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Striatal Microcircuitry and Movement Disorders

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Abstract

The basal ganglia network serves to integrate information about context, actions, and outcomes to shape an animal's behavior based on its past experience. Clinically, the basal ganglia receive the most attention for their role in movement disorders. Recent advances in technology have opened new avenues of research into the structure and function of basal ganglia circuits. One emerging theme is the importance of GABAergic interneurons in coordinating and regulating network function. Here, we discuss evidence that changes in striatal GABAergic microcircuits contribute to basal ganglia dysfunction in a number of movement disorders. Because interneurons are genetically and neurochemically unique from striatal projection neurons, they may provide promising therapeutic targets for treating a variety of striatal-based disorders.

Keywords

interneuron; basal ganglia; Parkinson's disease; Huntington's disease; dystonia; Tourette syndrome

Introduction

The 1980s were a golden era for basal ganglia research, culminating in circuit models that continue to guide hypothesis-based studies of basal ganglia function in clinical and experimental contexts [1–4]. Within the basal ganglia, the striatum is the most prominent nucleus, serving as a major site of input and integration for cortical, thalamic, and midbrain afferents. The striatum is functionally divided along a dorsolateral/ventromedial axis, where the dorsolateral portion subserves sensorimotor functions and the ventromedial portion is more involved in cognitive and limbic functions [5]. Because the focus of this review is neural circuits involved in movement disorders, much of our discussion is concentrated on neural circuits in the dorsolateral striatum.

The projection neurons of the striatum, called spiny projection neurons (SPNs), integrate glutamatergic inputs from the cortex and thalamus and send GABAergic projections to neurons in downstream basal ganglia nuclei. Based on anatomical projection patterns and biochemical differences, SPNs are divided into two classes. D1-type dopamine receptor–expressing neurons project directly to basal ganglia output nuclei and are called "direct-

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pathway" SPNs (dSPNs), while D2-type dopamine receptor–expressing neurons, known as "indirect-pathway" SPNs (iSPNs), project indirectly to basal ganglia output nuclei via the globus pallidus external segment (GPe) and the subthalamic nucleus (STN). These pathways are well segregated in the dorsolateral striatum, with fewer than 5% of SPNs expressing both classes of dopamine receptors [6]. Activity of dSPNs leads to the disinhibition of motor circuits to facilitate movement. Overactivity of the direct pathway has been proposed to cause hyperkinetic movement disorders such as Huntington's disease (HD), dystonia, and Tourette's syndrome. In contrast, iSPN activity inhibits motor circuits to suppress movement. Overactivity of the indirect pathway is thought to underlie hypokinetic motor symptoms in disorders such as Parkinson's disease (PD).

Approximately 80–90% of striatal SPNs in the dorsolateral striatum fall into the direct/indirect pathway classification system. The remaining 10–20% are found in neurochemically distinct patches throughout the striatum, called striosomes or patches [4]. SPNs in striosomes typically express D1 receptors and directly project to a subset of dopaminergic neurons in the substantia nigra compacta (SNc). Their direct projections to a subset of dopamine neurons suggest that striosomal SPNs are particularly important for regulating dopamine signaling, but their immediate effects on movement are not clear.

These classic models of basal ganglia function illustrate the importance of understanding how and when specific classes of SPNs are activated. Historically, the cellular and synaptic mechanisms controlling dSPN vs. iSPN activation were hard to elucidate, because SPN subtypes could only be differentiated using manually intensive anatomical methods or antidromic stimulation *in vivo*. This has rapidly changed thanks to the development of transgenic mouse lines that fluorescently label dSPNs, iSPNs, and local interneurons within the striatum [7–11].

Interneurons tune and regulate dynamical properties of neural circuits in many brain regions. Interneurons comprise only ~5% of all striatal neurons, but they critically regulate striatal output. Compared to the broad diversity of interneuron subtypes in the hippocampus [12] and cortex [13], interneurons in the striatum are considerably less heterogeneous (Figure 1). Electrophysiologically, most striatal GABAergic interneurons fall into two categories (1) fast-spiking interneurons (FSIs) and (2) persistent and low-threshold spike interneurons (PLTSs) [14]. Neurochemically, FSIs may be distinguished by their expression of the calcium binding protein parvalbumin (PV), while PLTS interneurons express neuropeptides such as somatostatin (SOM), neuropeptide Y (NPY), and the enzyme nitric oxide synthase (NOS). Neurons broadly classified physiologically as PLTSs might also include several subtypes of GABAergic interneurons, including those that express tyrosine hydroxylase (TH) [9]. In addition, about 20% of NPY-expressing interneurons have the electrophysiological properties of neurogliaform cells (NGF) [10]. The striatum also contains calretinin-expressing interneurons, but these cells are much sparser in rodents compared to primates [15] and their electrophysiological properties are not well characterized.

