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Striatal synaptic adaptations in Parkinson's disease

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Abstract

The striatum is densely innervated by mesencephalic dopaminergic neurons that modulate acquisition and vigor of goal-directed actions and habits. This innervation is progressively lost in Parkinson's disease (PD), contributing to the defining movement deficits of the disease. Although boosting dopaminergic signaling with levodopa early in the course of the disease alleviates these deficits, later this strategy leads to the emergence of debilitating dyskinesia. Here, recent advances in our understanding of how striatal cells and circuits adapt to this progressive de-innervation and to levodopa therapy are discussed. First, we discuss how dopamine (DA) depletion triggers cell type-specific, homeostatic changes in spiny projection neurons (SPNs) that tend to normalize striatal activity but also lead to disruption of the synaptic architecture sculpted by experience. Second, we discuss the roles played by cholinergic and nitric oxide-releasing interneurons in these adaptations. Third, we examine recent work in freely moving mice suggesting that alterations in the spatiotemporal dynamics of striatal ensembles contributes to PD movement deficits. Lastly, we discuss recently published evidence from a progressive model of PD suggesting that contrary to the classical model, striatal pathway imbalance is necessary but not sufficient to produce frank parkinsonism.

Keywords

Homeostasis; Synaptic plasticity; Levodopa-induced dyskinesia; Cholinergic interneuron; Spiny projection neuron; Low threshold spike interneuron; Thalamic input

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder in the world and is clinically defined by rigidity and slowness of movement (bradykinesia) (Hornykiewicz, 1966; Kish et al., 1988). These symptoms are caused by progressive degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNc) (Surmeier et al., 2014). The prevailing hypothesis about the network origins of motor

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disability in PD is that it arises from an imbalance in the excitability of striatal efferent projection systems, leading to disinhibition of the GABAergic projection neurons in the substantia nigra pars reticulata (SNr) and internal segment of the globus pallidus (GPi); this increased GABAergic activity is thought to inhibit forebrain and medullary motor control circuits, resulting in hypokinetic symptoms (Albin et al., 1989).

The trigger for this network pathophysiology is thought to be the loss of striatal dopamine (DA) release by SNc dopaminergic neurons (Albin et al., 1989). DA differentially modulates two principal populations of striatal GABAergic spiny projection neurons (SPNs), which constitute ~90% of all striatal neurons in rodents. These two roughly equally-sized types of SPN are defined by their size, axonal projection, expression of DA receptors and neuromodulator expression. Direct pathway SPNs (dSPNs) express D1 DA receptors (D1Rs) and primarily project to basal ganglia output nuclei (GPi and SNr), whereas indirect pathway SPNs (iSPNs) express D2 DA receptors (D2Rs) and project to the external segment of the globus pallidus (GPe) and thus are indirectly connected to the output nuclei (Galvan et al., 2015; Gerfen et al., 1990; Surmeier et al., 1996; Zhai et al., 2019; Zhai et al., 2018). Activation of dSPN D1Rs stimulates adenylyl cyclase (AC) and protein kinase A (PKA); generally speaking, PKA phosphorylation of targets increases somatodendritic excitability, enhances glutamatergic transmission, and facilitates long- term synaptic potentiation (LTP). In contrast, activation of iSPN D2Rs inhibits AC and PKA, and also activates phospholipase C (PLC) isoforms; in so doing, D2Rs decrease somatodendritic excitability, attenuate glutamatergic transmission, and promote long-term synaptic depression (LTD) (Surmeier et al., 2014). Because there is basal dopaminergic signaling, transient alterations in DA release can bidirectionally 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 competing or unwanted actions.

The phenotype of SPNs is well-suited to fulfill a role as a convergence detector. In the absence of synaptic input, SPNs rest near the K^+ equilibrium potential, far (~35 mV) from spike threshold (down-state) because of their robust expression of Kir2 K^+ channels (Kasanetz et al., 2002; Mahon et al., 2001; Nisenbaum and Wilson, 1995; Plenz and Kitai, 1998; Shen et al., 2007; Wilson and Groves, 1981; Wilson and Kawaguchi, 1996). In anesthetized animals, SPNs transition from the down-state to a depolarized up-state (~ − 60 mV) in phase with synchronized cortical activity (Kasanetz et al., 2002; Mahon et al., 2001; Plenz and Kitai, 1998; Tseng et al., 2001; Wilson and Groves, 1981). Once in the up-state, spike threshold (~ − 45 mV) can more readily be reached by asynchronous excitatory input (Stern et al., 1998). At the time these studies were conducted, SPN dendrites were thought to be passive and that up-state transitions required thousands of synchronized, but spatially dispersed glutamatergic inputs (to avoid destructive interference) (Stern et al., 1998; Wilson and Groves, 1981; Wilson and Kawaguchi, 1996). Subsequently, it became apparent that neuronal dendrites were not typically passive, but were invested with a variety of voltage-dependent ion channels that enabled regenerative events that could amplify excitatory synaptic activity, particularly in distal dendrites (Hausser et al., 1995; Major et al., 2013; Major et al., 2008; Schiller et al., 2000; Spruston et al., 1995). A similar phenomenon was found in SPNs, where 10–15 synchronized, glutamatergic synaptic inputs to a short stretch (~20 μm) of distal dendrite were capable of triggering *N*-methyl-D-aspartate receptor

(NMDAR)-dependent plateau potentials in SPNs that brought the somatic membrane to the typical up-state potential for several hundred milliseconds (Du et al., 2017; Oikonomou et al., 2014; Plotkin et al., 2011; Prager et al., 2020). This dendritic mechanism allows state transitions in SPNs to be driven by synchronous input from relatively small circuits processing particular types of information, like that associated with whisker movement or visual cues (Ketzef et al., 2017; Reig and Silberberg, 2014). Because the duration and amplitude of dendritic plateau potentials can be titrated by patterned synaptic input streams, they provide a ready explanation for the diversity of up-states, as well as complex spiking patterns seen in SPNs of unanesthetized animals (Cui et al., 2013; Parker et al., 2018; Reig and Silberberg, 2014; Sippy et al., 2015). Because this regenerative process transforms the location and synchrony of synaptic activity – long thought to be information-bearing in cortical circuits (Archie and Mel, 2000; Engel and Singer, 2001; Hausser and Mel, 2003; Losonczy et al., 2008; Salinas and Sejnowski, 2001) – into a differentiated postsynaptic signal, it adds to both the computational power of SPNs as well as their information storage capacity. At the simplest level, this property could allow SPN dendrites to act as tunable 'AND' gates capable of discerning associations, like those between action and reward.

