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Review

Striatal Plasticity and Basal Ganglia Circuit Function

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The dorsal striatum, which consists of the caudate and putamen, is the gateway to the basal ganglia. It receives convergent excitatory afferents from cortex and thalamus and forms the origin of the direct and indirect pathways, which are distinct basal ganglia circuits involved in motor control. It is also a major site of activity-dependent synaptic plasticity. Striatal plasticity alters the transfer of information throughout basal ganglia circuits and may represent a key neural substrate for adaptive motor control and procedural memory. Here, we review current understanding of synaptic plasticity in the striatum and its role in the physiology and pathophysiology of basal ganglia function.

Introduction

The basal ganglia consist of interconnected subcortical nuclei that serve critical motivation, motor planning, and procedural learning functions (Graybiel et al., 1994; Hikosaka et al., 2000; Nicola, 2007; Packard and Knowlton, 2002; Yin and Knowlton, 2006). Neural circuits involving the basal ganglia form a key part of the extrapyramidal motor system, and dysfunction of these circuits is associated with prominent neurological disorders including Parkinson's disease (PD) and Huntington's disease (HD) (Albin et al., 1989; DeLong, 1990; DeLong and Wichmann, 2007; Graybiel, 2000), as well as psychiatric disorders such as obsessive-compulsive disorder (OCD) (Aouizerate et al., 2004; Graybiel and Rauch, 2000). The primary input nucleus is the striatum, which receives excitatory afferents from the cortex and thalamus, as well as dense innervation from midbrain dopamine neurons, and represents a major site of synaptic plasticity in the basal ganglia (Bolam et al., 2000; Gerdeman et al., 2003; Gerfen, 2000; Wilson, 1998).

For such a large nucleus, the striatum is unique in its complete lack of glutamatergic neurons. Instead, most cells are GABAergic, including a large population of principal cells and a small interneuron population. Striatal GABAergic interneurons can be divided into at least two classes, based on their physiological properties: (1) fast-spiking (corresponding to histochemically identified parvalbumin-positive cells) and (2) low-threshold spiking (corresponding to histochemically identified somatostatin-, nitric-oxide-synthase-, and neuropeptide-Y-positive cells; also potentially calretinin-positive interneurons) (Kawaguchi et al., 1995; Tepper and Bolam, 2004). The striatum also contains a small population of giant cholinergic interneurons distinguished by their large cell bodies, tonic activity in vivo, and dense local axonal arborizations (Zhou et al., 2002). However, the vast majority of striatal neurons are medium spiny neurons (MSNs), characterized by their high spine density, negative resting potential, and low firing rates in vivo (Table 1). They can be categorized into at least two different subtypes, based on their gene expression and axonal projections (Gerfen et al., 1990; Smith et al., 1998). Striatonigral MSNs exhibit high expression of dopamine D1 and muscarinic M4 receptors and project directly to basal ganglia output nuclei: the internal globus pallidus (GPi in primates, GPm in rodents) and substantia nigra pars reticulata (SNr). In contrast, striatopallidal MSNs exhibit high expression of dopamine D2 and adenosine A2A receptors and send axons to the external globus pallidus (GPe in primates, GP in rodents). Both types of MSN integrate vast numbers of inputs to generate spikes that represent the sole output of the striatum to downstream basal ganglia nuclei. Synaptic plasticity in the striatum is thus well-suited for regulating basal ganglia circuit activity.

The most influential model of basal ganglia circuit function is based on the segregation of information processing into direct and indirect pathways (Figure 1), which act in opposing ways to control movement (Albin et al., 1989; Alexander and Crutcher, 1990; DeLong, 1990). In its simplest anatomical form, it describes two parallel cortex-basal ganglia-thalamus-cortex loops that diverge within the striatum and are differentially modulated by dopamine. In more complex schemes, these circuits are integrated within an ascending hierarchy of open, interconnected loops emerging from limbic cortex and ventral striatum into associative and motor regions (Haber et al., 2000; Joel and Weiner, 1994; Parent, 1990).

The direct-pathway circuit originates from striatonigral MSNs, which receive excitatory glutamatergic afferents from sensorimotor cortex and thalamus. Direct-pathway MSNs project to GABAergic neurons in the GPi and SNr, which in turn send axons to motor nuclei of the thalamus. In a simplified "rate model" of basal ganglia function, in which neural information is encoded by firing rate alone, the net effect of direct-pathway activity is a disinhibition of excitatory thalamocortical projections, leading to activation of cortical premotor circuits and the selection or facilitation of movement.

Table 1. Striatal Cell Types

Cell Type	Abundance[a]	R_{input}	V_{rest}[b]	Axonal Targets	Key Metabotropic Receptors	References
Striatonigral MSN	49%	<100 MΩ	−80 to −90 mV	GPi, SNr	D1, M1, M4, mGluR1/5	Cepeda et al., 2008; Hersch et al., 1994; Ince et al., 1997; Kreitzer and Malenka, 2007
Striatopallidal MSN	49%	<100 MΩ	−80 to −90 mV	GPe	D2, A2A, M1, mGluR1/5	Cepeda et al., 2008; Hersch et al., 1994; Kreitzer and Malenka, 2007; Pollack et al., 1993
FS interneuron	0.5%	<100 MΩ	−80 mV	MSNs	D5	Centonze et al., 2003b; Kawaguchi, 1993
LTS interneuron	1.5%	>200 MΩ	−60 mV	MSNs	D1-like	Centonze et al., 2002; Kawaguchi, 1993
Cholinergic interneuron	0.5%	>200 MΩ	−60 mV	MSNs, FS interneurons	D2, D5, M2, M4	Kawaguchi, 1993; Koos and Tepper, 2002; Wilson et al., 1990; Yan and Surmeier, 1996

[a] Abundance based on discussion in Rymar et al. (2004), rounded to the nearest half-percent. Fifty percent of MSNs were assumed to be striatonigral (Huang et al., 1992). LTS interneurons were assumed to include both somatostatin- and calretinin-positive subtypes.
[b] Experimental variability due to different extracellular potassium concentrations.

