IN THIS ISSUE

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

Mechanisms of Addiction

Bebawy *et al.* (pages 223–230) report that orphanin FQ/nociceptin (OFQ/N), the endogenous ligand of the opioid receptor-like (ORL1) receptor, not only blocked but also reversed behavioral adaptive changes that occured following repeated cocaine treatment in mice. Accordingly, the OFQ/N/ORL1 receptor system may represent a potential target for the development of drugs to curb cocaine addiction.

Stress exacerbates behavioral responses to distinct classes of drugs of abuse, including cocaine and morphine. Using a mouse model to investigate the molecular underpinnings of these responses, **Barik *et al.*** (pages 231–240) found that glucocorticoid receptor gene inactivation in dopamine sensitive neurons markedly reduced behavioral, transcriptional and neurochemical responses to cocaine but not to morphine. These findings have identified a subset of neurons in which glucocorticoid receptor differentially influences responses to cocaine and morphine.

Hao *et al.* (pages 240–248) examined whether dysregulation of metabotropic glutamate receptor (mGluR) function is a factor in escalating cocaine self-administration in rats. They report that an mGluR2/3 agonist, LY379268, and the mGluR5 antagonist, MTEP, had more pronounced effect on reducing cocaine consumption when animals had relatively long and short access, respectively, to cocaine. In parallel, the authors reported that long access to cocaine increased mGluR2/3 and decreased mGluR5 function in the nucleus accumbens. These data suggest that drugs acting at mGluR2/3 and mGluR5 receptors may play somewhat complementary roles in reducing cocaine consumption.

Kalirin-7 is essential for dendritic spine formation and maintenance both *in vitro* and *in vivo*. Using animals with a genetic deletion of Kalirin-7, **Kiraly *et al.*** (pages 249–255) show that Kalirin-7 is essential for cocaine-induced dendritic spine proliferation in the nucleus accumbens. Additionally, they demonstrate that Kalirin-7 plays an essential role in locomotor sensitization and conditioned place preference behaviors after cocaine treatment.

Animal models for addiction indicate that stress effects on increasing drug use depend upon the context where these drugs are administered. Less is known about how stress in novel contexts influences drug use. **Conrad *et al.*** (pages 303–305) show that cold swim stress experienced outside the self-administration environment reinstated cocaine-seeking behavior in rats for up to three days, providing a novel and relevant model to study the latent effects of stress on relapse to drug abuse.

Peroxisome proliferator-activated receptor-α (PPARα), a family of nuclear receptor transcription factors involved in the modulation of various peripheral physiological responses and energy metabolism, may influence the activity of dopamine nerve cells by regulation of nicotinic acetylcholine receptors (nAChRs). nAChRs containing β2 subunits are essential for the addictive properties of nicotine, and their stimulation switches dopamine cells from a resting state to an excited state. Here, **Melis *et al.*** (pages 256–264) report that activation of PPARα reduces dopamine neuronal activity by reducing nAChRs. These data suggest a novel mechanism for modulating nAChR function that may have implications for addiction and other disorders.

Recent evidence suggests that damage to the insular cortex disrupts tobacco addiction in human smokers. Using a preclinical approach in rats, **Forget *et al.*** (pages 265–271) report that reversible inactivation of the granular insular cortex reduced motivation to self-administer nicotine and relapse to nicotine seeking. In contrast, no effects were found in motivation to obtain food pellets or food seeking behavior. This study suggests that targeting the insular cortex through non-invasive techniques may represent a novel therapeutic strategy for smokers.

Biomarker Panel for Alcohol Abuse?

Laboratory tests for illicit drugs of abuse are commonly used to detect drug abuse. However, such tests for alcohol abuse have been more challenging to develop. **Freeman *et al.*** (pages 219–222) performed a plasma proteomic study to identify proteins that could be used to classify subjects' drinking levels. In monkeys, drinking history (non-drinking, non-abusive drinking, or alcohol abuse) was accurately classified using a set of seventeen proteins. If replicable, this biomarker panel may help to guide the development of informative biomarkers for alcoholism.

Emotional Processing in Conduct Disorder

Relatively little is known about emotional processing in females with conduct disorder (CD). **Fairchild *et al.*** (pages 272–279) demonstrate that recognition of angry and disgusted expressions was impaired in female adolescents with CD. Furthermore, CD participants high in psychopathic traits showed impaired sadness recognition. Girls with CD also displayed deficient fear conditioning, indicating that both implicit and explicit aspects of emotional functioning are compromised in males and females with CD.

Examining Alcohol Effects

Using a neurobiological model of posttraumatic stress disorder, **Bisby *et al.*** (pages 280–286) investigated the effects of acute alcohol intoxication on multiple memory processes in healthy volunteers. They examined relative performance on a virtual reality spatial memory task focused on one's own perspective (egocentric) or a shifted perspective (allocentric). The study also assessed intrusive recollections after subjects watched a trauma video. The authors found that low doses of alcohol impaired allocentric memory and increased the number of post-video intrusive traumatic memories. In contrast, high doses of alcohol impaired both egocentric and allocentric memory. This study highlights differential dose-related alcohol effects on learning and memory.

Using functional magnetic resonance imaging, **Heitzeg *et al.*** (pages 287–295) examined impulse control in individuals with and without a parental history of alcoholism who themselves did or did not have alcohol problems. They found that family-history positive children, regardless of problematic alcohol use, displayed impairment in inhibiting the ventral striatum during the suppression of a motor response, suggesting that this impairment may be linked to risk for later alcoholism. They also found that

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with problem alcohol use, the prefrontal "control" mechanism in the brain lost efficiency, which could lead to further impairment in motivational circuitry.

Dopamine Release in Decision-Making

Optimal decision making requires that organisms correctly evaluate both the costs and benefits of multiple potential choices. Dopamine transmission within the nucleus accumbens has been heavily implicated in reward learning and decision making, but it is unclear whether reward cost is encoded by dopamine release. In rats, **Day *et al.*** (pages 306–309) show that phasic dopamine signals reflect two different types of reward cost and encode potential rather than chosen value under choice situations.

Implanted Long-Acting Naltrexone for Heroin Dependence

In a randomized, controlled trial, **Hulse *et al.*** (pages 296–302) found that sustained-release implant naltrexone was superior to oral naltrexone in preventing heroin relapse in heroin-dependent individuals. Effective treatment for all patients was achieved at blood naltrexone levels of 1-3 ng/ml, with higher levels associated with greater efficacy. For both groups, level of heroin craving was related to relapse risk, suggesting that craving assessments might be important clinically.