This cellular insight helps to lay a mechanistic foundation for how iSPN and dSPN ensembles work together to help select contextually and motivationally appropriate actions and veto inappropriate ones (Cui et al., 2013; Graybiel, 2008; Mink, 1996). Generally, dSPN ensembles are thought to encode previously rewarded actions, whereas iSPN ensembles are thought to code competing actions that are unlikely to result in either positive or negative reward (Cui et al., 2013). Striatal ensemble activity is translated into temporally patterned signals in the GABAergic interface nuclei (GPe, SNr) that modulate the activity of motor control centers in the thalamus, mesencephalon and brainstem.

In addition to controlling the 'vigor' of movement by modulating the moment-to-moment excitability of SPNs and striatal interneurons, DA is thought to sculpt the functional connectivity of SPNs by providing feedback about the outcome of previously chosen actions (Berke, 2018; Klaus et al., 2019). In the early stages of PD, this feedback control is lost as the distal axons of SNc dopaminergic neurons begin to fail (Cheng et al., 2010). Although in the original formulation some 30 years ago, the loss of striatal DA signaling was envisioned to simply de-facilitate the excitability of dSPNs (by decreasing D1R signaling) and dis-inhibit the excitability of iSPNs (by decreasing D2R signaling), it has become apparent that the situation is considerably more complex. Similarly, levodopa therapy was originally aimed at re-balancing the excitability of dSPNs and iSPNs to allow normal processing of cortical and thalamic inputs. But, now it is evident that levodopa therapy is capable of inducing a wide range of lasting changes in striatal circuits that become particularly problematic in the later stages of the disease when the amount of levodopa needed to achieve symptomatic benefit rises. The large, slow oscillations in striatal DA concentration that result from high doses of orally-delivered levodopa lead to abnormal involuntary movements or levodopa-induced dyskinesia (LID) (de la Fuente-Fernandez et al., 2004; Pavese et al., 2006).

Besides being dependent upon extrinsic excitatory synaptic input, the spatiotemporal dynamics of SPN activity are controlled by an intricate network of interneurons (Tepper

et al., 2018; Tepper et al., 2004). Two of these interneurons will be discussed at some length here in large measure because they endow the striatum with unusual biochemical features. One of these is the giant, aspiny cholinergic interneuron (ChI). Striatal markers of cholinergic transmission are among the highest of any brain region (Lehmann and Langer, 1983). Moreover, acetylcholine (ACh) and DA have long been hypothesized to play antagonist roles in regulating striatal circuits, particularly with the context of PD (Barbeau, 1962), although recent studies suggest a much more complicated dynamics between the two (Cai et al., 2021; Threlfell and Cragg, 2011). Another less well appreciated striatal interneuron is the low-threshold spike interneuron (LTSI) that releases nitric oxide (NO), in addition to GABA and somatostatin. Although NO plays an important role in regulating the vasculature, SPNs also express very high levels of signaling molecules activated by NO, including soluble guanylyl cyclase (sGC), cyclic-guanosine monophosphate (cGMP) phosphodiesterases (PDEs) and cGMP-activated protein kinases (Ariano, 1983). Recent work suggests that these LTSIs also are important determinants of striatal adaptations in PD and LID.

The principal goal of this review is to summarize recent advances in our understanding of how SPNs, ChIs and LTSIs respond to DA depletion and subsequent levodopa therapy. These adaptations and their effects on striatal circuits are then considered within a translational context.

2. Striatal homeostatic plasticity: keeping striatal pathways in balance

In the healthy striatum, DA differentially modulates somatodendritic excitability of dSPNs and iSPNs, as well as the induction of long-term synaptic plasticity at glutamatergic synapses (Surmeier et al., 2014). As long-term synaptic plasticity in SPNs is activity-dependent, these two effects are not completely independent. At the time the original hypothesis about the network basis of PD motor symptoms was formulated, the role of DA in regulating synaptic plasticity was not appreciated and, as a consequence, only the impact of DA depletion on the excitability of dSPNs and iSPNs was considered. Despite this limitation, the hypothesis that dSPN hypoactivity and iSPN hyperactivity drive disinhibition of GABAergic basal ganglia output in PD has been of great heuristic value.

Another factor that was not appreciated in the late 1980's was that when pushed away from their spiking set-point, neurons manifest intrinsic and synaptic forms of homeostatic plasticity (Marder and Prinz, 2003; Turrigiano, 2012). For example, when induced to spike at higher-than-normal rates of activity for a prolonged period (~day(s)), neurons can up-regulate the expression of K^+ channels to lower intrinsic excitability and slow spiking down. Similarly, sustained suppression of spiking can induce strengthening of excitatory synapses to bring spike rate up into a desired range. Both mechanisms are bidirectional. Interestingly, in hippocampal neurons synaptic homeostatic plasticity appears to result in global scaling of synaptic strength, preserving the relative weighting of different inputs. In this way, 'memories' stored in the relative weighting are preserved.

In animal models of late-stage PD, both iSPNs and dSPNs are pushed away from their spiking set-point (as posited by the classical model), but the extent to which they exhibit

