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THE INS AND OUTS OF THE STRIATUM: ROLE IN DRUG ADDICTION

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Abstract—Addiction is a chronic relapsing disorder characterized by the loss of control over drug intake, high motivation to obtain the drug, and a persistent craving for the drug. Accumulating evidence implicates cellular and molecular alterations within cortico-basal ganglia-thalamic circuitry in the development and persistence of this disease. The striatum is a heterogeneous structure that sits at the interface of this circuit, receiving input from a variety of brain regions (e.g., prefrontal cortex, ventral tegmental area) to guide behavioral output, including motor planning, decision-making, motivation and reward. However, the vast interconnectivity of this circuit has made it difficult to isolate how individual projections and cellular subtypes within this circuit modulate each of the facets of addiction. Here, we review the use of new technologies, including optogenetics and DREADDs (Designer Receptors Exclusively Activated by Designer Drugs), in unraveling the role of the striatum in addiction. In particular, we focus on the role of striatal cell populations (i.e., direct and indirect pathway medium spiny neurons) and striatal dopaminergic and glutamatergic afferents in addiction-related plasticity and behaviors.

Key words: addiction, DREADDs, optogenetics, basal ganglia, cortex, striatum.

Contents

INTRODUCTION

Drug addiction is a costly and incapacitating disease characterized by uncontrollable drug-taking and drug-seeking, and a high likelihood of relapse, even long after the cessation of drug use. The cortico-basal ganglia-thalamic circuit (Fig. 1) has long been known to regulate the development and maintenance of addictive behaviors (Lobo and Nestler, 2011; Luscher and Malenka, 2011; Nestler, 2013; van Huijstee and Mansvelder, 2014). In particular, the striatum, which serves as a central interface of the circuit, has been identified as a key site for the neuroplastic events that underlie addictive processes (Lobo and Nestler, 2011; Luscher and Malenka, 2011; Nestler, 2013; van Huijstee and Mansvelder, 2014). Nonetheless, because of the vast complexity of this circuit, our ability to gain a precise understanding of how the specific subcomponents and cell types within areas such as the striatum contribute to addiction has remained elusive. This review will focus on the emergence of new technologies and how they are now allowing us to advance our understanding of the role of striatal afferents and efferents in shaping this chronic, relapsing disease.

STRIATAL CIRCUITRY

The striatum is the major integration site of the cortico-basal ganglia-thalamic circuit, and as such receives a

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Abbreviations: BLA, basolateral amygdala; CPP, conditioned place preference; DREADDs, Designer Receptors Exclusively Activated by Designer Drugs; FSCV, fast scan cyclic voltammetry; GPe, globus pallidus external; LTD, long-term depression; MD, mediodorsal thalamus; MSNs, medium spiny projection neurons; NAc, nucleus accumbens; PFC, prefrontal cortex; PVT, paraventricular nucleus of the thalamus; SNr, substantia nigra; STN, subthalamic nucleus; VP, ventral pallidum; VTA, ventral tegmental area.

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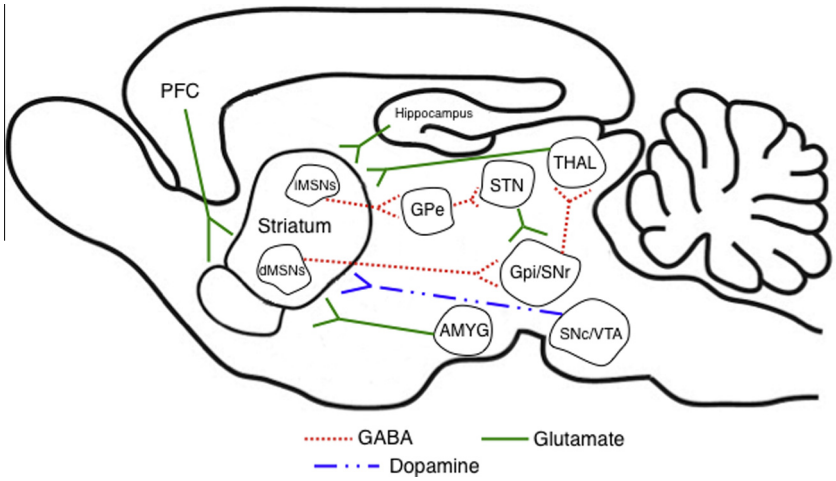