Although this review will focus on inhibitory microcircuits within the striatum, it is important to note the presence of an additional type of interneuron in the striatum that releases the neurotransmitter acetylcholine. Cholinergic interneurons play an important role in regulating striatal output [16, 17], possibly through the modulation of local inhibitory circuits [18, 19].

GABAergic Microcircuits in the Striatum

FSIs give rise to one of the best-characterized inhibitory microcircuits in the striatum. They are thought to mediate feedforward inhibition because they are activated earlier and at lower thresholds than SPNs [20, 21]. FSIs make strong, dense projections onto SPNs within a 300 μm

radius and inhibit SPN firing [8, 21–23]. A single FSI inhibits an estimated total of 135–541 SPNs [24] of both the direct- and indirect-pathway subtypes [8, 23].

NGF cells that express NPY represent a second major class of densely-projecting interneuron [10, 19]. Whereas FSIs are connected to SPNs with connection probabilities ranging from 25% [24] to 75% [23], NPY-NGF neurons are connected to SPNs with >86% connection probability [10]. However, the comparatively low number of NPY-NGF interneurons in the striatum relative to FSIs might explain why the influence of NPY-NGF interneurons on striatal function has not been more apparent. Inhibitory postsynaptic currents (IPSCs) from NPY-NGF neurons give rise to distinct, long-lasting IPSCs in SPNs that have nearly 10-fold longer decay kinetics than those from FSIs (123 ms vs. 8 ms) [10, 25]. Interestingly, NPY-NGF interneurons are activated by acetylcholine released from synchronously firing cholinergic interneurons, suggesting that NPY-NGF interneurons may be an integral part of cholinergic-mediated control of striatal output [19].

SPNs make collateral projections onto other SPNs, creating a lateral inhibitory network whose strength and function has been the topic of much theoretical work and some controversy [26]. Unitary connections between SPNs are individually weak and connectivity is sparse [22, 27, 28], but in aggregate, lateral inhibition from thousands of SPNs can generate substantial inhibition [29] that might be important for creating distinct cell assemblies within the striatal circuit [30–32].

SPNs also receive inhibitory inputs from TH-positive interneurons and PLTS interneurons. Inhibitory inputs from these neurons are not readily detected with somatic whole-cell recordings and connectivity is sparse [8–10], so the extent to which inhibitory synaptic transmission from these interneurons contributes to striatal function is unclear. A more intuitive role for TH-positive and PLTS interneurons would be as sources of neuropeptides and neuromodulators such as dopamine, SOM, NPY, and NO, although further investigation will be required to clarify their functions.

GABAergic microcircuits are emerging as important coordinators of activity across distinct information processing streams within the striatum including the direct- and indirect-pathways and the patch/matrix compartments. FSIs, for example, are synaptically connected to both dSPNs and iSPNs [23, 25], and their dendrites cross the boundaries between the patch and matrix compartments, unlike the dendrites of SPNs which are restricted to their respective compartments [33]. The dendrites of PLTS-like interneurons also cross the boundaries between patch and matrix compartments [33] and their release of neuromodulators and neuropeptides may enable regulation of large areas of the striatum by volume transmission. In this review, we discuss evidence that dysfunction of striatal GABAergic microcircuits leads to imbalances in striatal output pathways in a number of movement disorders. We hope that a better understanding of microcircuit dysfunction may open the door for new therapeutic strategies for the treatment of striatal-based movement disorders

Parkinson’s Disease

Hypokinetic motor impairments in PD patients are thought to arise from the loss of dopamine neurons in the substantia nigra that densely innervate the striatum. In rate-based models of striatal function, dopamine depletion leads to increased firing rates of iSPNs and excessive activity of neurons in basal ganglia output nuclei [1, 3, 34]. In support of these rate-based models, a recent study demonstrated that increased firing of iSPNs was sufficient to decrease movement, and motor impairments in dopamine-depleted mice were diminished by increasing the firing rates of dSPNs [35].