intrinsic and synaptic homeostatic plasticity is somewhat controversial. In our hands, a month after unilateral 6-hydroxydopamine (6-OHDA) injection into the medial forebrain bundle (MFB), which depletes the entire basal ganglia of virtually its entire dopaminergic innervation (>90% loss of TH immunoreactivity), both iSPNs and dSPNs appear to have undergone cell-type specific homeostatic changes that tend to normalize their spike activity (Day et al., 2006; Fieblinger et al., 2014). Specifically, iSPNs (rendered hyper-excitable by loss of D2R signaling) prune cortical and thalamic excitatory axospinous synapses and decrease their intrinsic excitability (as measured by intrasomatic current injection with a patch electrode). In contrast, dSPNs (rendered hypoexcitable by loss of D1R signaling) maintain their spine density and undergo an intrinsic form of homeostatic plasticity to up-regulate their somatic excitability. These complementary changes would, in principle, serve to diminish the imbalance in the excitability of direct and indirect striatal efferent pathways. A similar, selective loss of iSPN spines following MFB 6-OHDA lesioning was reported by Nishijima et al. (Nishijima et al., 2014) and Schuster et al. (Schuster et al., 2009). In addition, Ketzef et al. (Ketzef et al., 2017) found that MFB lesioning decreased the differences in intrinsic excitability between iSPNs and dSPNs (Gertler et al., 2008; Kreitzer and Malenka, 2007) in vivo, in agreement with our ex vivo work. However, in other models of PD, the picture is not as simple. For example, 2–3 weeks after an intranigral 6-OHDA lesion, which does not typically result in the same level of DA depletion (70–90%) as MFB lesioning, iSPNs in D1-tdTomato transgenic mice do not appear to change their intrinsic excitability (Maurice et al., 2015). Similarly, 2–3 weeks following intrastriatal 6-OHDA injections, iSPNs were reported to have increased their intrinsic excitability, but to have pruned axospinous synapses (Suarez et al., 2016). In both of these preparations, dSPNs appear to have increased their intrinsic excitability (as reported by our group), but with intrastriatal 6-OHDA lesions, dSPNs also were reported to have paradoxically lost axospinous synapses (Suarez et al., 2016).

How can these discrepancies be resolved? Clearly, these studies differ in methodology, particularly in the extent and location of the 6-OHDA lesion, as well as how long after the lesion the assessment was made. Generally, in models in which DA has been depleted by MFB 6-OHDA lesioning for 3–4 weeks, dSPN spine density does not change (Day et al., 2006; Fieblinger et al., 2018; Graves and Surmeier, 2019; Nishijima et al., 2014; Schuster et al., 2009). In more chronic models (>2 months post-lesion) or in postmortem striatal tissue of PD patients, spine pruning is detected in both dSPNs and iSPNs (Gagnon et al., 2017; McNeill et al., 1988; Stephens et al., 2005; Suarez et al., 2018; Villalba et al., 2009; Zaja-Milatovic et al., 2005). Recent work by our group has shown that indeed if spine density is assessed in mice 3 months after 6-OHDA lesion, then a significant pruning of dSPN spines can be detected (Graves and Surmeier, 2019). This difference suggests that spine losses in iSPNs and dSPNs are mediated by distinct mechanisms. The maladaptive spine loss in dSPNs is attributable to sustained loss of D1R and elevated M4R signaling in the parkinsonian state, which induces a progressive depression of synaptic transmission at axospinous synapses (Ding et al., 2006; Shen et al., 2008; Shen et al., 2015). This process is evident 3–4 weeks after 6-OHDA lesioning as a drop in average amplitude of cortical EPSCs in dSPNs (Fieblinger et al., 2014). As this change in synaptic strength should be accompanied by a reduction in the size of spines, methods for spine counting that miss

thin and stubby spines (which are abundant in SPNs (Wilson et al., 1983)) will lead to the conclusion that spines are lost, when they are not. For example, (Gomez et al., 2019) used Lucifer Yellow fills to estimate spine density in SPNs, which resulted in an estimate of spined density in control SPNs that was roughly 50% of that measured with two-photon imaging of Alexa-filled SPNs (Crittenden et al., 2021; Day et al., 2008; Fieblinger et al., 2014) or with a high voltage stereo electron microscopy (Wilson et al., 1983). The mechanisms responsible for the relatively rapid loss of spines reported in dSPNs following intrastriatal 6-OHDA injections is less clear (Suarez et al., 2016; Suarez et al., 2014). One possibility is that the striatal cannula placement and toxin injection trigger inflammation that precipitates axonal and spine degeneration that is independent of DA (Mendes-Pinheiro et al., 2021).

Lastly, there is the discrepancy about changes in the intrinsic excitability of iSPNs. Again, this could depend upon the extent of DA depletion in the basal ganglia and the resulting network deficits it produces (Fieblinger et al., 2014; Maurice et al., 2015; Suarez et al., 2016). Interestingly, recent work by our group with a progressive mouse model of PD (Gonzalez-Rodriguez et al., 2021) suggests striatal DA depletion prior to the emergence of parkinsonian motor symptoms triggers spine loss in iSPNs, but not changes in intrinsic excitability (unpublished data). Given that the elevated spike activity nominally driving intrinsic homeostatic plasticity in iSPNs depends upon excitatory input from corticostriatal and thalamostriatal glutamatergic neurons (SPNs do not spike without this input), it could be that the change in intrinsic excitability requires both loss of striatal D2R signaling and hyper-activity glutamatergic neurons projecting to iSPNs – which may vary from preparation to preparation.

However, not all the changes in SPNs induced by DA depletion are homeostatic. The dendritic trees of both iSPNs and dSPNs shrink after lesioning (Fieblinger et al., 2014; Nishijima et al., 2014). Also, unlike the situation in hippocampal neurons, there is no evidence of synaptic scaling. In iSPNs, although many axospinous synapses are pruned, the remaining corticostriatal axospinous synapses are on average stronger (Fieblinger et al., 2014). Similarly, axoshaft glutamatergic synapses made by parafascicular nucleus (PFN) neurons on iSPNs are functionally stronger (as a consequence of a presynaptic modulation) (Tanimura et al., 2019). On the other hand, in dSPNs, while spine density is initially normal, average strength of corticostriatal axospinous synapses falls (Fieblinger et al., 2014). These non-homeostatic adaptations are very likely to contribute to network dysfunction and PD symptoms (e.g., (Tanimura et al., 2019)).

