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Dopaminergic modulation of striatal function and Parkinson's disease

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Abstract

The striatum is richly innervated by mesencephalic dopaminergic neurons that modulate a diverse array of cellular and synaptic functions that control goal-directed actions and habits. The loss of this innervation has long been thought to be the principal cause of the cardinal motor symptoms of Parkinson's disease (PD). Moreover, chronic, pharmacological overstimulation of striatal dopamine (DA) receptors is generally viewed as the trigger for levodopa-induced dyskinesia (LID) in late-stage PD patients. Here, we discuss recent advances in our understanding of the relationship between the striatum and DA, particularly as it relates to PD and LID. First, it has become clear that chronic perturbations of DA levels in PD and LID bring about cell type-specific, homeostatic changes in spiny projection neurons (SPNs) that tend to normalize striatal activity. Second, perturbations in DA signaling also bring about non-homeostatic aberrations in synaptic plasticity that contribute to disease symptoms. Third, it has become evident that striatal interneurons are major determinants of network activity and behavior in PD and LID. Finally, recent work examining the activity of SPNs in freely moving animals has revealed that the pathophysiology induced by altered DA signaling is not limited to imbalance in the average spiking in direct and indirect pathways, but involves more nuanced disruptions of neuronal ensemble activity.

Keywords

Parkinson's disease; levodopa-induced dyskinesia; striatum; dopamine; synaptic plasticity; interneurons

Introduction

The cardinal motor symptoms of Parkinson's disease (PD) are caused by progressive degeneration of dopaminergic neurons in the substantia nigra (SN) (Surmeier et al. 2014). In the early stages of the disease, these symptoms of PD are effectively alleviated by dopamine

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Conflict of interest

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(DA) replacement therapy. However, as the disease progresses, the administration of levodopa at the high doses required to achieve symptomatic relief brings about maladaptive changes that eventually lead to debilitating hyperkinetic movements, so termed levodopa-induced dyskinesia (LID).

The motor symptoms of PD and LID are commonly attributed to pathophysiology in the dorsal striatum (caudate-putamen) (Zhai et al. 2018) because it is the main recipient of dopaminergic innervation from SN (Albin et al. 1989; Calabresi et al. 2013; Galvan et al. 2015). As the major input nucleus of the basal ganglia, the striatum is thought to play a primary role in selection and chunking of action components (Graybiel 2008; Mink 1996): it evaluates “action plans” generated by the cortex, builds motor patterns based upon sensory and motivational states as well as past experience, and then passes its evaluation on to other basal ganglia nuclei. This ‘recommendation’ is translated into temporally patterned signals in the GABAergic interface nuclei (globus pallidus interna and substantia nigra pars reticulata) that modulate the activity of motor control centers in the thalamus and brainstem. Because it is a major target of dopaminergic modulation and because of its critical role in motor control, the dorsal striatum is the focus of this review. After a brief introduction, we will discuss four areas in which there have been significant recent advances in our understanding of striatal function and its role in parkinsonism.

The principal neurons of the striatum are GABAergic spiny projection neurons (SPNs), which constitute ~90% of total striatal neurons in rodents. In addition to dopaminergic inputs from SN, SPNs in the dorsal striatum also receive glutamatergic inputs from the cortex and thalamus (Bolam et al. 2000), long-range GABAergic input from the cortex (Melzer et al. 2017), GABA co-released with DA from SN (Tritsch et al. 2012), and serotonergic input from raphe nuclei (Mathur and Lovinger 2012). About half of SPNs—the direct pathway SPNs (dSPNs)—project directly to the internal segment of the globus pallidus and substantia nigra pars reticulata (but see (Cazorla et al. 2014)). The other half, the indirect pathway SPNs (iSPNs), project to the external segment of the globus pallidus and thus are indirectly connected to the output nuclei (Graybiel 1990). The dSPNs and iSPNs are modulated by dopamine in opposing ways, due to their differential expression of dopamine receptors. The dSPNs express $G_{s/olf}$-coupled D1 DA receptor (D1R) whose activation of adenylyl cyclase increases the activity of protein kinase A (PKA); generally speaking, PKA phosphorylation of targets increases somatodendritic excitability, enhances glutamatergic transmission, and facilitates long-term synaptic potentiation (LTP). On the contrary, iSPNs express Gi-coupled D2 DA receptor (D2R) whose activation inhibits adenylyl cyclase and activates phospholipase C isoforms; in so doing, it generally decreases intrinsic excitability, attenuates glutamatergic transmission, and promotes long-term synaptic depression (LTD) (Figure 1) (Surmeier et al. 2014). Because there is basal dopaminergic signaling, transient alterations in dopamine release can bi-directionally modulate the activity in dSPNs and iSPNs – leading to a coordinated modulation of circuits controlling both the endorsement of specific actions and the suppression of specific competing or unwanted actions.

In addition to this elegant modulatory mechanism, the striatum also houses diverse array of interneurons that create local circuits that shape SPN activity. These interneurons are

typically subdivided on the basis of their neurotransmitters (e.g., GABA, acetylcholine), but they also differ in their physiological properties and connectomes. Although only comprising 5% of total striatal neurons, striatal interneurons control striatal function and influence behavior (Silberberg and Bolam 2015; Straub et al. 2016). Like SPNs, all striatal interneurons express DA receptors, adding an extra dimension to how striatal network activity is modulated by DA and how it is impaired in PD and LID (Hernandez et al. 2013).

Striatal homeostatic plasticity – keeping striatal pathways in balance?

