In this Issue

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

Investigations into the Altered Neurobiology of Alcohol Dependence

Excessive oxidative stress and apoptosis are implicated in alcohol dependence. Monoamine oxidase A (MAO-A) is an enzyme that metabolizes monoamines and participates in the cellular response to mitochondrial toxicity and oxidative stress. Using positron emission tomography, **Matthews *et al.*** (pages 756–764) found that MAO-A V_T, an index of MAO-A density, was globally elevated and associated with duration of heavy drinking in alcohol-dependent subjects compared with healthy controls. This finding identifies a potential new therapeutic target for the treatment of alcohol dependence.

The gamma-aminobutyric acid type B (GABAB) receptor is a target for alcoholism treatment, but there is little information about the splicing changes that occur in its subunit, GABAB1. **Lee *et al.*** (pages 765–773) compared GABAB1 splice junctions in prefrontal cortical postmortem tissue from alcoholic and control brains. They show novel splicing complexity of the *GABAB1* gene, suggesting that this gene is much longer than previously known. They also found that chronic alcohol altered exon/intron expression and splice junction levels.

Kissler *et al.* (pages 774–782) used a mouse model of alcohol self-administration to investigate the dynorphin/kappa-opioid receptor (KOR) system following chronic alcohol exposure and withdrawal. They found that this system is dysregulated in the central amygdala of alcohol-dependent mice, showing increased dynorphin A and increased KOR signaling. In addition, using site-specific antagonism of amygdalar KORs, they observed that this dysregulation directly contributes to the excessive alcohol consumption that occurs during withdrawal.

Genetic Contributions to Addictions

Vrieze *et al.* (pages 783–789) identified and tested nonsynonymous exonic variants in a community sample for association with behavioral disinhibition and substance use or abuse, including nicotine, alcohol, and illicit drugs. Their analysis found no individual rare variant or gene that was associated with any phenotype. However, they did detect a potential aggregate effect of rare coding variants on illicit drug use, which now requires replication.

A single nucleotide polymorphism located on the *GATA4* gene involved in the encoding of atrial natriuretic peptide has recently been implicated in alcohol dependence. Using functional magnetic resonance imaging in alcohol-dependent patients, **Jorde *et al.*** (pages 790–797) provide evidence that *GATA4* genotype influences alcohol-cue processing in the amygdala and that it modulates the relationship between amygdala responsivity and relapse risk. These findings illuminate potential underlying mechanisms of the involvement of the *GATA4* gene in the etiology of alcohol dependence.

Alcohol Responding Predicts Future Alcohol Use

King *et al.* (pages 798–806) examined the role of alcohol response in relation to future drinking problems in young, heavy social drinkers over a six year period. Overall, greater sensitivity to alcohol stimulation and reward (liking, wanting) and lower sedation at baseline testing predicted greater alcohol problems through follow-up, including escalation of binge drinking. These drinking escalations occurred during a developmental transition period when many young heavy drinkers mature out of such behaviors and binge drinking becomes less normative.

Risky Decision-Making is Encoded by Nucleus Accumbens Neurons

Sugam *et al.* (pages 807–816) investigated the role of nucleus accumbens neurons in risk-based decision-making behavior. Electrophysiological recordings showed that nucleus accumbens neurons differentially encode information related to risk versus safe outcomes, and reflect individual behavioral preferences in rats performing the decision task. These data suggest that nucleus accumbens neurons contribute to subjective encoding of anticipated outcomes and may bias future risk-based decisions.

Novel Treatment Avenues for Compulsive Behaviors

Prior work has shown that rats, like humans, show evidence of a near-miss effect in a slot machine task, responding to "almost-win" trials as if they predicted reward delivery. **Cocker *et al.*** (pages 817–824) found that a dopamine D_4 receptor agonist enhances, whereas a D_4 receptor antagonist reduces, these errors in reward learning. Drugs acting at dopamine D_2 and D_3 receptors were without effect on these behaviors. These data suggest that D_4 receptor-selective compounds could play a role in reducing some forms of gambling or other risky behaviors.

The factors contributing to the development and severity of compulsive disorders remain poorly understood. Here, **Ansquer *et al.*** (pages 825–832) demonstrate that a high-impulsivity trait in rats predicts an increased propensity to develop a compulsive anxiolytic behavior. The impulsivity/compulsivity relationship was lost following treatment with atomoxetine, a noradrenergic reuptake inhibitor used to treat attention-deficit/hyperactivity disorder. These observations suggest that atomoxetine may be a potentially useful treatment for impulse control problems associated with attention-deficit/hyperactivity disorder.

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