The indirect-pathway circuit originates from striatopallidal MSNs. Indirect-pathway MSNs form inhibitory synapses on GABAergic pallidal neurons, which in turn project to glutamatergic neurons in the subthalamic nucleus (STN). Subthalamic neurons send axons to basal ganglia output nuclei (GPi and SNr), where they form excitatory synapses on the inhibitory output neurons. The net effect of indirect-pathway activity is thought to involve an inhibition of thalamocortical projection neurons, which would reduce cortical premotor drive and inhibit movement.

An important aspect of this model is the role of dopamine in regulating direct- and indirect-pathway activity through modulation of MSN firing in the striatum. G_s-coupled dopamine D1 receptors are proposed to facilitate MSN output, whereas G_i-coupled dopamine D2 receptors inhibit MSN firing. Thus, dopamine has been proposed to exert opposite effects on the direct and indirect pathway (Surmeier et al., 2007), but in both cases it ultimately enhances movement (Albin et al., 1989).

While aspects of this scheme are oversimplified and not consistent with all the functional and anatomical data, it has nevertheless proven extremely valuable in guiding both basic and clinical investigations into basal ganglia function. However, despite its simplicity it has proven difficult to test empirically due to the anatomical complexity of the striatum. Recently the development of BAC transgenic mice has enabled the dissection of striatal circuitry with unprecedented specificity. In this review, we focus on the role of synaptic plasticity in regulating striatal output through the direct and indirect pathways. In addition to the well-characterized glutamatergic synapses on MSNs, we also consider plasticity at interneuronal synapses and dendritic integration of excitation and inhibition in MSNs. Although much remains speculative, we review potential roles for synaptic plasticity in striatal function and dysfunction. The role of the ventral striatum (nucleus accumbens) in motivation, reward, and addiction has been widely described elsewhere (Berridge, 2007; Hyman et al., 2006; Kalivas and Volkow, 2005; Kenny, 2007; Nicola, 2007) and will not be covered, except in instances where analogies or extrapolations to dorsal striatum can be drawn.

Synaptic Plasticity in the Striatum

Synaptic modification is a fundamental mechanism for altering neural circuit function. In the striatum, MSN firing output to the direct and indirect pathways is influenced by fast excitatory and inhibitory synaptic inputs as well as slower modulation by dopamine and other signaling molecules. Whereas the spiking of glutamatergic afferents originates outside of the striatum, inhibitory inputs are controlled within the striatum (Gustafson et al., 2006; Tepper et al., 2004). Synaptic plasticity at multiple sites within the striatal microcircuit can therefore regulate striatal output (Figure 2).

Corticostriatal and Thalamostriatal Synapses on MSNs

The majority of striatal physiology studies have examined synaptic transmission and plasticity at glutamatergic synapses on MSNs. Until recently, however, little attention was paid to the source of afferents (thalamus or cortex) or the MSN subtype targeted (direct- or indirect-pathway). Recent work has attempted to distinguish striatal afferents with mixed results. Paired-pulse and mean-variance analysis indicate that thalamic inputs exhibit higher release probability than cortical inputs at both direct- and indirect-pathway MSNs (Ding et al., 2008). However, a different study concluded that cortical synapses have a higher—not lower—release probability than thalamic synapses, based on analysis of paired-pulse ratios (Smeal et al., 2007). Moreover, the frequency of strontium-evoked asynchronous EPSCs was actually higher at cortical synapses than thalamic synapses (Ding et al., 2008). One factor confounding the interpretation of these experiments is that both cortical and thalamic projections are themselves heterogeneous (Lacey et al., 2007; Lei et al., 2004). Further study using more specific methods of stimulation will be required to characterize the properties of striatal afferents.

When the properties of excitatory synapses on direct- and indirect-pathway MSNs were examined using intrastriatal stimulation, synapses on indirect-pathway MSNs were found to exhibit lower paired-pulse ratios, indicative of a higher probability of glutamate release, relative to direct-pathway synapses (Ding et al., 2008; Kreitzer and Malenka, 2007). This finding suggests that