3. Determinants of striatal synaptic plasticity in the healthy striatum

To understand how the synaptic connectivity of SPNs changes in the PD state, it is necessary to briefly review what is known about the factors governing synaptic plasticity in the healthy striatum. Bidirectional synaptic plasticity at corticostriatal glutamatergic synapses has long been suggested to be a key cellular substrate for goal-directed and habitual learning (Yin and Knowlton, 2006). Among the various forms of plasticity reported, endocannabinoid (eCB)-dependent LTD is best understood (Kreitzer and Malenka, 2008; Lovinger, 2008). This form of plasticity is induced by postsynaptic mobilization of intracellular Ca^{2+} stores

by postsynaptic G_q-coupled type 5 metabotropic glutamatergic receptors (mGluR5s) and Cav1 Ca^{2+} channels. This mobilization triggers the generation of eCBs that bind to presynaptic CB1 eCB receptors (CB1Rs) that lower glutamate release probability in an activity- dependent manner (Lovinger, 2008). In iSPNs, eCB generation is enhanced by $G_{i/o}$-coupled D2Rs inhibition of AC/PKA signaling that stimulates regulator of G protein signaling 4 (RGS4) – a negative regulator of mGluR5 signaling (Lerner and Kreitzer, 2012). In dSPNs, type 4 muscarinic receptors (M4Rs), which are coupled to $G_{i/o}$ proteins, mimic the actions of D2Rs in iSPNs and promote LTD induction by suppressing RGS4 activity (Shen et al., 2015). Also in parallel with D2Rs (Higley and Sabatini, 2010), M4R signaling attenuates the enhancement of PKA-mediated NMDAR-mediated Ca^{2+} influx (Shen et al., 2015). In both iSPNs and dSPNs, corticostriatal LTP induction requires co-activation of NMDARs, tyrosine receptor kinase B (TrkB) receptors and PKA signaling (Plotkin et al., 2014). In dSPNs, D1R signaling promotes LTP induction through activation of PKA and extracellular signal-regulated kinase (ERK) (Shen et al., 2008). D1R signaling also enhances NMDAR currents (Murphy et al., 2014) while inhibiting LTD induction through RGS4 (Shen et al., 2015). In iSPNs, the $G_{s/olf}$-coupled adenosine A2a receptor (A2aR) plays a role that is similar to that of the D1R in dSPNs (Higley and Sabatini, 2010; Lerner and Kreitzer, 2012).

Although these plasticity mechanisms are at work at corticostriatal synapses, it is becoming evident that not all synapses manifest these forms of activity-dependent plasticity. Recently, using optogenetic tools, Wu et al. revealed that eCB-LTD was clearly inducible at corticostriatal, but not thalamostriatal synapses (Wu et al., 2015). Corroborating the physiology, immunostaining found abundant CB1R expression in cortical neurons but not in the thalamus (Wu et al., 2015). This is not to say that LTD is not inducible at thalamic synapses – it is (Cavaccini et al., 2018; Ellender et al., 2013; Parker et al., 2016). However, other than data implicating a gating role for type 4 5-hydroxytryptamine (5-HT) receptors in dSPNs (Cavaccini et al., 2018), relatively little is known about the signaling mechanisms involved. One obstacle to sorting this out is that thalamic synapses on SPNs are not homogeneous (Smith et al., 2014). Although many thalamic nuclei project to the striatum, the major thalamostriatal projections arise from the parafasicular nucleus (PFN) and the centrolateral nucleus (CLN). CLN synapses are axospinous, creating the same sort of postsynaptic signaling environment that promotes plasticity at corticostriatal synapses. In contrast, PFN synapses are formed on dendritic shafts where it should be more difficult to control the chemical environment (c.f., (Goldberg et al., 2003)). The determinants of plasticity at these two types of synapses have not been systematically studied with the sort of tools necessary to provide a rigorous picture (Tanimura et al., 2019).

This kind of heterogeneity also may be present at corticostriatal synapses. Although there is a topography to the corticostriatal projection, SPN receive convergent input from many regions of the cerebral cortex spanning motor, sensory, limbic and associative regions (Wilson, 1984). It is easy to imagine that activity-dependent plasticity might not be desirable at all of these synapses. Indeed, using a ‘sledgehammer’ chemical induction strategy with visualized individual axospinous synapses, postsynaptic LTP was inducible at only about half of the synapses on distal SPN dendrites (Plotkin et al., 2014). Another source of heterogeneity in the corticostriatal projection is based upon connectivity. SPNs

receive convergent input from both intratelencephalic (IT) and pyramidal tract (PT) neurons (Shepherd, 2013). Recent work by our group has shown that IT, but not PT, axon terminals undergo a form of presynaptic LTD (similar to eCB-LTD) in response to intrastriatal muscarinic ACh receptor (mAChR) signaling (Pancani et al. unpublished observations). In agreement with this dichotomy, corticostriatal synaptic transmission at PT synapses are facilitated by nicotinic AChR (nAChR) signaling (Morgenstern et al., 2022). Whether IT and PT synapses differ in their susceptibility to other forms of activity-dependent plasticity is unclear. Lastly, it should also be noted that it is likely that not all dSPNs and iSPNs are equivalent (Gokce et al., 2016). In addition to the predominant matrix region of the striatum, there are striosomal (patch) regions where the circuitry, SPN properties and local chemical environment differ (Crittenden and Graybiel, 2011; Prager et al., 2020).

Another factor that has not been systematically considered is the role of dendritic location in dictating the factors governing the induction of plasticity. For example, spike-timing dependent plasticity (STDP), which depends upon back-propagation of axon initial segment spikes into the dendrites, is very likely to be significant for synapses in the proximal dendrites, as spikes don’t invade more distal regions in SPNs (Carter and Sabatini, 2004; Day et al., 2008). A similar situation is found in pyramidal neurons (Spruston, 2008). In more distal dendrites, spatiotemporal cooperativity between input channels should dictate plasticity rules, rather than whether a spike was generated at the right time. If these inputs are able to generate a plateau potential that produces a persistent opening of NMDARs, it should create a window of time in which GPCR signaling associated with action outcome can act to trigger lasting changes in synaptic strength. The induction of plasticity in this case could apply not only to active synapses but those that are nearby (Sjostrom et al., 2008). Sorting these rules out and determining what this means for striatally based learning will be a major challenge going forward.