Fig. 1. Simplified schematic view of striatal inputs and outputs. The striatum receives glutamatergic inputs (denoted in green) from the cortex, amygdala, hippocampus and thalamus and dopaminergic inputs (denoted in blue) from the VTA and SNc. Direct pathway striatal neurons (dMSNs) project monosynaptically to the GPi/SNr whereas indirect pathway striatal neurons (iMSNs) project to the GPi/SNr via the GPe/VP and STN. Red dashed lines denote GABAergic inhibitory projections.

large variety of inputs (Fig. 1). In particular, it receives cholinergic inputs from striatal interneurons and brainstem sources (e.g., laterodorsal tegmental area and the pedunculopontine nuclei) and GABAergic inputs from striatal interneurons (Kita, 1993; Dautan et al., 2014). Additionally, it receives dopaminergic inputs from the ventral tegmental area (VTA) and the substantia nigra (SNr) and glutamatergic inputs from several areas, including the cortex, hippocampus, amygdala, and thalamus (Swanson, 1982; Phillipson and Griffiths, 1985; Finch, 1996; Groenewegen et al., 1999; Britt et al., 2012). These glutamatergic inputs make contact on the heads of dendritic spines of the striatal GABAergic medium spiny projection neurons (MSNs) whereas dopaminergic inputs synapse onto the spine neck, allowing for an important and complex interaction between these two inputs in modulation of MSN activity (Freund et al., 1984; Xu et al., 1989).

The striatum itself can be divided into two main regions, the dorsal striatum and the nucleus accumbens (NAc), and is comprised of multiple neuronal phenotypes including four different types of interneurons (i.e., cholinergic interneurons and GABAergic interneurons, which express either parvalbumin, calretinin, or nitric oxide synthase/neuropeptide Y/somatostatin) (Kemp and Powell, 1971). However, the majority of striatal neurons (~95%) are MSNs (Kemp and Powell, 1971); these will be the focus of this review. The striatal MSNs in the dorsal striatum can be subdivided into two classes based on their projection patterns, as well as their neuropeptide and receptor expression. MSNs that send monosynaptic projections to the basal ganglia output nuclei (i.e., the SNr and the globus pallidus internal (GPi)) and express dopamine D1 receptors along with the neuropeptides dynorphin and substance P, form part of the direct pathway (dMSNs). MSNs that indirectly project to basal ganglia output nuclei via the globus pallidus external (GPe) and the subthalamic nucleus (STN) and express dopamine D2 receptors and the neuropeptide enkephalin, form part of the indirect pathway (iMSNs) (Gerfen and Surmeier, 2011; Wall et al., 2013). However it should be noted that the MSN projections are not entirely segregated, as some dMSNs send axon collaterals to the GPe/ventral pallidum (VP) (Fujiyama et al., 2011).

Classically, these two striatal MSN populations are thought to have opposing effects on basal ganglia output. Activation of the dMSNs causes a net excitation of the thalamus resulting in a positive cortical feedback loop; thereby acting as a 'go' signal to initiate behavior. Activation of the iMSNs, however, causes a net inhibition of thalamic activity resulting in a negative cortical feedback loop and therefore serves as a 'brake' to inhibit behavior (Gerfen et al., 1982; Albin et al., 1989; Deniau and Chevalier, 1992; Gerfen and Surmeier, 2011; Calabresi et al., 2014). Additionally, basal ganglia output can be influenced via the hyperdirect pathway, which is a monosynaptic excitatory projection from the cortex to the STN that results in SNr excitation upon activation (Kita et al., 1983). Adding to the complexity of this circuit, the SNr itself projects back to the striatum as well as to the cortex, providing dopaminergic feedback to these structures (Gerfen et al., 1987).

Although these two striatal output pathways also exist in the NAc, the efferent targets of the MSNs are distinct from those in the dorsal striatum and the pathway segregation is much less complete. Specifically, iMSNs in the NAc (i.e., those neurons that express dopamine D2 receptors) project to the VP whereas dMSNs in the NAc (i.e., those neurons that express dopamine D1 receptors) project primarily to the VTA and SNr but also send axon collaterals to the VP (Chang and Kitai, 1985; Lu et al., 1998; Zhou et al., 2003; Tripathi et al., 2010, for a review see Smith et al., 2013). It should also be noted that there is a small population of neurons in the NAc that coexpress both D1 and D2 receptors, though this is largely restricted to the NAc shell (Bertran-Gonzalez et al., 2008). For the purpose of providing clarity in this review, we have operationally defined dMSNs as neurons that express dopamine D1 receptors and