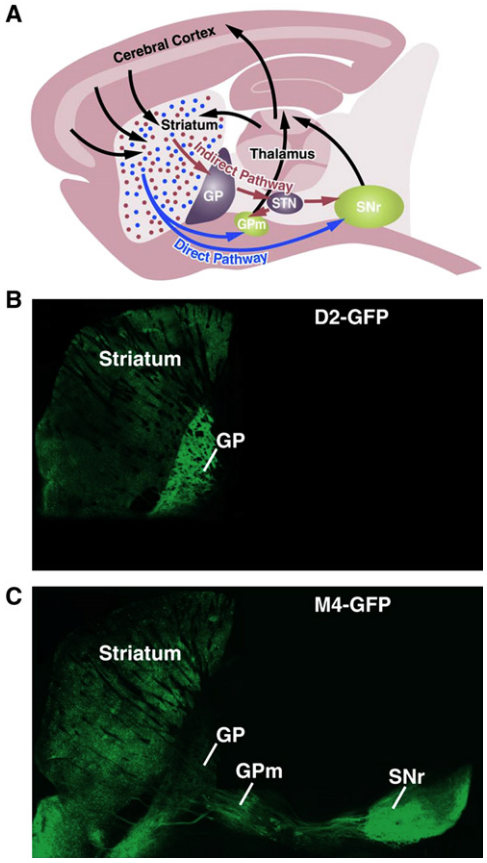

Figure 1. Direct- and Indirect-Pathway Basal Ganglia Circuits
Sagittal view of a mouse brain (A), depicting cortex-basal ganglia-thalamus-cortex circuits. Axons from the thalamus and striatum form excitatory synapses onto striatonigral/direct-pathway medium spiny neurons (MSNs) (blue) and striatopallidal/indirect-pathway MSNs (red). Direct-pathway MSNs send axons directly to basal ganglia output nuclei (GPm, medial globus pallidus; SNr, substantia nigra pars reticulata), where they form inhibitory synapses. Indirect-pathway MSNs inhibit neurons in the globus pallidus (GP), which in turn make inhibitory connections with the subthalamic nucleus (STN). STN projections target the GPm and SNr, where they form excitatory synapses onto GABAergic basal ganglia output neurons. These inhibitory output neurons send axons to ventroposterior thalamic motor nuclei. Finally, glutamatergic neurons in the thalamus project back to cortex, completing the circuit. Sagittal slices from a BAC transgenic mouse expressing GFP under the control of genomic regulatory elements for the dopamine D2 receptor (D2-GFP) (B), or the muscarinic M4 receptor (M4-GFP) (C), which labels indirect- and direct-pathway MSNs, respectively, are also shown. Figure inspired by Gerfen (2006).

synapses on indirect-pathway MSNs are more efficacious, a property that may partly underlie the relatively higher firing rates of indirect-pathway MSNs observed in vivo (Mallet et al., 2006). Interestingly, when stimulation was performed in either cortex or thalamus, no differences were observed in release probability between synapses on direct- and indirect-pathway MSNs (Ding et al., 2008), suggesting the possibility that different sets of afferents innervate direct- and indirect-pathway MSNs.

Despite the critical role of dopamine in striatal function, surprisingly there is no firm evidence for direct presynaptic modulation of glutamate release by dopamine in the dorsal striatum (Nicola et al., 2000). However, striatal dopamine D2 receptor activation mobilizes endocannabinoids (Giuffrida et al., 1999; Kreitzer and Malenka, 2005), which are released from MSNs and exert apparent presynaptic effects (Yin and Lovinger, 2006) that may account for some of the reported actions of dopamine on synaptic vesicle cycling (Bamford et al., 2004; Bamford et al., 2008).

LTD at Excitatory Synapses on MSNs

High-frequency stimulation (HFS) of excitatory striatal afferents in vitro leads to a long-lasting reduction in synaptic strength at MSN synapses (Calabresi et al., 1992a; Lovinger et al., 1993; Walsh, 1993) that is initiated postsynaptically, but expressed through a presynaptic reduction in neurotransmitter release (Choi and Lovinger, 1997). HFS-induced striatal LTD requires dopamine D2 receptors, G_q-coupled group I mGluRs, L-type calcium channels, and CB1 receptor activation, but notably, not NMDA receptors or mAChRs (Calabresi et al., 1992a, 1997; Choi and Lovinger, 1997; Gerdeman et al., 2002; Kreitzer and Malenka, 2005; Sung et al., 2001).

The basic model that has emerged from these results is that HFS in or near the dorsolateral striatum stimulates both glutamatergic and dopaminergic fibers. HFS-induced elevations of glutamate activate postsynaptic mGluRs, while increases in dopamine activate D2 receptors. In field recordings, HFS also depolarizes MSNs enough to activate L-type calcium channels, whereas in whole-cell voltage-clamp recordings, MSN depolarization using cesium-filled electrodes is required to trigger LTD. Activation of mGluRs and L-type channels leads to endocannabinoid production and release, possibly through phospholipase Cβ, which is both G_q receptor dependent and calcium sensitive (Hashimotodani et al., 2005). Dopamine D2 receptor activation enhances the production of endocannabinoids (Giuffrida et al., 1999), which are released from MSNs and activate CB1 receptors on excitatory presynaptic terminals for several minutes (Ronesi et al., 2004), leading to the induction of presynaptic LTD. Some studies have also suggested a role for dopamine D1 receptors, nitric oxide release from interneurons, and DARPP-32 (Calabresi et al., 1999, 2000), although it is unclear how these signaling molecules relate to endocannabinoid signaling and presynaptic inhibition of neurotransmitter release.

One major question is whether LTD is expressed in both types of MSNs. The apparent requirement for D2 receptor activation in HFS-LTD might suggest that indirect-pathway MSNs selectively express LTD, given their high expression of D2 receptors. However, the first study to examine this issue found HFS-LTD at both direct- and indirect-pathway MSNs. In these experiments, higher-intensity macrostimulation was applied in the white matter separating cortex from striatum, which likely gives rise to broad and diffuse activation of striatal neurons. The requirement for D2 receptor activation was attributed to its inhibitory action at cholinergic interneurons (Wang et al., 2006). In this model, D2 receptor activation transiently inhibits release of ACh (Maurice et al., 2004; Yan et al., 1997), which in turn reduces cholinergic tone and relieves muscarinic-M1-receptor-mediated inhibition of L-type calcium channels present in both types of MSN (Howe and Surmeier, 1995), thus enabling endocannabinoid release. The same group also observed endocannabinoid-dependent LTD at both direct- and indirect-pathway MSNs, using intrastriatal microstimulation and a spike-timing-dependent plasticity (STDP) protocol (Shen et al., 2008). However, this STDP-LTD in direct-pathway MSNs could only be observed under conditions in which