As mentioned earlier, DA modulates not only the strength of corticostriatal synapses, but also the integration of synaptic currents by SPNs. To recap, DA enhances glutamatergic transmission and increases intrinsic excitability of dSPNs, while it decreases the synaptic strength and intrinsic excitability of iSPNs (Surmeier et al. 2014). In parkinsonian animals, the loss of DA modulatory control triggers cell-specific alterations in intrinsic excitability and synaptic connections: iSPNs, whose activation suppresses movement, become hyperactive, whereas dSPNs, whose activation promotes movement, become hypoactive (Albin et al. 1989; Kravitz et al. 2010; Mallet et al. 2006). This imbalance in the activity of direct and indirect pathways, which is very evident with the rapid and profound destruction of the nigrostriatal DA projection, has long been believed to underlie the hypokinetic symptoms of PD.

However, our models do not accurately recapitulate the slow, progressive nature of PD. What has been unappreciated is the ability of striatal network to adapt to this perturbation. In response to DA depletion, SPNs undergo homeostatic adaptations that tend to restore the balance. In iSPNs, loss of D2R signaling and resultant hyperactivity eventually lead to compensatory reduction in intrinsic excitability. In dSPNs, loss of D1R signaling and resultant hypoactivity bring about elevation in intrinsic excitability over time (Fieblinger et al. 2014). In addition to these homeostatic changes in intrinsic excitability, homeostatic plasticity of synapses is also engaged: iSPNs undergo substantial loss of dendritic spines following DA depletion (Day et al. 2006; Fieblinger et al. 2014; Nishijima et al. 2014; Suarez et al. 2014). Although the pruning is homeostatic, synaptic scaling, like that seen in the hippocampus (where the strengths of synapses are uniformly altered (Turrigiano 2012)), is not seen in iSPNs. Rather, the strength of the remaining synapses is increased (Escande et al. 2016; Fieblinger et al. 2014; Flores-Barrera et al. 2010). This absence of synaptic scaling may be due, at least in part, to the fact that LTP at iSPN glutamatergic synapses is facilitated by loss of D2R signaling (Shen et al. 2008).

In contrast to the robust spine pruning easily observed in iSPNs of parkinsonian animals, there has been a controversy about whether spines are pruned in dSPNs. One possible explanation for the discrepancy in results is that the duration of dopamine depletion matters. Generally, in models in which dopamine has been depleted for 2–3 weeks, no change in dSPN spine density is observed (Day et al. 2006; Fieblinger et al. 2014). In more chronic models with two months or longer dopamine depletion, spine pruning is detected in both dSPNs and iSPNs (Gagnon et al. 2017; Suarez et al. 2018; Villalba et al. 2009). Recent work by our group has shown that indeed if spine density is assessed 3 months after a 6-OHDA lesion, then a significant pruning of dSPN spines can be detected (Graves and Surmeier

2019). The differences in timing of spine loss in dSPNs and iSPNs suggests that these events are mediated by distinct mechanisms. Indeed, spine pruning in dopamine-depleted, hypoactive dSPNs is not homeostatic. A more plausible hypothesis is that the sustained loss of D1R and elevated M4R signaling in the parkinsonian state induces a progressive depression of axospinous synapses that ultimately results in their elimination (Ding et al. 2006; Shen et al. 2008; Shen et al. 2016). Thus, spine loss in iSPNs is adaptive, whereas that in dSPNs is maladaptive.

Repeated administration of levodopa reverse some of the dopamine depletion-induced adaptations but introduces new ones (Fieblinger et al. 2014; Fieblinger et al. 2018; Suarez et al. 2018; Suarez et al. 2014). The most intriguing change induced by dyskinesiogenic doses of levodopa is the restoration of axospinous synapses on iSPNs (Fieblinger et al. 2014; Nishijima et al. 2014; Suarez et al. 2014). Although LID was traditionally attributed largely to abnormal signaling within dSPNs (Cenci and Konradi 2010; Feyder et al. 2011), this alteration in iSPN connectivity suggests that they may also be part of the pathophysiology underlying LID. This conclusion is consistent with an elegant study in which chemogenetics was used to manipulate the excitability of iSPNs and dSPNs in dyskinetic mice (Alcacer et al. 2017); the study demonstrated that both pathways participate in the control of LID. One unanswered question is the extent to which the alterations in synaptic connectivity and somatodendritic excitability are state-dependent. Thus far, the assessment of corticostriatal connectivity and intrinsic excitability in LID mice has been performed in the “off-state” — hours after the last injection of L-DOPA (i.e. “off-state”). By that time, the striatal level of dopamine is very low and mice have long ceased dyskinetic behaviors. It is unclear how intrinsic excitability and synaptic connection would change in the “on-state”—within hours of L-DOPA injection when the behavioral manifestation of LID is the strongest. It also remains to be determined whether the levodopa-induced spine restoration in iSPNs re-establishes prior connectivity or whether the re-wiring is aberrant and contributes to the emergence or expression of dyskinesia.