One of the conundrums in the striatal literature has been the apparent absence of a postsynaptic form of LTD to counter-balance the postsynaptically expressed LTP described above. Recent work has resolved this issue and shown that nitric oxide (NO) signaling arising from LTSIs that express nitric oxide synthase (NOS) induces a robust form of postsynaptic LTD in both iSPNs and dSPNs (Rafalovich et al., 2015). NO signaling molecules (e.g., sGC, protein kinase G) have long been known to be abundantly expressed in the striatum (Ariano, 1983; Ding et al., 2004), but their role in striatal physiology has been unclear. Calabresi and colleagues initially reported that pharmacological suppression of NO and cGMP signaling 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, demonstrating that cGMP- dependent LTD is a postsynaptically expressed form of LTD (Rafalovich et al., 2015). Importantly, this form of LTD can be induced by optogenetic activation of LTSIs, eliminating concerns about the specificity of the pharmacological tools commonly used to study this form of signaling. NO-LTD also can be induced at both corticostriatal and thalamostriatal synapses, contrasting it with eCB-LTD (Wu et al., 2015). Also in contrast to eCB-LTD, NO-LTD appears to be blunted by

local depolarization and Ca^{2+} entry through Ca_v1 Ca^{2+} channels (Zhai et al., unpublished observations). Thus, there appear to be opposing signaling mechanisms in SPNs that lead to one or the other form of LTD. The mechanisms mediating this interaction remain to be elucidated. Still, given the constraint placed upon it by local activity, it is interesting to speculate that NO-LTD may play a role in attenuating the strength of inactive synapses and keeping overall synaptic strength within acceptable bounds. At the striatal level, it may be necessary to unlearn previously rewarded associations to acquire new ones. Indeed, a recent study found that LTSIs were recruited when mice learned new sequential stepping patterns (Nakamura et al., 2017), suggesting that NO-LTD may be essential for certain types of striatum-dependent learning.

4. Alterations in striatal synaptic plasticity in parkinsonism

How does bidirectional plasticity at glutamatergic synapses change in the parkinsonian state? There seems to be two phases in animal models of PD induced by near complete lesioning of the nigrostriatal projection. In the acute phase (<1 week of DA depletion), bidirectional plasticity at corticostriatal glutamatergic synapses is disrupted in a cell type-specific manner. In iSPNs, the loss of D2R signaling disrupts eCB-LTD induction; in dSPNs, the loss of D1Rs signaling disrupts LTP induction (Kreitzer and Malenka, 2007; Shen et al., 2008). However, in iSPNs, LTP induction is intact (as it is dependent upon A2aRs) and in dSPNs eCB-LTD is intact (as it depends upon M4Rs) (Shen et al., 2008). However, in the chronic phase (>3–4 weeks), neither form of long-term synaptic plasticity can be induced in SPNs (Calabresi et al., 1992; Picconi et al., 2003; Shen et al., 2015). Why this is the case remains to be rigorously determined. One possibility is that the homeostatic adaptations that take place in iSPNs and dSPNs blunt the induction of synaptic plasticity by altering the engagement of Cav1 Ca^{2+} channels or NMDARs, both of which are key players in the induction of plasticity (Adermark and Lovinger, 2007; Kreitzer and Malenka, 2005; Shen et al., 2008). Another possibility is that running unopposed, LTD becomes saturated in dSPNs and LTP becomes saturated in iSPNs. That is, persistent loss of D2Rs signaling should bias plasticity mechanisms toward LTP, leading to gradual strengthening of synapses where the requisite receptors and signaling molecules are present. The converse should happen in dSPNs. Indeed, an examination of the strength of axospinous synapses in iSPNs 3–4 weeks after lesioning revealed a shift toward larger amplitudes in iSPNs and a shift toward smaller amplitudes in dSPNs (Fieblinger et al., 2014).

These observations suggest that the synaptic architecture of iSPNs and dSPNs is undergoing a complex re-organization in the parkinsonian state. First, rather than being shaped by DA release that is contingent upon the need to move or action outcome, the loss of DA signaling creates a sustained plasticity signal that strengthens glutamatergic synapses on iSPNs and weakens them on dSPNs. This is equivalent to a persistent signal not to move or that movement has not led to the expected outcome and should be suppressed. Second, NO-LTD, which may normally serve to counter ‘run-away’ potentiation of glutamatergic synapses (on iSPNs in this case), appears to be lost in the parkinsonian state (Picconi et al., 2011). This deficit appears to be caused not by any alteration in postsynaptic signaling machinery (unpublished observations) but rather by impairment in NO generation, which is dependent upon DA modulation of LTSIs and NO synthesis (Centonze et al., 2002; Sammut et al.,

2006). Third, DA depletion elevates the excitability of ChIs (Sanchez et al., 2009; Tanimura et al., 2019; Tubert et al., 2016) and ACh release from ChIs (Barbera et al., 2016; DeBoer et al., 1993; Ding et al., 2006; Ikarashi et al., 1997; Shen et al., 2007); unpublished work by our group using a genetically encoded optical sensor for ACh release is consistent with this long-standing point of view. Elevated ACh release will promote LTP in iSPNs (Crittenden et al., 2021; Shen et al., 2007) and promote LTD in dSPNs (Shen et al., 2015).

The combination of elevated ACh release and loss of D2R and NO-LTD 'brakes' on synaptic plasticity, appears to drive homeostatic mechanisms in iSPNs, as described above. How aberrant DA-dependent plasticity and homeostatic synaptic plasticity interact to remodel the synaptic connectome of iSPNs remains to be worked out. Although the remodeling in dSPNs does not appear to be as dramatic, it nevertheless must be disrupting the synaptic architecture shaped by experience. Cell-type specific mapping methods, like monosynaptic rabies virus mapping (Wall et al., 2013), should provide a powerful means of assessing these connectomic changes. It also remains to be determined how dendritic integration is affected by DA depletion and how these changes interact with the observed homeostatic shifts in somatic excitability to shape spiking.

PD patients are given levodopa to lessen their movement disability. While increasing striatal DA concentration should serve to 'rebalance' the excitability of iSPNs and dSPNs, both directly and indirectly (e.g., suppression of ACh release), what does it do to synaptic function? It is unclear. Both phasic and tonic DA signaling needs to be considered. Phasic DA signaling activates both D1Rs and, as recently found, D2Rs (Marcott et al., 2014). In addition to gating circuitry by altering intrinsic excitability (Howe and Dombeck, 2016), phasic signaling may be crucial for properly sculpted synaptic plasticity. In ventral striatum, two recent studies have revealed a critical time window of phasic DA (<1–2 s) for synaptic plasticity induction (Wieland et al., 2015; Yagishita et al., 2014). In this time window, an eligibility trace has been left at recently activated synapses, allowing DA signaling to induce plasticity at just those synapses related to the preceding action. With partial striatal DA depletion, this phasic (but not tonic) DA signal is predicted to be lost (Dreyer, 2014). Based upon the principles outlined above, this should result in attenuation in the functional connectivity of dSPNs and maintenance or enhancement of iSPN functional connectivity. Indeed, this is what has been reported in following partial MFB lesions (Escande et al., 2016). With partial DA lesions, levodopa may be effective in restoring both phasic and tonic DA signaling necessary for normal striatal function and synaptic plasticity. In fact, in the early stages of the MCI-Park model, levodopa restores motor learning, but fails to do so in fully parkinsonian mice (Gonzalez-Rodriguez et al., 2021). Similarly, in late-stage patients, where the dopaminergic innervation of the striatum is gone (Chu et al., 2020), levodopa treatment will not restore the properly timed, contextually determined phasic DA release that underlies movement initiation or learning. These distinctions underscore the importance of studying progressive models of PD, like the MitoPark and MCI-Park models (Ekstrand and Galter, 2009; Gonzalez-Rodriguez et al., 2021).