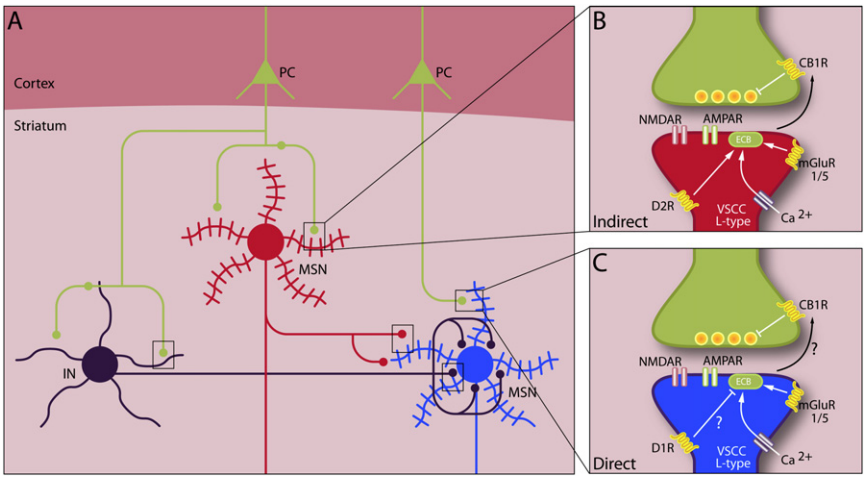

Figure 2. Synaptic Plasticity in the Striatum

(A) Simplified schematic of striatal neurons and their interconnections. Cortical pyramidal neurons (green) project to striatal interneurons (INTs) and medium spiny neurons (MSNs) of the direct (blue) and indirect (red) pathways. Interneurons also form synapses on MSNs. Rectangles highlight potential sites of synaptic plasticity that could alter striatal output from MSNs. Corticostriatal synapses on direct- and indirect-pathway MSNs are expanded at right.

(B) Indirect-pathway spines contain dopamine D2 receptors (D2R), group I mGluRs (mGluR1/5), and L-type voltage-sensitive calcium channels (VSCCs), which synergistically mobilize endocannabinoid (eCB) release that can induce presynaptic LTD by acting at cannabinoid receptors (CB1R).

(C) Direct-pathway spines contain dopamine D1 receptors (D1R), group I mGluRs, and L-type VSCCs. Endocannabinoid-dependent LTD reportedly occurs at direct-pathway MSNs under conditions in which D1 receptors are not activated.

dopamine D1 receptors were blocked or not activated. Unlike HFS-LTD elicited using macrostimulation, STDP-LTD in direct-pathway MSNs did not require D2 receptor activation (Wang et al., 2006). STDP-LTD in indirect-pathway MSNs, on the other hand, was readily elicited under standard conditions and did require D2 receptors (Shen et al., 2008), as previously reported for HFS-LTD.

An independent study of HFS-LTD using intrastriatal microstimulation obtained different results in that HFS induced robust LTD at indirect-pathway MSNs, but no LTD at direct-pathway MSNs (Kreitzer and Malenka, 2007). Moreover, direct activation of group I mGluRs gave rise to endocannabinoid-mediated inhibition in indirect-pathway, but not direct-pathway, MSNs (Kreitzer and Malenka, 2007), suggesting that, independent of the type of induction protocol, indirect-pathway MSNs more readily release endocannabinoids in response to mGluR activation. It is difficult to completely reconcile the sets of results from the independent studies, and thus the prominence of endocannabinoid release and the expression of HFS-LTD at direct-pathway MSNs remains a controversial topic.

What is agreed upon is that D2 receptors serve to enhance endocannabinoid release at indirect-pathway MSNs (Kreitzer and Malenka, 2007). One role of postsynaptic G_i-coupled D2 receptors may be to potentiate and extend endocannabinoid signaling during the critical time window following HFS, possibly through $G_{\beta/\gamma}$ signaling. Indeed, $G_{\beta/\gamma}$ subunits liberated following D2 receptor activation bind and activate PLCβ (Hernandez-Lopez et al., 2000). In support of this model, LTD is not induced by depolarization or brief application of group I mGluR agonists alone, both of which only transiently elevate endocannabinoids. However, brief application of group I mGluR agonists in the presence of a D2 agonist is sufficient to elicit LTD (Kreitzer and Malenka, 2007). Thus, dopamine mediates a form of long-lasting inhibition at indirect-pathway synapses, consistent with (1) dopamine as an inhibitor of indirect-pathway function (Albin et al., 1989), and (2) dopamine as a learning signal that gates synaptic plasticity (Schultz, 2002). In contrast, LTD at direct-pathway MSNs is reportedly blocked by increased dopamine (Shen et al., 2008), consistent with its role as a potentiator of direct-pathway function (Albin et al., 1989).

The slow kinetics of mGluR-driven endocannabinoid release at indirect-pathway MSNs provide a mechanism, at least in theory, for how dopamine could regulate changes in synaptic plasticity that were initiated prior to the onset of the dopamine signal. In this scheme, activation of a particular motor program would yield striatal mGluR activation and MSN depolarization that would drive endocannabinoid release for several seconds. Yet this alone would not induce sufficient endocannabinoid release to elicit LTD (Chevaleyre et al., 2006; Ronesi et al., 2004). However, if dopamine levels increase in the striatum within a few seconds of the initiation of endocannabinoid signaling (perhaps in response to a positive behavioral outcome), the ongoing release of endocannabinoids would be augmented, LTD induction would occur, and the motor program that led to the positive outcome would be reinforced.