Aberrant synaptic plasticity — a continuing theme in PD and LID pathophysiology

Bidirectional synaptic plasticity at corticostriatal glutamatergic synapses is widely hypothesized to be a key cellular substrate of goal-directed and habitual learning (Yin and Knowlton 2006). But this is unproven. As a consequence, there has been a great deal of effort made to bridge the gap between striatal synaptic plasticity and striatum-dependent learning (recently reviewed by (Perrin and Venance 2018)). Among the various forms of striatal synaptic plasticity reported, the canonical, endocannabinoid (eCB)-dependent LTD is best understood: it is induced by activation of postsynaptic Cav1 (L-type) calcium channels and metabotropic glutamate receptor 5 (mGluR5), which promote the generation of eCBs that act on presynaptic CB1 receptors (CB1Rs), leading to long-lasting reduction in glutamate release (Gerdeman et al. 2002; Kreitzer and Malenka 2005) (Figure 2). In iSPNs, D2R activation, through $G_{i/o}$ signaling, inhibits RGS4 signaling and disinhibits mGluR5-mediated eCB production (Lerner and Kreitzer 2012). In dSPNs, the muscarinic M4 receptor (M4R)-$G_{i/o}$ signaling pathway, which is highly expressed in dSPNs (Yan et al. 2001), appear

to play a similar role. Using novel pharmacological and chemogenetic tools, Shen et al. demonstrated that activation of M4R facilitates LTD induction in dSPNs through suppression of RGS4 (Shen et al. 2016). Just like D2Rs (Higley and Sabatini 2010), M4R attenuates NMDA receptor (NMDAR)-mediated Ca^{2+} influx and thereby suppresses LTP induction (Shen et al. 2016). Also well understood is corticostriatal LTP which requires co-activation of NMDAR, TrkB receptor and cAMP signaling (Plotkin et al. 2014). In dSPNs, D1R activation, through G_{olf} signaling and adenylyl cyclase 5 (AC5) activation, elevates cAMP level, activates PKA and extracellular signal-regulated kinase (ERK). D1R signaling also enhances NMDAR currents (Murphy et al. 2014) while inhibiting LTD through RGS4 (Shen et al. 2016). In iSPNs, the G_{olf}-coupled adenosine A2a receptor (A2aR) plays the equivalent role of D1R, synergistically enhancing NMDAR current while suppressing LTD induction (Higley and Sabatini 2010; Lerner and Kreitzer 2012). Therefore, parallel mechanisms regulate synaptic plasticity in iSPNs and dSPNs: D2R and M4R promote LTD and suppress LTP induction, whereas D1R and A2aR facilitate LTP and inhibit LTD induction (Figure 2).

Does eCB-LTD occur equivalently at both corticostriatal and thalamostriatal synapses? This question was recently addressed using optogenetic tools (Wu et al. 2015). By crossing region-specific Cre recombinase mouse lines with Cre-dependent channelrhodopsin line, Wu et al. were able to isolate corticostriatal and thalamostriatal synapses. In response to an LTD protocol that activates mGluR5 and Cav1 L-type calcium channels (Kreitzer and Malenka 2005), a robust eCB-dependent LTD was induced at corticostriatal synapses, resembling the LTD recorded traditionally with electrical stimulation. In contrast, only a small depression was observed at thalamostriatal synapses and the depression was not blocked by CB1R antagonist. These data suggest that eCB-LTD is specifically induced at corticostriatal glutamatergic synapses. Corroborating this data, immunostaining has showed that CB1R is abundant in cortical neurons but barely detectable in the thalamus. However, the specificity of synaptic plasticity may not stop at this level. One extra layer of specificity comes from the heterogeneity of corticostriatal projections (e.g. intratelencephalic vs. pyramidal tract) which convey different types of information (Shepherd 2013). It is unlikely that all corticostriatal synapses undergo plasticity in a uniform manner. Furthermore, the striatum is divided to matrix and striosome compartments which differ not only in the molecules they express but also, more importantly, in their functional input and output connections (Crittenden and Graybiel 2011). So far, little is known about the plasticity mechanisms in striosomal SPNs which constitute only about 10% of the striatal volume but exert crucial and distinct functions.

More than one form of long-term depression in the striatum?

Although the existence of postsynaptic LTP and presynaptically expressed, eCB-dependent LTD are prominent in SPNs, it has been unclear whether there are postsynaptically expressed forms of LTD. Recent work has described a novel form of postsynaptic LTD in SPNs that is mediated by nitric oxide (NO). The NO- and cGMP-related signaling proteins are abundantly expressed in the striatum (Ariano 1983; Ding et al. 2004). The role of NO and cGMP in synaptic plasticity was first probed by Calabresi and colleagues, who found that inhibition of NO and cGMP synthesis prevented LTD induction by tetanic stimulation of

corticostriatal afferents (Calabresi et al. 1999). This led to the idea that NO played a permissive role in the canonical eCB-LTD (Centonze et al. 1999). However, using two-photon glutamate uncaging (which bypasses any potential presynaptic effect), Rafalovich et al. showed that a non-hydrolyzable cGMP analog persistently decreased uncaging-evoked glutamatergic responses, suggesting that cGMP-dependent LTD is a novel, postsynaptically expressed form of LTD (Rafalovich et al. 2015). This form of LTD can be induced physiologically by optogenetic activation of striatal interneurons that release NO. Moreover, NO-LTD can be induced at both corticostriatal and thalamostriatal synapses, contrasting it with eCB-LTD (Wu et al. 2015). Still, very little is known about how this new form of LTD is regulated in SPNs. For example, which cGMP-degrading phosphodiesterase expressed by SPNs negatively modulates NO-LTD? Furthermore, the functional significance of NO-LTD is unclear. A recent study shows that the NO-synthesizing plateau and low threshold spike interneurons (PLTSIs) are recruited (in addition to iSPNs and dSPNs) in learning of new sequential stepping patterns (Nakamura et al. 2017), suggesting that NO-LTD may be essential for certain types of striatum-dependent learning.

What happens to plasticity when striatal DA is lost?