Another important consideration in this context is pathophysiological activity outside the striatum. SPNs are completely dependent upon excitatory synaptic input to push them away from a down-state near the K^+ equilibrium potential to spike threshold. Furthermore, all

forms of striatal synaptic plasticity depend – either directly or indirectly – upon excitatory synaptic input to the striatum. In animal models of late-stage PD, cortical activity is clearly disrupted (Pasquereau and Turner, 2011). The contribution of this disruption to alterations in SPN activity, synaptic plasticity and architecture remains to be determined.

5. The contribution of thalamostriatal circuits to the parkinsonian state

Although the largest glutamatergic input to the striatum comes from the cerebral cortex, the thalamus also is a major source of excitatory drive to the striatum. Thalamostriatal afferents are highly heterogeneous in origin, synaptic properties, and function (Smith et al., 2014). Thalamostriatal afferents arise from a variety of thalamic nuclei (Guo et al., 2015; Wall et al., 2013), but the best characterized of these comes from the intralaminar nuclei: PFN and CLN (Smith et al., 2004). As mentioned above, PFN afferents synapse on SPN dendritic shafts, whereas CLN afferents make synaptic contacts mostly on SPN dendritic spines, like the corticostriatal inputs. Because of the high input impedance of dendritic spines, axospinous synapses engage the ionic mechanisms governing synaptic plasticity (Spruston, 2008; Yasuda, 2017). These mechanisms are probably absent at axoshaft PFN synapses (but see (Yuste, 2011)). That said, PFN synapses have a robust complement of NMDARs (Ellender et al., 2013). The significance of these unique properties of PF synapses is unclear but could be related to the polysensory, alerting nature of the information relayed by PFN (Smith et al., 2011). Furthermore, PFN – but not CLN – innervates striatal interneurons, most notably ChIs (Sadikot et al., 1992; Sciamanna et al., 2015; Sidibe and Smith, 1999).

What happens to this innervation of the striatum in PD? In both PD patients (Henderson et al., 2000) and MPTP-treated monkeys (Villalba et al., 2014) there is substantial loss of intralaminar neurons. In rodents, MPTP treatment has been reported to produce a loss of PFN neurons (Freyaldenhoven et al., 1997), but the reliance upon Fluoro-Jade to identify degenerating neurons makes this conclusion questionable. Following 6-OHDA injections, the situation is clearer. Despite the suggestion from an early study that had significant technical limitations (Aymerich et al., 2006), more recent work has failed to see any anatomical or functional evidence of PF degeneration following 6-OHDA lesioning (Orieux et al., 2000; Parker et al., 2016; Tanimura et al., 2019; Watson et al., 2021).

Of greater interest are the functional alterations in the thalamostriatal projection in rodent models of PD. Recently, Parker et al. (Parker et al., 2016) employed optogenetic techniques to argue that thalamic excitation of dSPNs selectively declines in parkinsonian mice, contributing to the ‘imbalance’ in the excitability of striatal efferent pathways underlying bradykinesia. They attributed this change to induction of a form of LTD. Moreover, they reported that chemogenetic inhibition of intralaminar neurons alleviated some of the motor deficits in lesioned mice. Although clearly implicating thalamostriatal afferents in striatal pathophysiology, the relative contribution of PFN and CLN projections was not assessed nor was the potential role of striatal interneurons innervated by PFN. To fill the first gap, Tanimura et al. used a combinatorial genetics approach in mice that expressed Cre recombinase selectively in CLN neurons (Tanimura et al., 2019). This allowed neighboring PF neurons to be selectively manipulated with optogenetic and chemogenetic approaches using Cre-off expression constructs. To fill the second gap, the responses of SPNs to

optogenetic stimulation of PFN axons was examined with and without propagated network activity. Taken together, Tanimura et al.'s results show that in isolation, PFN synaptic connectivity with SPNs does not change in the parkinsonian state. However, activation of a distinct subpopulation of PFN neurons led to activation of ChIs and selective enhancement of glutamate release by PFN synapses on iSPNs. This enhancement was dependent upon presynaptic nAChRs containing α6 subunits. Suppressing the PFN pathway through ChIs or knocking down thalamic α6 mRNA attenuated the change in network activity and improved motor performance in parkinsonian mice.

6. Is an imbalance in the excitability of dSPNs and iSPNs really responsible for PD symptoms?

Although on paper, the hypothesis that an imbalance in the activity of dSPNs and iSPNs provides a beautiful explanation for the hypokinetic features of PD, it has been difficult to test in practice (Albin et al., 1989; Nelson and Kreitzer, 2014). In vivo recording from anesthetized rats has provided support for this model (Mallet et al., 2006) (but see (Ketzef et al., 2017)). Additional support has come from studies using optogenetic (Kravitz et al., 2010) and chemogenetic (Alcacer et al., 2017; Armbruster et al., 2007) approaches. But 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 decrease in dSPN firing and an increase in iSPN activity in stationary mice. When mice were moving, dSPN activity was still depressed but the firing rate of iSPNs was not elevated. Why iSPN firing rate in moving mice is resistant to DA depletion is currently unclear, but it can be attributed, at least in part, to the homeostatic adaptations in iSPNs and the potentiation of a subset of axospinous glutamatergic synapses following DA depletion described above (Fieblinger et al., 2014). Adaptations in cortical projections to the striatum also could play a key role in this phenomenon (Xu et al., 2017). 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).

