In this Issue

Volume 76, Number 1, July 1, 2014

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

Dopamine-Related Processes in Addiction Development and Risk

Evidence implicates dopamine D1-receptor signaling in the nucleus accumbens in the motivation to use cocaine during the early stages of addiction, but less is known regarding its role following the development of addiction. Using both male and ovariectomized female rats with and without estrogen replacement, **Ramôa *et al.*** (pages 8–14) studied the impact of short-term and longer-term cocaine self-administration. Their data suggest that D1-receptor signaling is critical in "non-addicted" stages, but it becomes diminished once addiction has developed. These findings could potentially account for the disappointing results of dopamine-based pharmacotherapies for cocaine addiction.

Addiction is characterized by the transition from goal-oriented, i.e., voluntary, drug-seeking to compulsive use that is habitual, i.e., insensitive to the loss of reward or the presence of adverse consequences associated with drug use. **Murray *et al.*** (pages 15–22) identify the stages of this process that are sensitive to dopamine receptor blockade, a potential addiction pharmacotherapy. The authors show that there is a transition from insensitivity to sensitivity to the inhibitory effects of a dopamine receptor-blocking drug, α-flupenthixol, administered directly into the dorsolateral striatum on cocaine seeking across the phases of addiction. Early in the addiction process, rodents were insensitive to the effects of this drug, but it did suppress drug-seeking in animals with long-standing cocaine self-administration. They also showed that highly impulsive animals made the transition from drug insensitivity to sensitivity more slowly than animals with low levels of impulsivity. Together, these data highlight the addiction phase-specific nature of the biology and, by implication, pharmacotherapy of addiction and the impact of particular traits, like impulsivity, on the path from drug use to addiction.

The neurotransmitter dopamine is thought to be critically involved in drug use and addiction. Using positron emission tomography, **Casey *et al.*** (pages 23–30) provide evidence that amphetamine-induced dopamine responses are markedly reduced in non-dependent young adults with extensive family histories of addiction, compared with both stimulant-naïve controls and non-dependent users with no family history. This finding suggests that the altered dopamine response characteristic of dependence is present prior to dependence among youth at high familial risk for addiction.

Neuronal Processes Differ for Drug Intake Versus Drug Seeking

Using a rat model of addiction, **Guillem *et al.*** (pages 31–39) report that escalation of cocaine intake and incubation of cocaine craving evolve differently and independently during long-term abstinence from extended drug use and are correlated with dissociable and non-competing neuronal processes in different subregions of the nucleus accumbens. These findings suggest the existence of a high degree of functional modularity in the core and shell subregions that should be taken into account in future research on addiction neurobiology and treatment development.

Ketamine Effects in Cocaine-Dependent Volunteers

Recent research suggests that ketamine may relieve depression by targeting abnormalities in prefrontal brain regions, including improving glutamate homeostasis. Preclinical studies have suggested that cocaine dependence, which involves comparable prefrontal alterations, may be effectively treated through glutamatergic modulation. In a randomized, controlled, crossover trial, **Dakwar *et al.*** (pages 40–46) report that ketamine enhanced motivation to quit and reduced cue-induced craving in non-depressed, non-treatment seeking volunteers with cocaine dependence. These effects indicate that the activity of ketamine may extend beyond antidepressant efficacy.

Epigenetic Mechanisms of Methamphetamine Use

Methamphetamine exposure causes neuroadaptations at glutamatergic synapses. **Jayanthi *et al.*** (pages 47–56) administered methamphetamine injections to rats to further characterize the underlying epigenetic mechanisms. They report that methamphetamine decreased glutamate neurotransmitter receptor expression and increased the expression of histone deacetylases (HDACs) and MeCP2, a DNA-binding protein. They also observed increased binding of HDACs on DNA sequences that code glutamate receptors. Finally, treatment of rats with valproic acid, an HDAC inhibitor, blocked the drug-induced repression of glutamate receptors.

Using a mouse model, **Aguilar-Valles *et al.*** (pages 57–65) demonstrate that methamphetamine-associated memory is marked by a transcriptionally permissive epigenetic landscape and gene activation in the nucleus accumbens. Loss of the permissive H3K4 methyltransferase, *Mll1*, prevented formation of a methamphetamine-associated memory, while loss of the H3K4 demethylase and X-linked intellectual disability gene, *Kdm5c*, interfered with its expression. These findings represent potential new targets for the disruption of relapse-inducing memories associated with drugs of abuse.

Genomewide Association Study of Opioid Dependence

Gelernter *et al.* (pages 66–74) conducted a genomewide association study for opioid dependence in 3 different samples of African- and European-American subjects. Genomewide-significant associations were observed with single nucleotide polymorphisms from multiple gene loci, with the most compelling results showing association with genes involved in potassium signaling pathways (e.g., *KCNC1*, *KCNG2*, and *KCNA4*). Pathway analysis also implicated genes involved in calcium signaling and synaptic long-term potentiation. The results of this study have identified novel risk variants for opioid dependence.

Brain Potentials Predict Completion of Drug Treatment

Steele *et al.* (pages 75–83) measured event-related potentials during a response inhibition task in an effort to identify prison inmates who would later complete or discontinue treatment for substance use disorders. As expected, all measures differed between the groups. A combination of the P2 and Pe measures revealed a reliable prediction of 83% of inmates who discontinued treatment. Reliable predictors of treatment retention may allow for the development of enhancements to therapies designed specifically to target those at greatest risk for treatment discontinuation.

0006-3223/$36.00
http://dx.doi.org/10.1016/j.biopsych.2014.05.007