A great deal of work has been devoted to unraveling the cellular and synaptic mechanisms underlying the imbalanced firing rates of dSPNs and iSPNs following dopamine depletion. However, a purely rate-based model of basal ganglia dysfunction in PD remains controversial. Under conditions of low dopamine levels, neurons in the basal ganglia and motor areas of the cortex show profound changes in firing pattern. Neurons in these regions fire in bursts [36–38], and become highly synchronous, oscillating in the 5–30 Hz frequency range [36–43]. These dramatic alterations in firing pattern are thought to disrupt information processing throughout the basal ganglia-thalamo-cortical circuit [44–47].

In response to decreased dopaminergic signaling, SPNs in the striatum fire more synchronously and there is an increase in local field potential (LFP) power in the 10–30 Hz frequency range [38, 41–43, 48, 49]. In part, the emergence of aberrant synchrony and oscillations in the striatum could reflect increased cortical influence over striatal activity that develops under conditions of low dopamine levels [41, 50, 51]. Aberrant synchrony and oscillations could also reflect changes in inhibitory microcircuits. Acutely, dopamine signaling has been proposed to increase FSI excitability [52] through the activation of D5-type dopamine receptors [53, 54] and acute depletion of dopamine with α-methyl-paratyrosine in brain slices reduces FSI excitability [55]. During more prolonged dopamine depletion, however, changes in FSI excitability are no longer observed [8, 51], suggesting that excitability may be homeostatically regulated.

FSI microcircuits are dramatically altered by dopamine depletion. Under normal conditions, FSIs make synaptic contacts onto both dSPNs and iSPNs, but preferentially target dSPNs [8] (Fig. 2A). Dopamine depletion induces a rapid, pathway-selective plasticity whereby FSIs nearly double their innervation of iSPNs (Fig. 2B). This inverts the normal pathway preference expressed by FSIs and is sufficient to induce aberrant synchrony across the population of iSPNs in a computer model of the striatal circuit [25]. This suggests a mechanism through which the plasticity of striatal microcircuits could contribute directly to the amplification or propagation of pathological oscillations and synchrony in PD.

Under normal conditions, dSPNs and iSPNs extend collaterals to SPNs in both pathways, with the strongest connections between iSPNs→iSPNs and the weakest between dSPNs→ iSPNs [28]. Dopamine depletion weakens collaterals between all SPNs [28] (Fig. 2C), and the loss of SPN-SPN collaterals provides a mechanism through which SPN cell assemblies can become pathologically large and synchronous when dopamine levels are low [32, 56].

Although the effects of dopamine depletion on NPY-NGF microcircuits have not been studied, the cholinergic interneurons that drive NPY-NGF signaling show increased acetylcholine release due to reduced autoreceptor function after dopamine depletion [57] and fire in a pathologically synchronous manner [58]. Synchronous firing of cholinergic cells effectively drives NPY-NGF interneurons [19], so inhibitory signaling from NPY-NGF interneurons might be upregulated under conditions of low dopamine expression.

Finally, a fourth inhibitory microcircuit that might be affected by dopamine depletion arises from PLTS interneurons. Under normal conditions, PLTS interneurons make sparse, weak inhibitory projections onto SPNs [8, 10], but in dopamine-depleted mice, large, rhythmic inhibitory inputs develop onto SPNs that are thought to arise from PLTS interneurons [59] (Fig. 2D). Another possibility is that the large IPSCs observed after dopamine depletion arise from TH-positive interneurons [9], which increase in number after dopamine depletion [60].

Huntington's Disease

A pathological hallmark of HD is the progressive loss of striatal SPNs. Indirect-pathway SPNs are more susceptible at early stages of the disease, whereas iSPNs, dSPNs, and cortical neurons die at later stages [61]. Animal models of HD have revealed that dysfunction of neural circuits in the striatum and other brain regions can cause motor impairments even without cell death [62].