Additional support for the classical model has come from some recent studies of striatal mechanisms involved in LID. First, single unit recording and in vivo Ca^{2+} imaging both confirmed that levodopa increased the spiking of dSPNs while decreased that of iSPNs (Parker et al., 2018; Ryan et al., 2018). Furthermore, optogenetic or chemogenetic stimulation of dSPNs produced 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 ameliorated dyskinetic movements triggered by levodopa (Alcacer et al., 2017). These studies support the proposition that an imbalance between direct and indirect pathways is necessary for LID. However, there are reasons to think the situation is not so simple. For example, simultaneous activation of dSPNs and iSPNs produces dyskinesia in a rat model of PD (Hernandez et al., 2013). Moreover, Girasole et al. found that although the majority of activated neurons were dSPNs, a portion

(~ 10%) were iSPNs, suggesting that the activity of iSPNs and dSPNs may be more than merely oppositional (Girasole et al., 2018). 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 (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. (2018) showed that the coupling of dSPN and iSPN activity to locomotion was impaired by DA 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. One important limitation is that they are unilateral models of a bilateral disease. Another 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 result in model-specific network pathophysiology that has nothing to do with a slowly progressing disease like PD. Moreover, contrary to the implicit assertion of the classical model of network pathophysiology underlying PD, SNc dopaminergic neurons release DA throughout the basal ganglia, not just the striatum. While the significance of this extrastriatal DA release has yet to be fully explored in PD and LID models, there is compelling evidence that dendritic release of DA is an important modulator of activity in the interface nuclei of the basal ganglia, particularly the SNr (e.g. (Ruffieux and Schultz, 1980; Waszcak and Walters, 1983)). Recent work by our group using a progressive, axon-first, bilateral model of PD suggests that while striatal DA depletion is necessary for the expression of ambulatory deficits in PD, it is not sufficient and that restoring DA signaling in the SNr alone restores ambulation (Gonzalez-Rodriguez et al., 2021). SNr DA signaling also may be important to the expression of LID (Borgkvist et al., 2015).

7. Striatal mechanisms underlying LID

Levodopa administration in parkinsonian mice is capable of restoring LTP in dSPNs and LTD in iSPNs (Shen et al., 2015), suggesting that the biochemical machinery underlying the induction and expression of synaptic plasticity is intact in the parkinsonian state.

What is different in levodopa-treated mice is the spatio-temporal pattern of DA receptor stimulation. Rather than being briefly stimulated by phasic DA, D1Rs in levodopa-treated mice are stimulated for long periods of time (Bastide et al., 2015); this abnormally sustained stimulation is likely to underlie both the synaptic and biochemical signatures of LID in dSPNs. The sustained elevation of extracellular DA concentration following levodopa administration (Bastide et al., 2015) also prevents iSPNs from responding to patterned activity appropriately (Shen et al., 2015). In this state, STDP protocols that normally induce Hebbian LTP induce LTD in iSPNs. Because DA signaling is no longer governed by behavioral outcome or the need to move, and the engagement of the homeostatic mechanisms described above, it is easy to imagine that synaptic strengths become randomized, leading to purposeless, 'random' movement or dyskinesia (Picconi et al., 2003; Shen et al., 2015). In agreement with this perspective, M4R activation in dSPNs suppressed aberrant LTP and alleviated dyskinetic movements (Shen et al., 2015). In contrast, chemogenetic activation of $G_{s/olf}$ signaling in dSPNs (mimicking ON-state D1R signaling) aggravated dyskinesia (Alcacer et al., 2017). Other strategies for reducing aberrant synaptic plasticity also improve behavior, further implicating striatal synaptic plasticity in LID mechanisms (Ghiglieri et al., 2016; Trusel et al., 2015).

Although 'aberrant' DA signaling undoubtedly plays a key role in the network dysfunction underlying LID, the interaction of these processes with those governing homeostatic plasticity needs to be carefully considered. For example, the homeostatic pruning of iSPN axospinous synapses following 6-OHDA lesioning is reversed by dyskinesiogenic doses of levodopa (Fieblinger et al., 2014; Nishijima et al., 2014; Suarez et al., 2014). While LID has traditionally been attributed to abnormal signaling within dSPNs (Cenci and Konradi, 2010; Feyder et al., 2011), this alteration in iSPN connectivity suggests that they may also be a 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 levodopa (i.e., "off-state"). By that time, the striatal level of DA 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 levodopa 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. The fact that the induction phase of LID typically takes several rounds of levodopa administration to be fully manifest, suggests that there are progressive changes in the striatal circuitry that drive its expression. Whether the mechanisms that promote induction and expression of LID are the same or different is unclear.

What happens to NO-mediated synaptic plasticity in LID? As outlined above, striatal NO generation appears to be lost in PD models (Picconi et al., 2011; Sagi et al., 2014;

Sancesario et al., 2004) (but see (Chalimoniuk and Langfort, 2007)). If this is caused by a deficit in D1/5R signaling in LTSIs (Hoque et al., 2010; Picconi et al., 2011; Sammut et al., 2006), then levodopa therapy should restore NO signaling and NO-LTD. Could sustained stimulation of NO signaling lead to aberrant LTD and contribute to the network disruption underlying LID? The literature on this point is conflicting, with some studies suggesting the answer to this question is yes (Padovan-Neto et al., 2011; Solis et al., 2015), but other studies suggest otherwise (Giorgi et al., 2008; Picconi et al., 2011). Resolving these apparent discrepancies will require more selective pharmacological tools (e.g., a selective neuronal NOS inhibitor) and better ways of monitoring NO signaling. In addition, clearly defining the cGMP signaling pathways in SPNs and targets other than glutamate receptors with newly developed tools (e.g. caged cGMP (Agarwal et al., 2017)) should allow a broader functional context for NO signaling in the striatum to be constructed. One of the other targets of NO signaling that could play an important role in LID is the ChI (Agarwal et al., 2017; Centonze et al., 2001; Elghaba et al., 2016).

DA replacement therapy is remarkably effective at reducing the motor symptoms of PD in its early stages. However, with the progressive loss of dopaminergic neurons that convert levodopa to DA, the therapeutic window of levodopa narrows, the effective dose of levodopa required to achieve symptomatic benefit rises, and the severity of the dyskinesia increases. The dyskinesiogenic potential of levodopa therefore limits its effectiveness as a symptomatic therapy for PD. Although amantadine is currently used clinically for alleviating LIDs, it has limited efficacy and has negative side-effects, including hallucinations, confusion, falling and nausea (Pahwa et al., 2015). Thus, there is a compelling need for strategies that limit LID without sacrificing symptomatic benefit.