LTP at Excitatory Synapses on MSNs

The induction and expression of LTP in the dorsal striatum is less well characterized. Early studies indicated that an NMDA-receptor-dependent form of LTP at excitatory MSN afferents could be elicited by HFS in the absence of extracellular magnesium (Calabresi et al., 1992b; Kerr and Wickens, 2001). It is perplexing, however, why depolarization of MSNs alone is not sufficient to unblock NMDA receptors and trigger LTP, as has been observed in the hippocampus and other brain regions. In studies performed in the dorsomedial striatum, HFS was reported to induce an NMDA-receptor-dependent LTP without removal of magnesium (Partridge et al., 2000), and in vivo, LTP has been elicited by pairing cortical stimulation with MSN depolarization (Charpier and Deniau, 1997). Dopamine D1-like receptors have been implicated in striatal LTP (Calabresi et al., 2000; Kerr and Wickens, 2001), while dopamine depletion has been reported to block LTP (Centonze et al., 1999). However, other studies demonstrate that striatal LTP can be induced in indirect-pathway MSNs of dopamine-depleted mice (Kreitzer and Malenka, 2007; Shen et al., 2008), suggesting that LTP mechanisms may differ in direct- and indirect-pathway MSNs. Unlike more extensively studied

forms of LTP in the hippocampus (Malenka and Bear, 2004), striatal LTP has proven difficult to reliably elicit, and therefore, little is known about the molecular pathways underlying its induction and expression, although PKA signaling has been implicated (Centonze et al., 2003a). More recently, LTP was studied at direct- and indirect-pathway MSNs using an STDP protocol (Shen et al., 2008). Under these conditions, LTP could be elicited at both direct- and indirect-pathway MSNs. However, D1 receptors were required only in direct-pathway MSNs. LTP in indirect-pathway MSNs was independent of dopamine, and instead required G_s-coupled adenosine A2A receptors, consistent with the presence of LTP at indirect-pathway MSNs in dopamine-depleted mice (Kreitzer and Malenka, 2007; Shen et al., 2008).

Corticostriatal and Thalamostriatal Synapses on GABAergic Interneurons

Corticostriatal and thalamostriatal axons form en passant synapses with multiple neurons, including interneurons, across large regions of striatum (Kemp and Powell, 1971; Lapper and Bolam, 1992; Parent and Parent, 2006). Some of these synapses occur at GABAergic interneurons, which despite their small numbers can significantly influence MSN firing properties (Koos and Tepper, 1999). Although the cellular physiology of these interneurons has been described (Kawaguchi, 1993), little is known about the properties of their glutamatergic inputs. However, it is clear that fast-spiking interneurons respond more rapidly and readily to stimulation of excitatory afferents both in vitro (Plotkin et al., 2005) and in vivo (Mallet et al., 2005), making them well-suited for mediating feedforward inhibition. Interestingly, dopamine inhibits GABAergic inputs onto fast-spiking interneurons via D2 receptor activation (Bracci et al., 2002), although the precise location of the D2 receptors and the possible role of endocannabinoid signaling in this inhibition has not been determined. Glutamatergic synapses onto striatal fast-spiking interneurons also exhibit LTP and LTD (Fino et al., 2008), suggesting that this synapse is a potentially important site for activity-dependent synaptic plasticity.

In the hippocampus, plasticity of glutamatergic synapses on aspiny interneurons has been well described (Buzsaki and Eidelberg, 1982; Gibson et al., 2008; Lamsa et al., 2007; McMahon and Kauer, 1997; Ouardouz and Lacaille, 1995), and it is possible that similar mechanisms underlie plasticity in the striatum. Of particular interest is the role of calcium-permeable AMPA receptors, which underlie a form of anti-Hebbian LTP in hippocampal interneurons (Lamsa et al., 2007) and have also been linked to endocannabinoid release from cerebellar interneurons (Soler-Llavina and Sabatini, 2006).

Interneuron Synapses on MSNs

Different classes of GABAergic interneurons have been shown to form synapses on MSNs with different properties. Synapses originating from fast-spiking interneurons display a relatively low failure rate and paired-pulse depression of IPSCs, consistent with a high probability of neurotransmitter release (Koos et al., 2004; Narushima et al., 2006). Synapses from low-threshold spiking interneurons are less well characterized, but one anatomical study found evidence of a consistently small active zone area that was independent of bouton size (Kubota and Kawaguchi, 2000). This was in contrast to parvalbumin-positive fast-spiking interneurons that exhibited larger active zones with increasing bouton volumes. Given the correlation between active zone size and release probability (Schikorski and Stevens, 1997), this may suggest that low-threshold spiking interneurons exhibit a lower release probability than fast-spiking interneurons. Short-term synaptic plasticity mediated by depolarization-evoked endocannabinoid release from MSNs has been observed at synapses originating from fast-spiking interneurons (Narushima et al., 2006). It will be important to test whether endocannabinoids can mediate LTD at inhibitory synapses, as has been demonstrated in the hippocampus (Chevaleyre and Castillo, 2003). In particular, differences in synaptic plasticity at inhibitory synapses on direct- or indirect-pathway MSNs could alter the relative output of these circuits and influence motor behavior.

The function of dopamine at inhibitory synapses on direct- and indirect-pathway MSNs also remains an open question. Dopamine was found to inhibit GABAergic currents in MSNs in a subpopulation of neurons (Delgado et al., 2000), perhaps due to differential effects on MSN subtypes. According to the classical model, inhibitory synapses onto direct-pathway MSNs might be inhibited by dopamine, whereas inhibition onto indirect-pathway MSNs might be enhanced by dopamine; these are predictions that need to be tested experimentally.