According to the classic model of basal ganglia function, reduced activity of iSPNs could underlie the hyperkinetic symptoms of HD [1, 2]. In support of the classic model, disrupting indirect pathway activity in mice has been shown to increase locomotion [63–65]. In a recent study, diphtheria toxin was injected into mice genetically engineered to express diptheria toxin receptors selectively in iSPNs, resulting in a ~90% reduction of these cells within 5 days. Loss of iSPNs specifically in the dorsomedial striatum increased locomotion and impaired learning of an accelerating rotarod task. Taking a different approach, a second group genetically deleted dopamine- and cAMP-regulated phosphoprotein-32 (DARPP-32)—a phosphatase that critically regulates dopamine receptor signal transduction—selectively in iSPNs to show that indirect-pathway disruption blocked long-term potentiation (LTP) and increased locomotor activity in an open field behavioral assay.

Reduced activity of iSPNs in HD could have dramatic effects on the structure and function of local cell assemblies in the striatum [30, 66, 67]. Indirect-pathway SPNs make stronger collateral projections onto other SPNs than do dSPNs [28]. Therefore, the loss of iSPNs could be particularly disruptive to lateral inhibitory circuits within the striatum.

The contribution of striatal GABAergic interneurons to circuit dysfunction in HD has not been well characterized. At early stages of motor impairments in two mouse models of HD, R6/2 and R6/1, IPSC frequency onto SPNs was nearly doubled, and SPNs showed increased expression of $GABA_A$ receptors [68]. Although this study demonstrated changes in striatal inhibitory circuits early in the progression of HD, it is not clear whether increased inhibitory signaling arises from SPNs, FSIs, or another population of local GABAergic interneurons.

There is some evidence to suggest striatal FSIs are susceptible to HD-mediated cell death. In the R6/2 mouse model of HD, the numbers of FSIs were reduced by ~50% [69]. In contrast, both calretinin-positive and NPY/SOM/NOS-positive interneurons were spared by the disease [70–72]. The extent to which changes in the proportions of interneurons contribute to striatal pathophysiology in HD remains an open question. The preferential death of SPNs and FSIs in HD results in an increased relative proportion of PLTS and CR interneurons in the striatum. Under normal conditions, PLTS interneurons do not produce strong IPSCs in SPNs [8, 10], although their inhibitory projections might be increased under some pathological conditions [59]. NO released from PLTS interneurons might increase the sensitivity of SPNs to their excitatory inputs [73], which could exacerbate glutamate excitotoxicity and contribute to cell death [74]. However, NO has also been shown to enhance long-term depression of excitatory inputs onto SPNs [75]. Thus, the overall effect of increased NO on striatal output remains controversial.

Dystonia

Dystonia is a clinical disorder in which involuntary and often painful muscle contractions generate twisting and repetitive movements. Although the pathophysiology of dystonia is still poorly understood, symptoms often correlate with increased striatal metabolic activity [76] and reduced GABAergic signaling [77], suggesting dysfunction of inhibitory circuits within the striatum.

A series of experiments characterizing striatal dysfunction in dystonia have been carried out in the dt^{sz} hamster model of dystonia [78, 79]. In dt^{sz} hamsters, the firing rates of SPNs are abnormally high at 32–43 days of age, when dystonic attacks are at their peak, but drop back to normal levels at 96–100 days of age, when attacks no longer occur[79]. One mechanism that could account for the abnormally high SPN firing rates is reduced inhibition from local inhibitory interneurons, and indeed, fewer numbers of PV-positive interneurons are found in the striatum of dt^{sz} hamsters relative to controls[80].

In a recent study, directly reducing the activity of PV-positive FSIs in the dorsolateral striatum was sufficient to induce dystonia-like dyskinesias in mice[81]. When FSI firing was transiently suppressed by the infusion of IEM-1460—an antagonist selective for GluA2-lacking AMPA receptors—into the dorsolateral striatum, the mice exhibited action-induced dyskinesias that were characterized by prolonged, twisted postures and jerky, repetitive movements, similar to symptoms of dystonia in human patients. Although SPN firing rates tended to be higher when FSIs were inhibited, the difference was not significant, suggesting that dystonia is not caused by a simple increase or decrease in overall SPN firing rates but perhaps by a more complex change in their activation pattern. This concept would be consistent with changes in firing patterns observed in downstream basal ganglia nuclei in patients with dystonia [34, 82, 83].