Such a therapy should come from a better understanding of the mechanisms governing LIDs. Several lines of evidence suggest that aberrant D1R-dependent potentiation of dSPNs glutamatergic synapses is a central feature of the LIDs pathophysiology (Feyder et al., 2011; Jenner, 2008; Picconi et al., 2003). This aberrant plasticity is attributable in part to slow oscillations in striatal DA levels after taking levodopa that result in sustained stimulation of $_{Gs/olf}$-coupled D1Rs necessary for the induction of dSPN LTP. Sustained D1Rs signaling also suppresses G_i-coupled M4Rs signaling in dSPNs that normally helps balance D1Rs signaling (Jeon et al., 2010; Sanchez et al., 2009). Indeed, endogenous cholinergic signaling through M4Rs promotes the induction of LTD at dSPN glutamatergic synapses through G_i-protein-mediated inhibition of AC. In a rodent model, boosting M4Rs signaling with positive allosteric modulators (PAMs) diminished dSPN LTP induction and alleviated dyskinetic behaviors (Shen et al., 2015).

Interestingly, longer term treatment with high doses of levodopa in PD animal models appears to result in enhanced, rather than depressed, ChI excitability (Choi et al., 2020; Paz et al., 2021). In homeodomain transcription factor Pitx3 deficient mice, in which there is developmental loss of dopaminergic neurons, high doses of levodopa (25 mg/kg/bid) lead to elevation in ChI activity and a form of dyskinesia that is alleviated by muscarinic receptor antagonism (Ding et al., 2011). However, in this developmental model, there are a variety of changes in properties of striatal cells and circuits. For example, ChIs autoreceptor function appears to be dramatically downregulated, as is the density of D2/D3 DA receptors (Cremer

et al., 2015). Although functional down-regulation of M2/4 muscarinic autoreceptors is common to the Pitx3 and 6-OHDA lesion models (Ding et al., 2006), the down-regulation of DA receptors is not. There could be other adaptations as well (Lim et al., 2015). These changes should have a profound effect on the striatal circuitry and how it responds to levodopa treatment.

That said, there is evidence from other models suggesting that ChIs are playing a role in LID. In a 6-OHDA lesioned mouse model, levodopa- induced abnormal involuntary movements are alleviated by selective ablation of ChIs (Won et al., 2014). Also, using the conventional, 6-OHDA lesion model of PD and lower (2–3 mg/kg/day) levodopa dosing, the Quik lab reported that optogenetic stimulation of ChIs with brief light pulses worsened LIDs through a mAChR-dependent mechanism but that stimulation with longer light pulses lessened LIDs severity through nAChR-dependent mechanism (Bordia et al., 2016). As intriguing as these results are, they are difficult to interpret because there was no attempt to correlate the optical stimulation protocol with ChIs spiking or ACh release. Moreover, the effects of ChI stimulation on the response to subsequent levodopa administration were not examined. Nevertheless, the implication that nAChRs are playing a role in the expression of LIDs is consistent with the ability of nAChR antagonists or desensitizing dose of nicotine to alleviate LIDs (Bordia et al., 2015; Quik et al., 2013a; Quik et al., 2013b) and needs to be rigorously pursued. Finally, a recent study shows that diminished sonic hedgehog (Shh) signaling in ChIs plays a role in LID formation and expression; specifically, pharmacological activation of a downstream effector of Shh attenuated LID behaviors, while suppressing Shh release from DA neurons or the effector signaling in ChIs promoted LID (Malave et al., 2021).

8. A caveat to the classical model of network dysfunction underlying PD

Throughout this review, the position taken has been that striatal pathophysiology triggered by regional DA depletion is necessary and sufficient to cause the motor symptoms of PD as well as those of LID. This has been the dominant view in the field for roughly 30 years. However, as noted above, the vast majority of evidence in support of this view comes from work in animal models in which the staged, axon-first dysfunction of SNc dopaminergic neurons seen in humans is not recapitulated. Thus, the impact of regional, as opposed to global, DA depletion has not been assessed. As DA release in other parts of the basal ganglia, including the GPe, STN and SNr, is significant, this is not a trivial gap in our knowledge. Recently, intersectional genetics was used to generate a mouse in which a key subunit of mitochondrial complex I (MCI) was deleted in dopaminergic neurons (Gonzalez-Rodriguez et al., 2021). In this mouse, there is an axon-first loss of dopaminergic signaling and the eventual development of a levodopa-responsive parkinsonism. The progressive nature of the dysfunction in dopaminergic neurons allowed the behavioral consequences of regional DA depletion to be monitored. Surprisingly, essentially complete loss of striatal DA release led to profound deficits in motor learning and a modest deficit in fine, sequential movement but not parkinsonism. Parkinsonism (bradykinesia in the open field, rearing deficits, gait and stance deficits) only appeared with loss of DA signaling outside of the striatum. Moreover, boosting SNr or striatal conversion of levodopa to DA using local viral delivery of an aromatic acid decarboxylase expression construct was very effective in

restoring running in mice that were parkinsonian. Thus, while striatal pathophysiology may be necessary for frank parkinsonian motor disability, it does not appear to be sufficient and deficits in extra-striatal regions plays an important role. This observation is consistent with the hypothesis that disrupting striatal DA signaling alone disrupts basal ganglia function but that these functions (at least in the motor domain) are capable of being performed (albeit not as well or as fast) by other brain circuits. However, with depletion of DA in GPe, STN and SNr, synchronous rhythmic bursting activity evolves and this 'toxic' patterning actively disrupts motor control by other parts of the brain. This hypothesis is consistent with what is known about the role of DA in these extra-striatal regions, with the patterning of basal ganglia output in models of late-stage disease and with the therapeutic benefit that accrues to patients receiving STN deep brain stimulation to blunt aberrant patterning of basal ganglia output (Sharma et al., 2019).

9. Concluding remarks

Acting through specific 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 DA 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. 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.

There have been major advances in our understanding of the role played by ChIs in the striatal circuitry and behavior in the last decade. This has largely been a consequence of advances in tool development. However, a host of major questions remain unanswered, particularly about the role of ChIs in controlling interneuronal circuits and in disease states, like PD. Answering these questions in the coming years should not only give us insight into what the striatal circuit is doing to control behavior, but also provide new therapeutics for psychomotor disorders involving the basal ganglia.

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