Biological Psychiatry

A Journal of Psychiatric Neuroscience and Therapeutics

In this Issue-February 1st*

Orbitofrontal Cortex: A Review of Drug-Induced Changes

Imaging studies in humans have suggested that core features of addiction may be mediated by drug-induced changes in the orbitofrontal cortex (OFC). **Schoenbaum and Shaham** (pages 256–262) review studies conducted in animals indicating that cocaine exposure produces alterations in the structure and function of neurons in this brain region that may contribute to the addiction process.

Neural Responses to Aggression

Does the male sex hormone, testosterone, make women more aggressive? To test this hypothesis, **Hermans *et al.*** (pages 263–270) used functional magnetic resonance imaging (fMRI) to assess neural responses to socially threatening stimuli, essentially pictures of angry faces in healthy women. Women with higher testosterone levels showed greater brain activation in regions implicated in aggression, and emotional behavior generally, including the amygdala, hypothalamus, and OFC. The administration of testosterone accentuated the activation of these brain regions in response to the angry faces. Thus, testosterone may play an important role in the response to threat in women, as in men.

Halasz *et al.* (pages 271–278) suggest a new mechanism to explore for the treatment of aggression problems in humans. Until very recently, the clinical significance of the neurokinin chemical messenger system was poorly understood. The authors now show that neurons that have receptors for one subtype of neurokinin receptor, neurokinin 1 (NK1) are activated during aggressive encounters in animals. The administration of a NK1 receptor antagonist reduced the behavioral and physiologic signs of aggression. Importantly, this drug reduced a particularly violent form of aggression where one animal physically harmed another animal that intruded into its home space, without disrupting normal behavior.

Fairchild *et al.* (pages 279–285) provide new support for the theory that adolescents with conduct disorder (CD) are less inhibited by the anticipation that their misbehavior might be punished and less motivated by delayed rewards. To explore one component of this hypothesis, the authors studied adolescents with CD. Although the adolescents with CD responded normally to an unpleasant noise, they showed a reduced capacity to learn danger cues (predictors of the noise) and safety cues (predictors of no noise), as measured by changes in the magnitude of their startle responses. These findings highlight a potential obstacle for treatment strategies for CD based upon learning theory.

Salvinorin A: Mechanisms of Reward for a New Drug of Abuse

Salvinorin A is an increasingly abused drug that stimulates a novel brain target, the κ-opioid receptor. **Braida *et al.*** (pages 286–292) now demonstrate that this drug shows rewarding properties similar to other drugs of abuse in animal models. Further, salvinorin A increases levels of the chemical messenger dopamine in a brain reward center, the nucleus accumbens. The authors also report that the rewarding effects of salvinorin A are blocked by pretreatment with either a cannabinoid-1 receptor antagonist or a κ-opioid receptor antagonist.

Modifying Addictive Behaviors

N-acetylcysteine (NAC) has been shown to inhibit cocaine craving in addicts and reduce cocaine relapse in animal models. **Zhou and Kalivas** (pages 338–340) now show that NAC has comparable effects in animal models of heroin addiction with NAC administration leading to decreased drug seeking behaviors.

Loss-chasing, the tendency to continue gambling in an effort to recover previous losses, is a central feature that distinguishes pathological gambling from recreational gambling. **Campbell-Meiklejohn *et al.*** (pages 293–300) use fMRI to monitor brain activity during a task where subjects were asked to choose between gambling to recover a loss (at the risk of doubling its size) or quitting (sustaining a certain loss). Choosing to chase losses was associated with increased activity in brain regions previously linked to motivation and reward, while choosing to quit gambling was associated with increased activity in brain regions previously linked with anxiety and conflict monitoring. The authors suggest that imbalance in the engagement of circuits involved in anticipating rewards and losses may contribute to pathological gambling.

There is strong association between impulsivity and smoking, but it is unclear whether an impulsive nature predisposes to smoking or is a consequence of prolonged nicotine exposure. **Diergaarde *et al.*** (pages 301–308) tested mice genetically predisposed to either high or low impulsivity in nicotine self-administration tasks and found evidence for a strong association between preexisting impulsivity and nicotine seeking behavior. The authors also find that impulsive mice have reduced release of dopamine, a neurotransmitter implicated in impulsive behavior, in specific brain regions.

Does prescription of methylphenidate for attention-deficit/hyperactivity disorder (ADHD) increase the risk for depression in adulthood? **Bolaños *et al.*** (pages 309–316) exposed rats to

*Contributions to this feature made by Srijan Sen, M.D., Ph.D.

0006-3223/08/$34.00

methylphenidate during their preadolescent developmental period and found that, as adults, these rats showed reduced responses to food and drug rewards as well as increased behavioral reactions to stress. These data raise the possibility that methylphenidate exposure during adolescence may contribute to a risk for developing depression. These behavioral alterations were reversed with the common antidepressant fluoxetine. These data highlight a new potential risk of methylphenidate treatment and they suggest a commonly available treatment strategy.

An Interaction Between a Genetic Variant and Prenatal Alcohol Exposure

The serotonin transporter is a key target of many of the most widely prescribed psychiatric medications. **Kraemer *et al*.** (pages 317–324) explored a possible interaction between variation within this gene and prenatal alcohol exposure in rhesus monkeys. The authors found that alcohol-exposed monkeys with a less functional "short" version of the serotonin transporter gene showed higher irritability during infancy and higher stress hormone responses at 6 months compared to monkeys with the long version of the gene and monkeys that were not exposed prenatally to alcohol. Thus, these data highlight the interplay between genetic vulnerability and environmental exposure in the risk for later behavioral problems.

Towards an Understanding of ADHD Pathophysiology

Nigg *et al.* (pages 325–331) confirm that low levels of blood lead are associated with ADHD, and provide the first data showing that this ADHD risk may be mediated by lead's effect on cognitive control functions.

Castellanos *et al.* (pages 332–337) provide new evidence that ADHD is associated with disturbances in the functional interactions or "connectivity" between particular brain regions. Using fMRI, the authors show that the normal functional relationships between the anterior and posterior cingulate cortices, brain regions implicated in attention and impulse control, are impaired.