At least two forms of dystonia are associated with the dysfunction of striosomal SPNs: dopa-responsive dystonia (DYT5) [84] and X-linked recessive dystonia parkinsonism (XDP; DYT3)[85]. In DYT3 dystonia, SPNs in striosomes degenerate, while DYT5 dystonia results from the selective reduction of dopaminergic innervation of striosomal SPNs, as evidenced by immunostaining [84] and reduced dopamine receptor binding by D3-type receptors that are enriched in striosomal compartments [86, 87]. Disruption of striosomal SPNs presumably alters dopaminergic signaling, which could alter striatal output through direct effects on SPNs or modulation of corticostriatal plasticity [88].

Tourette Syndrome

Tourette syndrome is a movement disorder that first presents during childhood and typically declines in adulthood [89]. Patients with Tourette syndrome exhibit highly stereotyped movements called tics. It has been proposed that the stereotyped motor patterns of tics are driven by some of the same motor circuits as those involved in habit learning [90] and highly repetitive behaviors or compulsions [89, 91].

A circuit-level model of Tourette's syndrome, put forward by Mink and colleagues, posits that tics arise from the aberrant activation of small "pockets" of SPNs that correspond to specific motor commands [89, 92]. Experimental support for these movement-related pockets of SPN activity comes from striatal recordings of monkeys performing a saccade task [93]. Just before saccade onset, small pockets of focal activity within the striatum "pop-out" from the global LFP, presumably reflecting activity of a small group of SPNs. Furthermore, microstimulation of small regions of the striatum elicit movements in individual body parts [94].

Disruption of local inhibitory circuits within the striatum could be a main contributor to the aberrant activation of small groups of SPNs. Small, local infusions of the $GABA_A$ blocker bicuculline into the striatum elicits tics [95–97]. An important outstanding question is whether bicuculline produces tics because of a disruption of local SPN-SPN collaterals, blockade of inhibition from FSIs, or blockade of inhibition from another source. Some support for a deficiency in FSI signaling comes from the observation that the brains of Tourette's patients have fewer striatal FSIs [98].

Drug-induced Motor Impairments

Many drugs that alter dopamine signaling can impact movement. Cocaine and amphetamine increase locomotion acutely and their chronic use can produce repetitive behaviors called motor stereotypies, which include head bobbing and lip smacking. Psychostimulant-induced hyperlocomotion may arise from increased dopamine levels caused by these drugs, but due to the complex and widespread actions of dopamine on most synapses and cell types in the striatum [99], the specific neural circuits involved remain unknown. In the doroslateral striatum, amphetamine has been shown to increase the firing rates of striatal FSIs [100], potentially through the activation of D5 receptors [52]. Increases in FSI firing rates, but not SPN firing rates, were correlated with increased locomotor activity [100].

In rats chronically treated with cocaine or amphetamine, the severity of motor stereotypies correlated with a unique pattern of neuronal activation in the striatum [101], where rats with the most severe stereotypies showed higher ratios of patch:matrix neuron activation than those with weaker stereotypies. Similar results were observed in monkeys [102]. Chronic cocaine and amphetamine treatments also resulted in increased c-fos expression in NOS-positive striatal interneurons, suggesting a role for these neurons in the manifestation of motor stereotypies.

Another common motor disorder that results from prolonged treatment with dopamine-enhancing drugs is L-DOPA-induced dyskinesia. The incidence of developing L-DOPA-induced dyskinesias is as high as 50% in patients with early-onset PD (i.e., between 40–59 years of age). These dyskinesias typically first present on the side most affected by PD, and are typically observed in the legs before the arms [103]. Although the cellular mechanisms of L-DOPA-induced dyskinesias remain unknown, a great deal of research has focused on altered glutamatergic plasticity onto SPNs [104]. However, there is also evidence to suggest that GABAergic signaling is altered in the striatum and thus could be a contributing factor. For example, treatment with L-DOPA in rats has been shown to increase glutamic acid decarboxylase (GAD) mRNA levels in the striatum, suggesting an increase in local GABAergic signaling [105].