How DA depletion affects bidirectional synaptic plasticity? There seems to be two phases in animal models of PD. In the acute phase (<1 week of DA depletion), loss of D2R signaling impairs LTD induction in iSPNs whereas absence of D1R signaling impairs LTP in dSPNs (Kreitzer and Malenka 2007; Shen et al. 2008). However, in the chronic phase (>3–4 weeks), all forms of synaptic plasticity in SPNs appear to be lost (Calabresi et al. 1992; Picconi et al. 2003; Shen et al. 2016). One possible explanation is that LTP in iSPNs and LTD in dSPNs, rather than being impaired, may have actually been saturated during chronic dopamine depletion. This hypothesis is supported by the observation that unitary synaptic response is enhanced in iSPNs and reduced in dSPNs at about three weeks after DA depletion (Fieblinger et al. 2014). Another piece of evidence in support of this conclusion is that levodopa treatment restores LTP in dSPNs and LTD in iSPNs in parkinsonian mice (Shen et al. 2016), suggesting that the cellular machinery for induction and expression of synaptic plasticity is intact after dopamine depletion. Levodopa treatment, however, lacks the spatiotemporal specificity of DA receptor stimulation by nigrostriatal DA input (Bastide et al. 2015). Abnormally sustained stimulation of D1R is likely to underlie the synaptic and biochemical signatures of LID in dSPNs, including the apparent loss of depotentiation (Picconi et al. 2003; Shen et al. 2016). The sustained stimulation of D2R also prevents iSPNs from responding to patterned activity appropriately: spike-timing-dependent plasticity (STDP) protocols that normally induce Hebbian LTP induce LTD in iSPNs (Shen et al. 2016). Because upon levodopa treatment, DA signaling and the bidirectional synaptic plasticity it gates are dissociated from the outcome of behavior, synaptic strengths may become randomized. It is easy to imagine that this randomization could result in the purposeless, ‘random’ movements characteristic of dyskinesia (Picconi et al. 2003; Shen et al. 2016). Activation of M4R and $G_{i/o}$ signaling in dSPNs suppresses aberrant LTP and alleviates dyskinetic movements (Shen et al. 2016). On the contrary, activation of G_s signaling in dSPNs, which promotes LTP (Shen et al. 2008), aggravates dyskinesia (Alcacer et al. 2017). Several other strategies of normalizing aberrant plasticity have ameliorated

behavioral abnormalities (Ghiglieri et al. 2016; Trusel et al. 2015), further implicating striatal synaptic plasticity as a promising target for treatment of LID.

Why does NO-LTD seem to be lost in PD models? Although there is some controversy about how dopamine depletion affects the generation of NO (Chalimoniuk and Langfort 2007; Giorgi et al. 2008; Sagi et al. 2014; Sancesario et al. 2004), two additional lines of evidence suggest that NO signaling is disrupted by dopamine depletion. First, D1/D5 receptor activation, which must be lost in the DA-depleted striatum, appears to be important to NO production (Sammut et al. 2006). Second, the number of NOS-expressing PLTSIs falls in the striatum of PD patients (Bockelmann et al. 1994) (although this has not been reported in mouse PD models). These two factors may be responsible for the apparent loss of cGMP-dependent LTD in PD models (Picconi et al. 2011), but clearly more work is needed. The role of NO signaling in LID is more confusing. Striatal level of cGMP seems to be dramatically lower in LID model (Giorgi et al. 2008), but cGMP-dependent LTD still can be induced (Picconi et al. 2011). To make the situation even more confusing, pharmacological approaches that reduce or elevate cGMP levels have both been reported to ameliorate abnormal movements of LID (Padovan-Neto et al. 2011; Picconi et al. 2011; Solis et al. 2015). Given the potential importance of this pathway in PD and LID, better tools need to be brought to bear on the question.

An increasing role for GABAergic interneurons

Although comprising only ~5% of all striatal neurons, GABAergic interneurons play important roles in gating signal flow and sculpting network dynamics (Tepper et al. 2018; Wickens et al. 2007). This is a diverse group of neurons, which differ in their morphology, expression of marker molecules, input and output connectivity, biophysical properties, and response to modulators (Gittis and Kreitzer 2012; Wilson 2007). Briefly, striatal GABAergic interneurons can be categorized into four types: fast-spiking interneurons (FSIs), PLTSIs, neurogliaform interneurons (NGFs) and tyrosine hydroxylase (TH)-expressing interneurons. Because modern genetic methods have allowed these different types of interneuron to be identified and manipulated (Lerner et al. 2016), our knowledge on striatal interneurons' intrinsic properties, connectivity, and role in striatal function and behavior has exponentially expanded in recent years. These studies have begun to reveal the roles of each interneuron class. As revealed by early anatomical studies and corroborated later by two-photon optogenetics, striatal GABAergic neurons synapse on SPNs at different locations. For example, FSIs synapse at perisomatic region of SPN while PLTSIs form GABAergic synapses at distal dendrites of SPNs (Kita et al. 1990; Kubota and Kawaguchi 2000; Straub et al. 2016). The proximal and distal dendrites of SPNs differ in their regenerative capacity: brief glutamate uncaging at distal dendrites, but not proximal dendrites, evokes dendritic regenerative events that depolarize somatic potential for hundreds of milliseconds—so termed dendritic plateau potential (Plotkin et al. 2011). Modeling predicts that spine calcium transients and dendritic plateau potentials are most effectively attenuated by distal GABAergic inputs at the site of excitatory inputs, whose primary function is to enhance input-specificity of local calcium elevation (Dorman et al. 2018; Du et al. 2017). Supporting this theoretical model, Du et al. showed that dendritic plateau potentials are effectively attenuated by optogenetic activation of GABAergic synapses or GABA uncaging at "on-

branch" dendritic site within a defined temporal window, but not by perisomatic GABAergic inhibition (Du et al. 2017).

