokinin-1 receptors. This was associated with a *TacR1* promoter polymorphism that drives elevated receptor expression in the amygdala, and amygdala microinjections of a neurokinin-1 antagonist replicated its systemic actions. These findings suggest that neurokinin-1 receptor antagonists may hold promise as alcoholism pharmacotherapy in genetically defined patient populations.

Cognitive Control, Substance Use, and Brain Activity

Lack of cognitive control may contribute to risk of relapse. **Marhe *et al.*** (pages 782–788) examined the association between cocaine use and error-related brain activity, an index of cognitive control, in cocaine-dependent patients. Reduced error-related negativity, measured during the first week of detoxification treatment, was associated with more days of cocaine use at 3-month follow-up. These results suggest that diminished error-related brain activity may be useful to identify patients at highest risk of relapse.

Schmaal *et al.* (pages 789–795) investigated the effects of modafinil on the interaction between intrinsic large-scale brain networks in alcohol-dependent patients. They report that modafinil increased the negative coupling between resting state executive networks and the default mode network. Moreover, this enhanced network relationship predicted modafinil-induced improvement in cognitive control. These findings suggest that modafinil may partly exert its effects by targeting intrinsic functional relationships between large-scale brain systems underlying cognitive control in alcohol-dependent patients.

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