MSN Synapses on MSNs

The vast majority of striatal neurons are MSNs, and anatomical studies long ago identified MSN axon collaterals that appeared to contact other MSNs (Somogyi et al., 1981; Wilson and Groves, 1980). However, these connections were weak and difficult to detect physiologically (Jaeger et al., 1994). It was eventually determined that only a fraction of MSNs are interconnected. MSN-to-MSN synapses are typically unidirectional and distally localized, and exhibit higher failure rates than synapses from fast-spiking interneurons (Koos et al., 2004; Plenz, 2003; Taverna et al., 2004; Tunstall et al., 2002). Direct-pathway MSNs preferentially innervate other direct-pathway MSNs, whereas indirect-pathway MSNs innervate both subtypes equally (Taverna et al., 2008). Functionally, this suggests that increased indirect-pathway activity, which is correlated with inhibition of movement, can influence direct-pathway function. Dopamine reportedly exerts both excitatory and inhibitory effects on MSN lateral connections. Enhancement has been reported via D1 receptors, whereas inhibition was found via D2 receptors (Guzman et al., 2003; Tecuapetla et al., 2007). The net effect of such modulation, as well as its possible MSN subtype specificity, remains unclear.

Synaptic Integration in MSNs

MSNs exhibit negative resting potentials due to their high expression of inwardly rectifying potassium channels (Nisenbaum and Wilson, 1995). However, as MSNs are depolarized, these inwardly rectifying channels close and MSNs are more readily depolarized to reach spike threshold. Thus, a barrage of excitatory synaptic inputs can depolarize MSNs and yield a spike, whereas less coherent input is ineffective (Wilson and Kawaguchi, 1996). Interestingly, the pattern of activation at individual synapses may also be critical. When individual spines are repetitively activated, glutamate receptors desensitize and reduce synaptic efficacy (Carter and Sabatini, 2007). If multiple spines are activated, the resulting postsynaptic potentials can summate more effectively, particularly when MSNs are more depolarized. These results suggest that MSNs are optimized for integrating multiple distinct inputs.

The influence of GABAergic synapses on MSN firing is more complicated. When MSNs are at rest, the reversal potential for chloride is significantly more positive than the typical MSN resting potential. GABAergic synaptic activation is therefore depolarizing under these conditions (Bracci and Panzeri, 2006; Misgeld et al., 1982). However, once MSNs become more depolarized than the chloride reversal potential, activation of GABAergic synapses inhibits further depolarization and limits MSN firing. Thus, GABAergic synapses may function to actually facilitate MSN excitability by slightly depolarizing MSN dendrites, thereby blocking inwardly rectifying potassium channels and priming MSNs to respond to subsequent synaptic excitation (Wilson, 2007).

The output from the striatum to downstream basal ganglia nuclei thus reflects a complex interplay between intrinsic properties of MSNs and their excitatory and inhibitory synaptic inputs. Neuromodulators such as dopamine can alter both cellular and synaptic function to adjust output through the direct and indirect pathways and regulate motor function. However, elucidating the specific relation between changes in cellular or synaptic function in the striatum and behavior remains a challenging endeavor that is likely to keep investigators busy for many years to come.

Basal Ganglia Circuit Function and Dysfunction

Goal-Directed Learning

A primary function of the basal ganglia may be the selection of appropriate actions (Balleine et al., 2007). Properly performed actions lead to successful and rewarding results, which reinforce the choice of actions that led to that outcome. Over time, sequences of actions can be associated with each other, enabling the rapid selection of motor routines that are no longer dependent on reward values and can thus be considered habits. An accumulating body of evidence suggests that rapid, goal-directed learning primarily involves the dorsomedial striatum, whereas the slower acquisition of habits, which are insensitive to changes in the reward value of the outcome, involves the dorsolateral striatum (Balleine et al., 2007; Yin and Knowlton, 2006). Importantly, goal-directed learning of new motor routines appears to be initiated in the dorsomedial striatum, whereas the long-term motor memory required to execute previously learned sequences may be stored in the dorsolateral striatum. Within this general context, activation of direct-pathway circuits has been proposed to facilitate or select appropriate movements, whereas activity in the indirect pathway may inhibit unwanted or inappropriate movements (Albin et al., 1989; DeLong, 1990). As learning progresses, a motor routine can be acquired as wanted movements are maintained and unwanted movements are eliminated in a precise temporal sequence. In the striatum, the primary instructive signal for learning is thought to be dopamine release, which, according to one prominent theory, can signal a "reward prediction error" (Montague et al., 2004; Schultz, 2007). At the cellular and synaptic level, such learning is thought to occur through long-term changes in synaptic strength at striatal synapses.

A major goal of current research is to understand how changes at the molecular and cellular level translate into altered neural circuit function and behavior. Thus, for example, injection of an NMDA receptor antagonist into dorsomedial striatum, which is predicted to disrupt LTP, also impairs goal-directed learning (Yin et al., 2005). Although NMDA receptors are important for other aspects of striatal information processing, this finding is nevertheless suggestive of an important role for LTP in motor learning. Another in vivo study found that the magnitude of LTP induced in vivo can be correlated with the acquisition speed of a lever-pressing task for intracranial self-stimulation (Reynolds et al., 2001). Thus, LTP in the dorsomedial striatum may partially underlie increases in striatal neuron firing observed during goal-directed learning. Blocking D1 receptors in the dorsomedial striatum, which may be required for LTP, also reduces reward-dependent learning in a saccadic eye movement task (Nakamura and Hikosaka, 2006), implicating a role for direct-pathway MSNs in this process. Together, these results suggest that LTP in the dorsomedial striatum is a key cellular mechanism for goal-directed learning. Far less is known about the in vivo role of LTD, although recent findings in PD models suggest that LTD at indirect-pathway synapses is critical for maintaining normal movement (Kreitzer and Malenka, 2007).