Another difference between interneurons is their afferent and efferent connectivity. FSIs receive excitatory input from not just cortex but also most areas of the thalamus and densely innervate nearby SPNs with large-amplitude, fast-kinetic responses (Gittis et al. 2010; Straub et al. 2016). In contrast, PLTSIs are only indirectly connected to the thalamus and make few synaptic contacts with local SPNs (Assous et al. 2017; Gittis et al. 2010; Straub et al. 2016), implying that they must play distinct roles in striatum-dependent learning (e.g, through NO production). Finally, the complex connectivity of striatal GABAergic interneurons revealed by recent optogenetic studies constitutes several circuit motifs, including feedforward inhibition and disinhibition (Assous and Tepper 2018). It has also become clear that a specific type of interneuron can be involved in more than one circuit motifs (see below).

All these layers of interneuron properties contribute to the computational power of the striatal network. A good example is the FSI. Although FSIs has been extensively studied in ex vivo and in vivo studies (reviewed by (Berke 2011; Tepper et al. 2018; Tepper et al. 2010)), their role in regulating striatal dynamics, plasticity and learning has been difficult to assess until recently. Being recipient of substantial cortical input and in turn forming strong GABAergic synapses on SPNs (with a slight preference for dSPNs) (Gittis et al. 2010; Straub et al. 2016), FSIs have been proposed to contribute to striatal function through feedforward inhibition of SPN activity. This model has been supported by several lines of evidence. First, in vivo recordings show that increases in FSI discharge rate are often associated with decreases in SPN firing rate (Gage et al. 2010; Mallet et al. 2005). More importantly, optogenetic activation of FSIs leads to significant inhibition of SPN firing rate (Lee et al. 2017; Owen et al. 2018). On the other hand, optogenetic silencing of FSIs was recently shown to increase bursting and uncontrolled calcium elevations in SPNs in vivo (Owen et al. 2018). Consistent with the prevailing view that calcium transients drive long-term synaptic plasticity (Jedrzejewska-Szmek et al. 2017), ablation of FSIs causes aberrant LTP at corticostriatal synapses in SPNs (evidenced by increased AMPAR/NMDAR ratio) (Owen et al. 2018). However, some other reports point to a more complex model. Pharmacological blockade of FSIs (using an inhibitor of GluA2-lacking AMPARs, IEM-1460, which has been shown to suppress the activity of FSIs but not SPNs) increases firing rate in some SPNs while decreasing it in others (Gittis et al. 2011). Chemogenetic inhibition of FSI activity with inhibitory DREADD hM4D causes an overall increase in SPN firing rate but reduces firing in a subset of SPNs that are firing at higher frequency (O'Hare et al. 2017). More intriguingly, optogenetic suppression of FSIs in a low-penetrance parvalbumin (PV)-Cre mouse line leads to decreases in SPN firing rate (Lee et al. 2017), suggesting disinhibition, not just feedforward inhibition, is a circuit function of FSI. This disinhibition is at least in part caused by the existence of di-synaptic inhibitory circuit mediated by NPY+ interneurons which receive inhibitory input from FSI and in turn inhibit SPNs (Lee et al. 2017). Thus, the circuit function of FSIs may be more complicated than originally thought. FSIs may monosynaptically inhibit the somatic region of SPN while disynaptically disinhibiting distal dendrites. Moreover, as the reversal potential of $GABA_A$ receptors in SPNs is ~−60 mV (Dehorter et al. 2009), GABAergic inputs can therefore be

hyperpolarizing or depolarizing, depending on the state of SPNs (up-state vs. down-state) (Fino et al. 2018). Finally, FSIs, far from being a static, homogeneous population, can undergo activity-dependent plasticity (Fino et al. 2008) and have distinct properties and connectivity depending on their striatal location (dorsolateral vs. dorsomedial) (Monteiro et al. 2018).

FSIs are key determinants of pathophysiology in movement disorders

The first hints of the FSI role came from studies of movement disorders (Burguiere et al. 2013; Gernert et al. 2000; Kalanithi et al. 2005; Kataoka et al. 2010). For example, in postmortem tissue of patients with Tourette syndrome (tics), the numbers of FSIs and cholinergic interneurons are reduced (Kalanithi et al. 2005; Kataoka et al. 2010), consistent with the simplistic model that FSIs (and cholinergic interneurons), probably through feedforward inhibition of SPNs, exert a brake on unwanted, competitive movements. Later, in vivo recording in behaving animals established a correlation between FSI spiking and behavior (Berke 2011; Gage et al. 2010). While FSI activation is generally correlated with behavioral tasks, its firing rate is commonly temporally aligned with a specific task event (i.e. choice execution) but not others (cue or reward). The causal role of FSI was first probed by pharmacological blockade: striatal local infusion of IEM-1460, which silences the FSI population, causes dyskinesia and tremor in mice (Gittis et al. 2011; Oran and Bar-Gad 2018), consistent with the role of FSI in tuning SPN activity and suppressing undesired movements. In more recent years, use of genetic tools has allowed selective, bidirectional manipulation of FSI activity to see the consequence on behavioral tasks. In contrast with the earlier view that FSI acutely gates sensorimotor output, selective silencing of FSI with either genetic ablation or optogenetic inactivation did not cause overt motor abnormalities or impaired motor performance (Owen et al. 2018; Xu et al. 2016). Instead, FSI silencing impeded striatum-dependent associative learning and egocentric learning (Lee et al. 2017; Owen et al. 2018). This is consistent with a refined model in which FSI-mediated inhibition confines calcium elevation and synaptic plasticity to the SPN ensemble involved in the specific task (Owen et al. 2018). Interestingly, with chemogenetic silencing of FSIs, O'Hare et al. showed that FSIs are not required for habitual learning but required for expressing the learned habit (O'Hare et al. 2017). FSI silencing also causes stress-triggered grooming and anxiety, characteristics of obsessive-compulsive disorder (Xu et al. 2016). Indeed, in a mouse model of obsessive-compulsive disorder, FSI number is reduced and restoring FSI activity by optogenetic stimulation of orbitofrontal cortex abolishes excessive grooming behavior (Burguiere et al. 2013). Taken together, as a result of multifaceted function of FSI in striatal microcircuit, its role in controlling behavior can vary greatly depending on the context. Future research is needed to understand how FSI is differentially recruited in various learning modalities. Also, it is unknown if striatal FSIs themselves would undergo experience-dependent plasticity like their counterparts in the cortex and hippocampus (Dehorter et al. 2015; Donato et al. 2013; Lagler et al. 2016).

