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

Mechanisms of Opioid Dependence and Tolerance

Glück *et al.* (767–774) evaluated the involvement of G protein-coupled receptor kinases (GRKs) in opioid dependence and in agonist-selective μ-opioid receptor phosphorylation using GRK-deficient mice. Their findings show that μ-opioid receptor phosphorylation in vivo is regulated by agonist-selective recruitment of distinct GRK isoforms that, in turn, influence different opioid-related behaviors. These findings suggest that modulation of GRK function may serve as a potential new approach for preventing opioid addiction, while retaining the clinical benefits of opioid drugs.

Reduction in the activity of neurogenic differentiation 1 (Neurod1), a transcription factor, impairs adult neurogenesis and drug-associated contextual memory, suggesting that it may be involved in the development of opioid tolerance. To investigate this hypothesis, **Li *et al.*** (775–784) modulated Neurod1 activity in mouse hippocampal dentate gyrus. They report that Neurod1 regulates the development of opioid tolerance via two distinct mechanisms, by affecting the antinociceptive median effective dose values of opioids and by altering the associative tolerance via contextual learning and memory.

Potential Therapeutic Targets for Cocaine Addiction

Stress is an important contributor to substance abuse. **Polter *et al.*** (785–793) demonstrate that a brief, acute stressor causes a days-long block of GABAergic synaptic plasticity onto dopamine neurons in the ventral tegmental area of rats, which is dependent on glucocorticoid and kappa opioid receptors (KORs). A KOR antagonist reversed these neuroadaptations and prevented stress-induced reinstatement of cocaine self-administration, even after the stressor had occurred. These data strengthen the association between KORs and stress-induced drug seeking and suggest that further study of GABAergic plasticity in the ventral tegmental area may provide novel targets for treating cocaine addiction.

Depression and addiction are highly comorbid, but the potentially shared neurobiology remains unclear. Using a multipronged approach, **Arango-Lievano *et al.*** (794–801) demonstrate that p11, a previously described pharmacogenetic target for depression, is also implicated in cocaine reward. They found that cocaine reduced the expression of p11 in the nucleus accumbens of mice, and that p11 downregulation in nigrostriatal neurons of the nucleus accumbens sensitized mice to the rewarding effects of cocaine. These data suggest that p11 may serve as a therapeutic target for both disorders.

Dopamine Uptake Inhibitors and Cocaine-Like Effects

Dopamine (DA) transporter blockade is a feature of drugs that promote alertness and attention and suppress appetite. This action also mediates subjective effects of cocaine. **Kohut *et al.*** (802–809) assessed the cocaine-like effects of standard and atypical DA uptake inhibitors (DUIs), which are differentially influenced by DA transporter conformation. They report that cocaine-like subjective effects and DA levels were directly related for standard DUIs, a relationship not observed in atypical benztropine analogs, which have low cocaine-like efficacy. These results suggest that atypical DUIs induce compensation for elevated DA, and may help to identify DA transporter-based medications with safer therapeutic profiles.

Addiction Development Shifts from Dopamine to Glutamate Signaling

Glutamatergic signaling plays an important role in drug-seeking and relapse, but its differential roles in the phases of the addiction process are unclear. **Doyle *et al.*** (810–815) assessed motivation for cocaine, along with the effects of CNQX, an AMPA glutamate receptor antagonist, following abstinence in mice given either short- or long-access to cocaine. They demonstrate that the role of glutamatergic signaling in the nucleus accumbens, though not essential for motivating cocaine use in "non-addicted" stages, becomes critical once addiction has developed. Thus, there is a shift from dopamine to glutamate signaling that appears essential for the progression of addiction.

Functional Receptor Alterations: Cocaine Dependence and Schizophrenia

Preclinical work has implicated the serotonin 1B receptor in mediating some neurobiological effects of cocaine. Here, **Matuskey *et al.*** (816–822) measured the level of serotonin 1B receptors in people using positron emission tomography imaging. They report serotonin 1B receptor reductions in cocaine-dependent subjects in the anterior cingulate, hypothalamus and frontal cortex, compared with healthy subjects. These differences were independent of possible partial volume effects and provide evidence of in vivo serotonergic alterations in humans with cocaine dependence.

Positron emission tomography imaging studies suggest an alteration in the activity of dopamine D2 receptors in schizophrenia, but have been unable to isolate the contribution of the structurally similar D2 versus D3 receptors. **Simpson *et al.*** (823–831) generated a transgenic mouse model to determine if an increase in D3 receptors in the striatum could produce phenotypes relevant to schizophrenia. They report that mice with D3 receptor overexpression present no cognitive deficits, but display a deficit in incentive motivation, a symptom associated with schizophrenia and other disorders associated with disturbances in reward processing.

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