Parkinson's Disease

The progressive loss of midbrain dopamine neurons leads to reduced dopamine levels in the striatum and the severe hypokinetic motor deficits characteristic of PD. Thus, PD provides powerful insight into the normal functions of dopamine in the striatum and its role in basal ganglia circuit function. Studies in both animal models of PD (Filion and Tremblay, 1991; Mallet et al., 2006) and human PD patients (Obeso et al., 2000) have indicated that striatal dopamine depletion leads to enhanced indirect-pathway MSN output and decreased direct-pathway MSN output, and a consequent decrease in activity in GPe and increase in activity in GPi. These in vivo results are generally consistent with cellular studies of the excitatory effects of dopamine D1 receptor activation on direct-pathway MSNs and the inhibitory actions of dopamine D2 receptors on indirect-pathway MSNs. Because the indirect pathway normally inhibits unwanted movements, its overactivity may lead to the inhibition of wanted movements and the disruption of learned motor routines. On the other hand, accepting that direct-pathway activity normally selects appropriate movements, its underactivity may additionally contribute to difficulties in initiating and performing movements in PD.

Given that the striatum is a primary target of dopamine innervation, it is likely that most of the pathophysiology observed in PD patients arises from striatal dysfunction, which can propagate throughout basal ganglia circuits. In response to the loss of dopamine innervation, a host of cellular and synaptic changes occur in the striatum. A compensatory increase in dopamine D1 and D2 receptor responses is observed (Mishra et al., 1974), as well as increased firing at indirect-pathway MSNs (Mallet et al., 2006). An increase in membrane resistance of MSNs has also been reported (Fino et al., 2007), along with a compensatory loss of spines specifically on indirect-pathway MSNs (Day et al., 2006), suggesting a reduced synaptic convergence onto indirect-pathway MSNs.

Among the most significant changes that occur following dopamine depletion is the loss of indirect-pathway LTD (Kreitzer and Malenka, 2007). Instead, LTP is observed with the original LTD-inducing stimulus protocol (Kreitzer and Malenka, 2007; Shen et al., 2008). This shift from LTD to LTP may importantly contribute to the increased activity in the indirect pathway,

ultimately resulting in excessive inhibition of movement. In fact, dopamine D2 receptor agonists are routinely prescribed as a first-line treatment for PD, and a recent study in mice showed that the efficacy of D2 receptor agonists in restoring locomotor activity could be significantly enhanced, even in severely dopamine-depleted animals, by coadministration of an endocannabinoid degradation inhibitor (Kreitzer and Malenka, 2007). Together these results indicate that striatal LTD may be critical for regulating indirect-pathway activity and motor control. An additional consequence of dopamine depletion and enhanced transmission at indirect-pathway MSNs could be increased entrainment to cortical and thalamic oscillations (Costa et al., 2006). In this scheme, synchronous firing of indirect-pathway projections to the GPe would be amplified by the recurrent GPe-STN circuit (Bevan et al., 2002), leading to abnormal oscillations that interfere with normal basal ganglia output, and that could also be associated with resting tremor in PD (Bevan et al., 2006).

Direct-pathway signaling may also be altered in PD (Albin et al., 1989; DeLong, 1990). In vivo evidence indicates that direct-pathway MSNs exhibit lower firing rates following dopamine depletion (Mallet et al., 2006). Consistent with this finding, recent work suggests that direct-pathway MSNs exhibit LTD instead of LTP following dopamine depletion (Shen et al., 2008). Similarly, as discussed previously, antagonists of D1 receptors reportedly block STDP-LTP and unmask STDP-LTD in direct-pathway MSNs (Shen et al., 2008). Further work will be required to confirm and extend these findings.

Of course, dopamine acts in numerous additional ways beyond effects on synaptic plasticity to shape the transfer of information through the striatum. In particular, the rapid and reversible actions of dopamine need to be distinguished from persistent changes that long outlast the dopamine signal itself. In the former case, dopamine can transiently alter synaptic integration, state transitions, and microcircuit function, which may enhance the transfer of certain kinds of information through the striatum. In the latter case, dopamine is gating changes in network function that may correspond to long-term motor memory itself.

Huntington's Disease

HD is a progressive neurological disorder resulting from a polyglutamine expansion in the ubiquitously expressed huntingtin (htt) protein, which for unknown reasons leads to the degeneration of certain types of neurons, including striatal MSNs. In particular, indirect-pathway MSNs appear to be selectively vulnerable to this disease process (Reiner et al., 1988). Their preferential loss is thought to reduce the amount of inhibitory control over unwanted movements, leading to the chorea and hyperkinesia typically associated with HD. However, neuronal death in HD may not be a purely cell-autonomous process (Gu et al., 2005). Additional evidence suggests that altered cellular and synaptic properties may result in aberrant overexcitation and eventual glutamate excitotoxicity (Cepeda et al., 2007; Gu et al., 2005).