Do striatal FSIs contribute to the pathophysiology of PD? Very likely, but these studies are just beginning. FSIs express D1/D5 type DA receptors and their excitability is increased by dopamine ex vivo (Bracci et al. 2002; Centonze et al. 2003). However, dopamine depletion does not affect either the number of striatal FSIs or their responsiveness to cortical

stimulation (Mallet et al. 2006; Trevitt et al. 2005). As shown by in vivo recording in awake mice, the FSI firing rate is lower in parkinsonian mice during epochs of movement (Chen et al. 2018), which was not found in recordings from anesthetized animals that lack burst activity of dopaminergic neurons (Mallet et al. 2006). How FSI control of SPNs changes in PD is controversial. Mallet et al. (2006) reported that feedforward inhibition of iSPNs by FSIs was reduced in PD models while that of dSPNs was not, adding to the activity imbalance between direct and indirect pathways. In contrast, Gittis et al. (2011) reported that in paired recordings from ex vivo slices dopamine depletion strengthened the probability of FSI-iSPN connections without changing unitary synaptic response. The discrepancy is yet to be resolved. Our understanding of the role of FSI in LID is even more primitive, but some initial clues include an elevation in firing rate around the time of a dyskinetic movement and activation of immediate early gene c-fos in FSI during a levodopa-session (Alberico et al. 2017; Girasole et al. 2018).

Is imbalanced direct and indirect pathway activity responsible for PD symptoms?

It was believed for decades that the direct and indirect pathways exert opposing influences on behavioral output: the direct pathway facilitates movement whereas the indirect pathway impedes movement. This so-called “Rate Model” easily explains the motor symptoms of PD and LID (Albin et al. 1989; Nelson and Kreitzer 2014). As outlined above, the imbalance created by the loss of dopaminergic modulation of iSPNs and dSPNs was thought to be responsible for the hypokinetic features of the disease. In vivo recording in anesthetized rats supported this classical model (Mallet et al. 2006) (but see (Ketzef et al. 2017)). Further support for the classical model has come from studies using optogenetic (Kravitz et al. 2010) and chemogenetic (Alcacer et al. 2017; Armbruster et al. 2007) approaches. More recently, two independent studies monitoring the activity of dSPNs and iSPNs in freely moving parkinsonian animals (one using in vivo Ca^{2+} imaging while the other using a combination of single-unit recording and optogenetics) have come to a similar, but more nuanced conclusion (Parker et al. 2018; Ryan et al. 2018). Both studies found that the parkinsonian state is accompanied by a persistent decrease in dSPN firing. In contrast, iSPN activity in the non-moving, resting state was increased following dopamine depletion. However, when mice were moving, the firing rate of iSPNs was not elevated in parkinsonian mice. This is most likely due to the homeostatic adaptations in iSPNs following dopamine depletion described above (Fieblinger et al. 2014). The slow maladaptive changes in dSPNs described above in PD models also may help to account for the failure of optogenetic activation of dSPNs to rescue the reduction in contralateral limb use in chronic PD models (Perez et al. 2017).

Support for the classical rate model also has come from some recent studies of striatal mechanisms involved in LID. First, single-unit recording and in vivo Ca^{2+} imaging both have confirmed that levodopa increased the firing of dSPNs while decreased firing of iSPNs (Parker et al. 2018; Ryan et al. 2018). Furthermore, optogenetic or chemogenetic stimulation of dSPNs produces dyskinesia in parkinsonian animals in the absence of levodopa (Alcacer et al. 2017; Girasole et al. 2018; Perez et al. 2017). On the other hand, chemogenetic stimulation of iSPNs ameliorates dyskinetic movements triggered by levodopa (Alcacer et

al. 2017). These studies support the proposition that an imbalance between direct and indirect pathways causes LID. However, there are conflicting results. For example, simultaneous activation of dSPNs and iSPNs produces dyskinesia in a rat model of PD (Hernandez et al. 2017). Moreover, when analyzing the striatal neurons activated during dyskinesia episodes, Girasole et al. found that although the majority of activated neurons were dSPNs, a small portion (~10%) were iSPNs, suggesting that the actions of iSPNs and dSPNs may be more than merely opposing each other in parkinsonian animals.