Increases in striatal GABA could reflect increased GABA release from SPN-SPN collaterals or increased FSI activity. Neither of these possibilities has been explicitly tested, but a recent study provides indirect evidence supporting the involvement of overactivity of striatal FSIs [106]. In this study, mice with L-DOPA-induced dyskinesias were given systemic injections of IEM-1460, a selective antagonist of GluA2-lacking, Ca^{2+}-permeable AMPA receptors. Co-administration of IEM-1460 with L-DOPA significantly reduced the development of L-DOPA-induced dyskinesias [106]. Although Ca^{2+}-permeable AMPA receptors are found throughout the brain, the only GABAergic neurons in the striatum that express these receptors are FSIs [81], suggesting that overactivity of striatal FSIs could contribute to the development of L-DOPA-induced dyskinesias. Future experiments are needed to determine whether there are structural or functional changes in FSIs that are consistent with this hypothesis.

Future research directions

A growing body of evidence points to dysfunction of striatal microcircuits as a common theme in a variety of movement disorders. Changes in FSIs, for example, are observed in both hypokinetic and hyperkinetic movement disorders. These observations are reconciled by the fact that FSIs target SPNs in a pathway-selective manner that is regulated by plasticity [8, 25]. The selective targeting of subsets of principal neurons by interneurons is an emerging theme in various neural circuits [107]. Identifying the molecular mechanisms that control interneuron target specificity holds great promise for developing new techniques that

could modulate neural circuits in highly selective ways. It will also be important to gain a better understanding of the extent to which changes in excitatory and inhibitory connections onto interneurons and the connections between them are involved in circuit dysfunction in movement disorders.

Many interneurons express unique receptors or ion channels compared to projection neurons. Thus, specific subsets of interneurons might represent pharmacologically tractable drug targets for movement disorders that would have fewer side effects than current drug treatments. Specific promoters also open the possibility for the selective targeting of interneuron subtypes with optogenetic or pharmacogenetic constructs such as opsins or engineered G-protein coupled receptors[108–111]. A number of questions still remain about the role of specific striatal microcircuits in regulating striatal output in health and disease. However, recent advances in our abilities to target and manipulate specific microcircuits in the striatum suggest that important new discoveries are just on the horizon.

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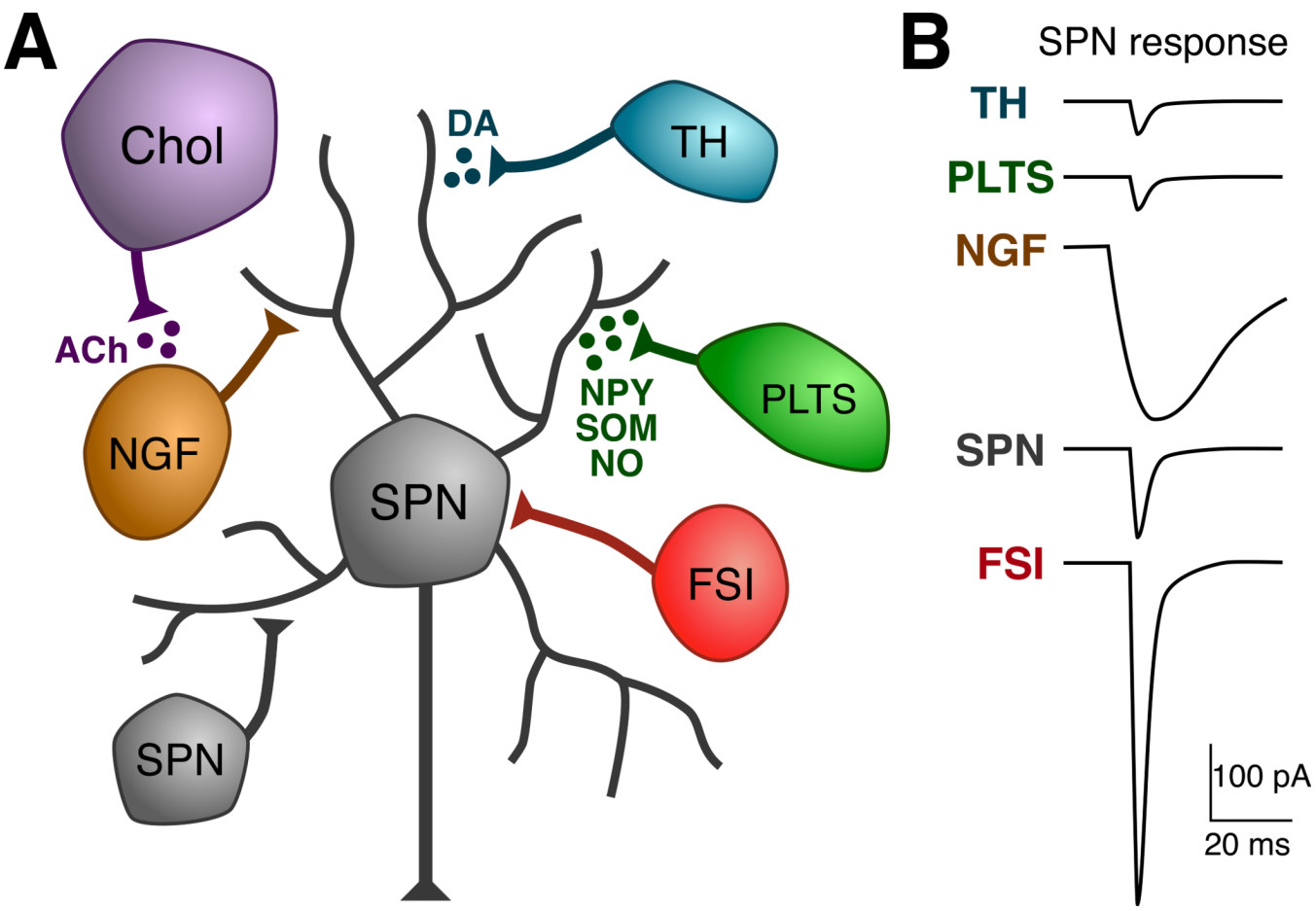