Early physiological changes in MSNs observed in animal models of HD are reminiscent of those observed in dopamine-depleted animals, including an increase in input resistance and a decrease in spine density (Klapstein et al., 2001), as well as increased expression of calcium binding proteins (Huang et al., 1995; Sun et al., 2005). While these changes may arise as a direct consequence of mutant htt expression in MSNs, another possibility is that they represent compensatory responses to increased excitatory drive from cortex. Indeed, in vivo experiments in mouse models of HD indicate an increase in MSN firing rate (Rebec et al., 2006). Expanded htt is also associated with abnormal trafficking and increased surface expression of NR2B-containing NMDA receptors (Fan and Raymond, 2007), which could contribute to excitotoxicity, particularly in indirect-pathway MSNs that already exhibit larger NMDA currents (Kreitzer and Malenka, 2007). Mutant htt may also enhance IP_3-mediated release of calcium from intracellular stores that could additionally contribute to dysregulation of calcium signaling (Tang et al., 2003).

Unfortunately, less is known about the role of striatal plasticity in the degeneration of MSNs in HD. In a pharmacological model of HD, field recordings in the striatum failed to show LTD, while LTP was readily observed (Dalbem et al., 2005). Another study found a loss of depotentiation following the induction of LTP at corticostriatal synapses (Picconi et al., 2006). Together, these studies suggest that a net enhancement of excitatory synaptic transmission in the striatum may contribute to the observed changes in MSN properties and their eventual cell death in HD.

Obsessive-Compulsive Disorder

In contrast to PD and HD, OCD and other OC-spectrum disorders such as Tourette's syndrome (TS) and trichotillomania (hair-pulling) are psychiatric disorders characterized by repetitive thought patterns (obsessions) and uncontrollable urges (compulsions) to perform motor routines (rituals), often directed at easing obsessions (Graybiel and Rauch, 2000). For example, someone with OCD may repeatedly verify that a door is locked or repeatedly wash their hands, displaying an addict-like need to perform these actions despite evidence that the appropriate outcome has been achieved. The neural circuits underlying OCD are thought to involve frontal and cingulate cortices, as well as the caudate nucleus and thalamus (Aouizerate et al., 2004), implicating basal ganglia circuitry required for reward-dependent learning. However, it remains unclear whether OCD represents a gain or loss of function in basal ganglia circuits. It is tempting to speculate that it may represent an enhanced propensity to form both cognitive and motor habits. In the case of TS, dopamine D2 antagonists are an effective treatment, suggesting perhaps that TS involves excessive D2 receptor-mediated striatal plasticity.

Although little is known about the causes of OCD, deletions in two genes have been shown to give rise to OCD-like behaviors in mice. *Hoxb8* is a transcription factor involved in early development that is expressed widely in the brain, including the cortex and striatum. *Hoxb8* knockout mice exhibit excessive grooming, leading to hair removal and self-inflicted wounds (Greer and Capecchi, 2002). More recently, a postsynaptic scaffolding protein expressed in the striatum, *Sapap3*, has been implicated in OCD behaviors including pathological overgrooming and anxiety (Welch et al., 2007). Remarkably, these behaviors are reversed by prolonged administration of a selective serotonin reuptake inhibitor, the most commonly used treatment for OCD. Furthermore, selective postnatal expression of *Sapap3* in the striatum eliminates the behavioral abnormalities. Consistent with a critical role for striatal circuitry in mediating the OCD-like behaviors, the *Sapap3* knockouts displayed complex abnormalities in

excitatory synaptic function and structure in the striatum including an apparent enhancement of NMDA-receptor-mediated synaptic responses. Further study is clearly warranted to elucidate the detailed synaptic abnormalities in the striatum caused by the loss of *Sapap3* and whether they are restricted to specific striatal neuron subtypes.

Conclusions and Future Directions

Over the past three decades, a vast amount of anatomical, experimental, and clinical data on the striatum and basal ganglia function has accumulated. However, the complex anatomy and difficulty in isolating specific subpopulations for experimental analysis has hampered progress in understanding the mechanisms and function of basal ganglia circuits. The development of transgenic mice that express proteins in specific neuronal populations represents a major step forward that should help unravel the complexity of striatal circuit function (Gong et al., 2003). Targeted whole-cell recording and analysis of direct- and indirect-pathway MSNs, as well as patch and matrix MSNs, and different classes of striatal interneurons has become possible for the first time. Indeed, it is now possible to generate transgenic mice that have different fluorophores in D1 and D2 MSNs simultaneously (Shuen et al., 2008). By gaining a precise understanding of the cellular and synaptic mechanisms that give rise to the functional properties of these neurons and their connections, novel approaches can be developed for selectively altering cellular and synaptic function in vivo, with the goal of understanding both the mechanisms' role in basal-ganglia-related behaviors and their potential as therapeutic targets for neurological disorders.

Expression of proteins enabling optical stimulation, such as channelrhodopsin and halorhodopsin (Boyden et al., 2005; Zhang et al., 2007), may also accelerate our understanding of basal ganglia function. It may soon be possible to control spiking of direct- or indirect-pathway MSNs, cholinergic interneurons, or midbrain dopamine neurons with millisecond precision both in vitro and in vivo. In vitro, this may allow the creation of arbitrary activity patterns across entire networks, thus enabling an examination of firing synchrony, synaptic integration, and striatal microcircuits in basal ganglia function with high resolution. In vivo, fiber optics implanted into specific brain regions may be able to excite or silence activity within distinct neuronal cell types (Adamantidis et al., 2007; Aravanis et al., 2007). In addition, molecular genetic manipulations in mice may allow alternative strategies for precise, drug-induced control over neuronal and circuit activity (Arenkiel et al., 2008; Conklin et al., 2008; Karpova et al., 2005; Lerchner et al., 2007). By applying these novel technologies to the striatum and associated basal ganglia circuitry, investigators may be able to make the critical leap from activity in specific striatal neurons and circuits to the role of those circuits in behaving animals.

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