The limitations of these studies also must be acknowledged. Both optogenetic and chemogenetic approaches produce gross perturbations in the striatal circuitry and do not allow the kind of spatial and temporal control of neuronal ensembles that is thought to underlie normal movement control. Studies that have been able to carefully monitor the activity of iSPNs and dSPNs suggest that the classical notion that iSPNs and dSPNs simply oppose one another is wrong (Barbera et al. 2016; Klaus et al. 2017; O'Hare et al. 2016; Sippy et al. 2015; Tecuapetla et al. 2016). This is beautifully illustrated in a recent paper by Parker et al. (Parker et al. 2018). Using in vivo imaging of calcium indicator genetically targeted to dSPNs or iSPNs, they confirmed that SPNs encode movement via spatially clustered bursts of activity and that both types of SPN were engaged in this process. Interestingly, in parkinsonian mice, iSPN activity lost spatial coordination and movement encoding; this deficit was reversed by therapeutic dose of levodopa. On the contrary, dSPN activity in parkinsonian mice, although persistently reduced, still encoded movement onset and retained spatial coordination. In the case of LID, however, dSPNs lost spatial coordination and failed to encode locomotion. These findings suggest that impairments in coordinated activity and spatiotemporal organization of neuronal ensembles are critical to the motor phenotypes in PD and LID. That said, there are still open questions about how this happens. Using in vivo recording of neuronal populations (<100) smaller than those monitored in the Parker et al. study, Ryan et al. showed that the coupling of dSPN and iSPN activity to locomotion was impaired by dopamine depletion and not restored by levodopa (Ryan et al. 2018).

Lastly, the limitations of the models used to study PD and LID mechanisms need to be acknowledged. A potentially very important limitation is that with toxins used to create these models, there is a rapid and massive loss of dopaminergic axons and cell bodies. This does not mimic the 'axon-first' pattern of pathology thought to occur in human PD (Tagliaferro and Burke 2016). This could alter the network pathophysiology in many ways that might be misleading. For example, in contrast to the implicit assertion of the classical model SN dopaminergic neurons release dopamine in all the basal ganglia nuclei, not just the striatum. While the significance of this extrastriatal dopamine release has yet to be fully explored in PD and LID models, there is compelling evidence that dendritic release of dopamine is an important modulator of activity in the interface nuclei of the basal ganglia, particularly the substantia nigra pars reticulata (SNr) (e.g. (Ruffieux and Schultz 1980; Waszcak and Walters 1983)). In fact, recent work by Borgkvist et al. suggests that this local dopaminergic regulation is very important to levodopa-induced dyskinesia (Borgkvist et al. 2015; Tagliaferro and Burke 2016).

Concluding remarks

Acting through specific types of DA receptors, DA modulates not only “moment-to-moment” intrinsic excitability and synaptic connection, but also bidirectional synaptic plasticity of SPNs. In PD models, the loss of dopamine triggers a range of homeostatic adaptations that serve to reduce the imbalance between direct and indirect pathways and minimize network pathophysiology thought to underlie hypokinetic symptoms. However, the disruption in DA signaling also produces maladaptive changes, the best described of which are in dSPNs. Using new genetic tools, some recent studies targeted scarcely populated striatal interneurons and revealed their important functions in controlling network activity and behavior. Loss of the DA modulation of these interneurons also appears to contribute to the network pathophysiology driving symptoms. Finally, monitoring and manipulating SPN activity in freely moving animals, enabled by recent technical advances promises to fundamentally change our understanding of how DA modulates the striatal circuitry but also to provide new insight into the mechanisms responsible for the motor symptoms of PD and LID.

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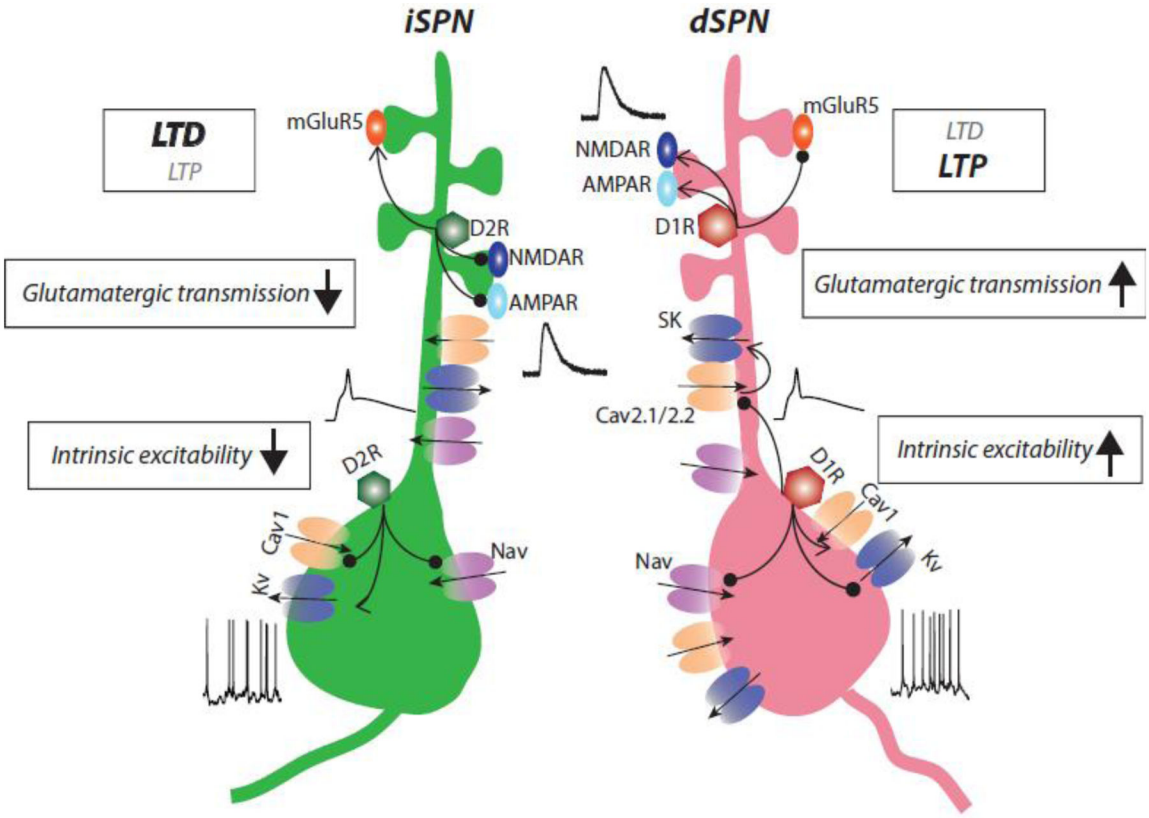

Figure 1.