Figure 1.

GABAergic microcircuits in the striatum. **A.** Schematic showing different classes of striatal neurons that contribute to local inhibitory networks. **B.** Illustration comparing the typical time course and amplitudes of unitary IPSCs (uIPSCs) observed in SPNs from each class of inhibitory neuron. FSIs typically synapse onto the somatic compartment of SPNs [112] and produce large amplitude, fast kinetic responses in SPNs [8, 22–24]. PLTS interneurons are sparsely connected to SPNs and their synapses are found on the dendrites of SPNs [112]. uIPSCs from PLTS interneurons are very small compared to those from FSIs, typically < 100 pA [8]. A more important role for PLTS interneurons in regulating SPN function may be the release of neuromodulators such as NPY, SOM, and NO. TH-positive interneurons are similar electrophysiologically to PLTS interneurons. They also make inhibitory connections onto the distal dendrites of SPNs and produce small amplitude uIPSCs [9]. The local release of dopamine by these neurons may be particularly important in diseases like PD, where the normally massive dopaminergic innervation of the striatum from the SNc is lost. NPY-NGF interneurons likely target the distal dendrites of SPNs [10, 113]. Although NPY-NGF interneurons receive some excitatory inputs (presumably from both cortex and thalamus), they are also well activated by acetylcholine (ACh) release from striatal cholinergic interneurons [19]. The uIPSCs from NPY-NGF interneurons have distinctive slow kinetics compared to uIPSCs from all other cell types [10, 19]. Finally, SPNs also make lateral inhibitory connections with each other and these collateral synapses also target the dendritic compartments of SPNs [28, 114]. Although the probability of finding a connection between any two SPNs is small and uIPSCs are weak, due to the large number of SPNs in the striatum relative to all other cell types (95% of striatal neurons are SPNs), this inhibitory collateral

network may be a major source of local inhibition [29]. Abbreviations: Chol, cholinergic interneuron; DA, dopamine.

