The 'ins' and 'outs' of the striatum: Mapping the neural circuits that regulate addiction.

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Addiction is a chronic disease characterized by loss of control over drug intake, high motivation to obtain drug, and persistent drug craving. Although cellular and molecular alterations within the striatum are thought to regulate addictive behaviors, the striatum is a heterogenous structure that sits at the interface of the highly interconnected cortico-basal ganglia-thalamic circuit. Thus, it has been difficult to isolate how individual afferent/efferent projections and cellular subtypes within the striatum modulate addiction. To begin to address these issues, we used novel viral vector targeting approaches to express inhibitory $G_{i/o}$-coupled DREADDs (Designer Receptors Exclusively Activated by Designer Drugs) selectively in striatal cells of the indirect or the direct pathways or in prefrontal cortical or thalamic afferents to the striatum. Activation of DREADDs by the otherwise inert ligand clozapine-*n*-oxide produces transient decreases in neuronal activity and allowed us to examine the effect of these targeted cellular manipulations on behaviors associated with addiction (psychomotor sensitization, drug self-administration, cue- and drug prime-induced reinstatement). We found that decreasing activity of the indirect pathway enhanced the development of psychomotor sensitization whereas decreasing activity of the direct pathway blocked the persistence of this phenomenon. Although decreasing direct pathway activity had no effect on compulsive drug-taking behavior, it did reduce cue-induced reinstatement of drug-seeking. Similarly, decreasing activity of cortical afferents to the striatum had no effect on drug-taking behaviors. However, this manipulation during drug use enhanced conditioned responding to the drug-associated context as well as produced slower rates of extinction and increased responding during drug prime-induced reinstatement – an effect that was normalized by inhibiting these corticostriatal afferents immediately prior to the drug prime. Additionally, decreasing thalamic activity decreased both drug primed- and cue-induced reinstatement to drug seeking whereas decreasing thalamostriatal afferent activity decreased drug primed-reinstatement but enhanced cue-induced reinstatement. These studies use cell-specific targeting and novel molecular tools to begin to isolate the contributions of specific striatal afferent and efferent projections in behaviors related to addiction. The findings from these studies support the hypothesis that an imbalance between direct and indirect striatal pathway activity may mediate a transition to addiction, and that activity of these pathways is regulated by top-down control from both the cortex and the thalamus. However, they also demonstrate that the cortico-basal ganglia-thalamic circuitry is more complex and dynamic than has been revealed previously.

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