Postsynaptic functions of DA signaling in SPNs. Arrowheads indicate positive regulation and black circles indicate negative regulation. In iSPNs, D2R activation suppresses intrinsic excitability by modulating ion channels, reduces moment-to-moment glutamate transmission, and promotes LTD induction; in dSPNs, D1R activation increases intrinsic excitability (partly through inhibiting N- and P- type calcium channels and suppressing small-conductance calcium-activated potassium channels (SK channels)(Surmeier et al. 1995; Vilchis et al. 2000)) , enhances glutamate transmission, and promotes LTP. Presynaptic or indirect, interneuron-mediated functions of DA are not illustrated here.

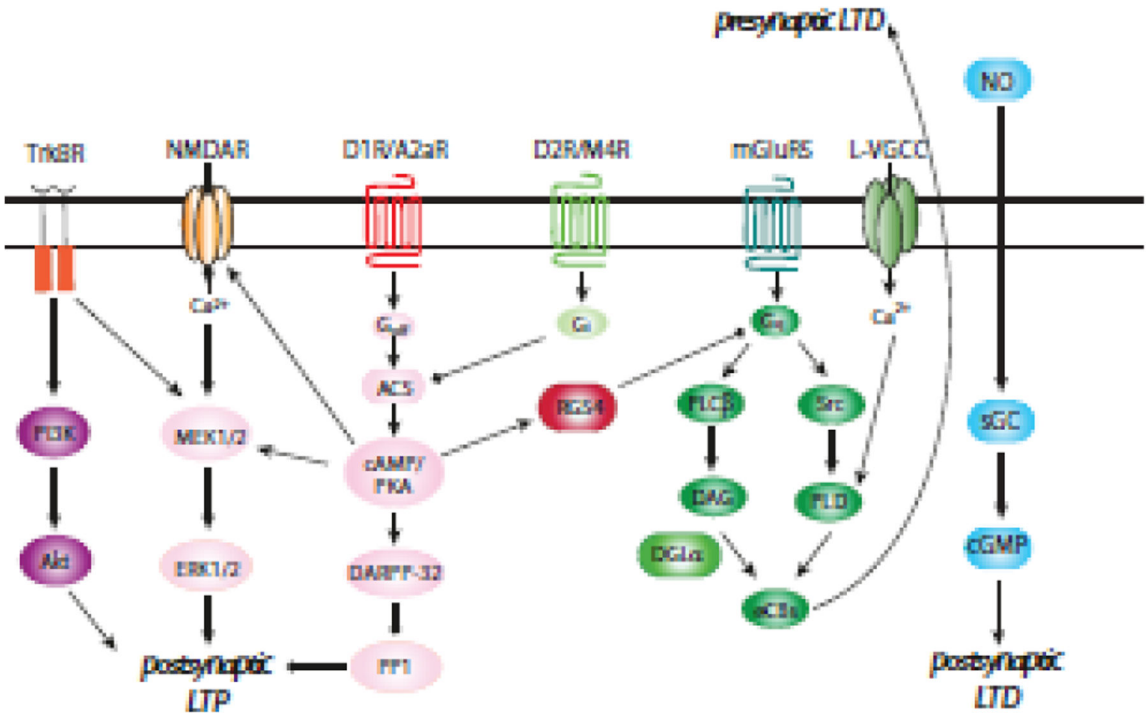

Figure 2.

Schematic depicting signaling pathways mediating long-term synaptic plasticity in striatal SPNs. Black arrowheads indicate positive regulation and black circles indicate negative regulation. G_i-coupled D2R and M4R promote eCB-mediated presynaptic LTD and suppress postsynaptic LTP in iSPNs and dSPNs, respectively. On the other hand, D1R and A2aR promote LTP and inhibit presynaptic LTD in dSPNs and iSPNs, respectively. NO released by PLTS interneurons induces a cGMP-dependent, postsynaptic form of LTD. Abbreviations: 2-AG, 2-arachidonoylglycerol; A2aR, adenosine receptor 2a; AC5, adenylyl cyclase 5; Akt, Protein Kinase B; CaMKII, Ca^{2+}/calmodulin-dependent protein kinase II; cAMP, 3′−5′-cyclic adenosine monophosphate; cGMP, 3′−5′-cyclic guanosine monophosphate; D1R, dopamine D1 receptor; D2R, dopamine D2 receptor; DAG, 1,2-diacylglycerol; DARPP-32, dopamine- and cAMP-regulated phosphoprotein of 32 kDa; DGLα, diacylglycerol lipase α; eCBs, endocannabinoids; ERK, extracellular signal-regulated kinase; M4R, muscarinic receptor 4; MEK, mitogen-activated protein kinase kinase; mGluR5, metabotropic glutamate receptor 5; NMDAR, N-methyl-D-aspartate receptor; NO, nitric oxide; PI3K, phosphatidylinositide 3-kinase; PKA, protein kinase A; PLCβ, phospholipase Cβ; PLD, phospholipase D; PP1, protein phosphatase 1; RGS4, regulator of G-protein signaling 4; Src, Src-family kinases; TrkBR, tropomyosin related kinase B receptor.