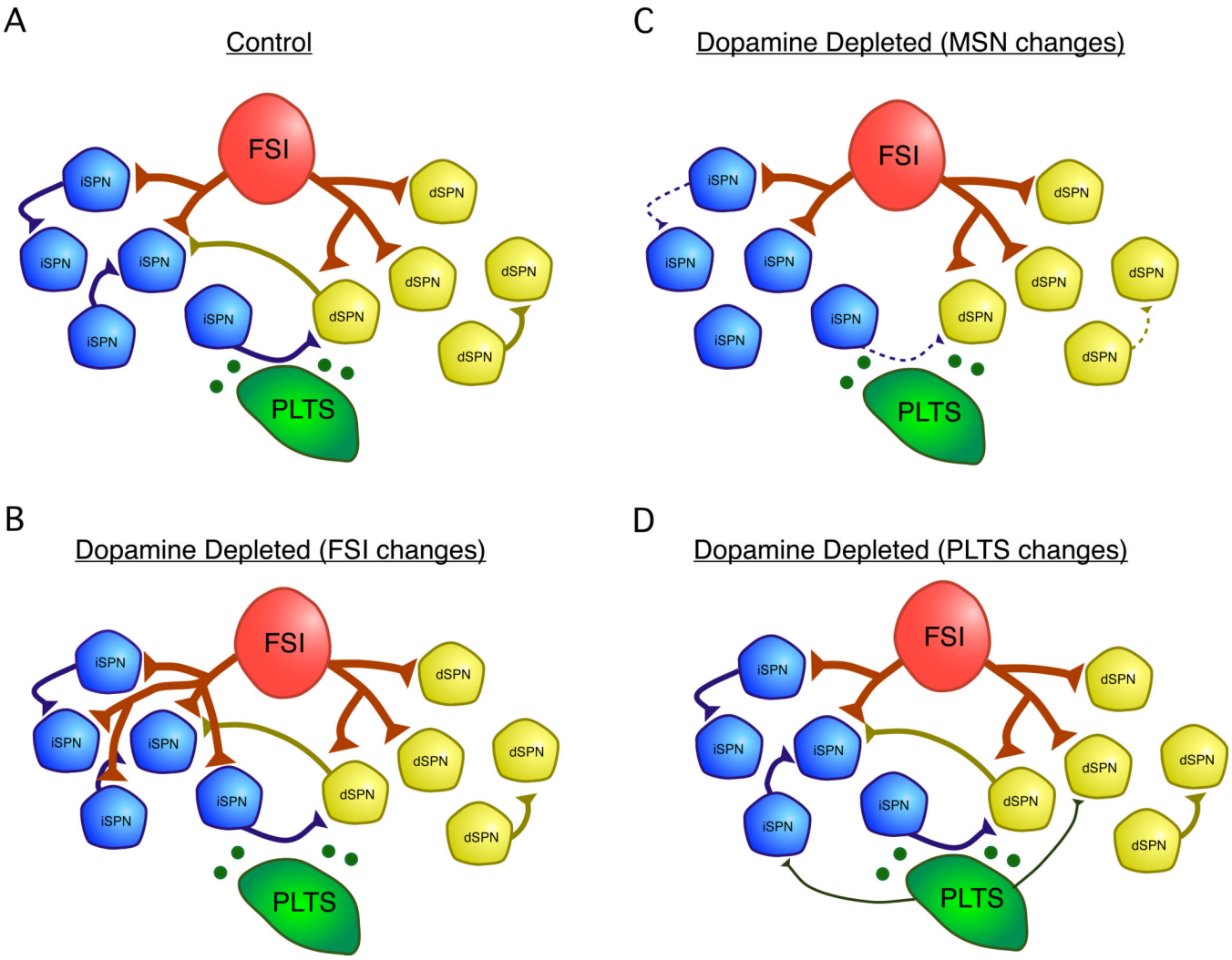

Figure 2.

Summary of changes in GABAergic microcircuits following dopamine depletion. **A.** Under normal conditions, SPNs laterally inhibit each other and inhibition is observed both across and within dSPN and iSPN subtypes [28]. FSIs inhibit both dSPNs and iSPNs, but preferentially target dSPNs [8]. PLTS interneurons release neuropeptides such as NPY and SOM and the neuromodulator NO which can modulate SPN activity [14]. Under control conditions, inhibitory synapses from PLTS interneurons onto SPNs are hard to detect [8]. The following changes have been observed to GABAergic microcircuits following pharmacological dopamine depletion in mice: **B.** Sprouting of FSI axons and the formation of new axons specifically onto iSPNs. This causes an inversion of the normal pathway-selectivity of FSIs such that after dopamine depletion, FSIs are more likely to target iSPNs than dSPNs [25]. **C.** Reduction in connectivity and unitary strength of lateral inhibition between SPNs. Connections between dSPNs were sparse under control conditions and were no longer detected in dopamine depleted mice [28]. **D.** An increase in the strength or connectivity of inhibitory inputs from PLTS interneurons onto SPNs may occur. This finding is based on increases in the frequency of large amplitude inhibitory postsynaptic currents (IPSCs) observed in SPNs after dopamine depletion [59], presumably arising from spontaneously active PLTS interneurons in the slice.