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Striatal synapses, circuits, and Parkinson's disease

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Abstract

The striatum is a hub in the basal ganglia circuitry controlling goal directed actions and habits. The loss of its dopaminergic (DAergic) innervation in Parkinson's disease (PD) disrupts the ability of the two principal striatal projection systems to respond appropriately to cortical and thalamic signals, resulting in the hypokinetic features of the disease. New tools to study brain circuitry have led to significant advances in our understanding of striatal circuits and how they adapt in PD models. This short review summarizes some of these recent studies and the gaps that remain to be filled.

Introduction

PD is a progressive neurodegenerative disorder charac- terized by hypokinetic motor impairments, such as bradykinesia and rigidity. The hypokinetic motor symptoms of PD result from selective loss of DAergic neurons in the substantia nigra pars compacta (SNc) innervating the basal ganglia [1]. Therefore, as a dopamine (DA)- deficiency condition, PD is standardly treated with drugs intended to boost DA or DA receptor signaling. Indeed, in the early stages of the disease, the motor symptoms of PD are effectively alleviated by the DA therapies. However, as the disease progresses and the drug dose needed to achieve symptomatic benefit rises, severe motor complications develop, including abnormal involuntary movements — levodopa-induced dyskinesia (LID).

Striatum, the major input nucleus of the basal ganglia, receives the densest DAergic innervation from the SNc. However, the SNc also sends DAergic projections to other brain regions, leading to widespread network adaptations with their loss in PD [2,3]. Nevertheless, this review will focus on synaptic changes within the striatum that contribute to PD and LID. The principal neurons of the striatum are spiny projection neurons (SPNs), which constitute rv90% of total striatal neurons in rodents. SPNs can be divided to two populations of similar size: direct pathway SPNs (dSPNs) that primarily project directly to the internal segment of the globus pallidus and substantia nigra pars reticulata (but see [4]), and indirect pathway SPNs (iSPNs) that project only to the external segment of the globus pallidus and thus are indirectly connected to the output nuclei [5]. The two pathways are differentially modulated by DA, due to their selective expression of DA receptor subtypes: dSPNs express Gs/olf-

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coupled D1 receptors (D1Rs) while iSPNs express Gi/o-coupled D2 receptors (D2Rs). However, the segregation is not complete. A small fraction of SPNs co-express D1Rs and D2Rs and constitute a distinct population that is differentially altered in Parkinson's disease [6,7].

Striatal interneurons, accounting for 5–10% of all striatal neurons, consist of at least four well-characterized types: cholinergic interneurons (ChIs), fast-spiking interneurons (FSIs), calretinin-expressing interneurons, and persistent and low threshold spiking interneurons (PLTSIs). Striatal interneurons are integral players in striatal function, exerting GABAergic inhibition and neuromodulation of SPNs [8*,9]. All types of interneurons express differential combinations of DA receptors, adding extra layers to how striatal network activity is regulated by DA and goes awry in the case of PD and LID [10].

Despite the complexity of cellular and network changes caused by DA depletion and DA restoration therapy, the development of new genetic, optical, chemogenetic, and optogenetic tools has led to remarkable progress in the last couple of years. In this short review, we focus on recent work that have provided new insights into the synaptic and network mechanisms of PD and LID.

Striatal homeostatic plasticity — diminishes the consequences of disease progression?

SPNs receive extra-striatal synaptic inputs from diverse brain areas, but the majority of their inputs are glutamatergic and arise from cortical and thalamic regions [11,12]. The strength of corticostriatal inputs, as well as how responsive SPNs are to these inputs, is under control of DA: D1R activation increases intrinsic excitability and promotes synaptic potentiation, while D2R activation decreases intrinsic excitability and promotes synaptic depression [1]. In parkinsonian animals, DA depletion triggers cell-specific alterations in intrinsic excitability and synaptic plasticity that lead to an imbalance in the activity of iSPNs and dSPNs: iSPNs, whose activation promotes movement suppression [13], become hyperactive, whereas dSPNs, whose activation promotes movement initiation, become hypoactive [14]. This imbalance has long been thought to be central to the hypokinetic symptoms of PD.

What has long been overlooked is that the striatal network is not static. In response to the loss of DA signaling, SPNs undergo homeostatic changes that tend to restore the balance. In iSPNs of DA-depleted striatum, hyperactivity triggered by the loss of D2R signaling leads to reduced intrinsic excitability over time. In parallel, loss of D1R signaling in DA-depleted dSPNs leads to compensatory elevation in intrinsic excitability [15*]. In addition to these adaptations in intrinsic excitability, synaptic homeostatic plasticity is also engaged: iSPNs undergo substantial spine pruning in PD models [15*,16–18]. However, unlike the situation in hippocampus, there is no obvious synaptic scaling; in fact, the strength of the remaining synapses is increased [15•,19,20]. This may be due, at least in part, to the fact that the loss of D2R signaling promotes LTP by dis-inhibiting A2a receptor (A2aR) signaling [21], which may disrupt scaling mechanisms.

Is the homeostatic pruning of axospinous excitatory synapses random, or is it targeted? Since this process is driven by DA depletion, it might be expected that local DA signaling plays a role. But it is unclear whether this is uniform or not. One clue has come from studies

asking whether all axospinous glutamatergic synapses are capable of DA-dependent plasticity. With the single-synapse precision enabled by two-photon glutamate uncaging, Plotkin *et al.* demonstrated that only a subset of corticostriatal axospinous synapses are subject to DA-dependent synaptic plasticity [22]. This finding argues that dendritic spines are not uniform in their makeup — some spines possessing cellular machinery for plasticity while others not, although the identity of such synapse-specific machinery is unknown. The heterogeneity of corticostriatal synapses is actually not so surprising, considering the heterogeneity of corticostriatal projections (e.g. intra- telencephalic vs. pyramidal tract) and, in turn, the different types of information conveyed by these projections [23]. Whether some subset of synapses is more susceptible or resistant to spine pruning remains to be determined.

Nevertheless, what these studies demonstrate is that striatal cells and circuits compensate for the loss of DAergic signaling by manifesting both intrinsic and synaptic homeostatic plasticity. This plasticity should lessen the consequences of DA depletion and could help explain why well over half of the DAergic innervation of the striatum needs to be lost before parkinsonian symptoms become obvious [24].

DA replacement with repeated levodopa introduces a second perturbation to the system and brings with it a second set of homeostatic adaptations. Many of the PD-induced adaptations are reversed, particularly in iSPNs [15*,16]. The most intriguing is the restoration of corticostriatal axospinous synapses on iSPNs by dyskinesiogenic, but not non-dyskinesiogenic, doses of levo- dopa [15*,16,17]. Up to this point, LID pathology was largely presumed to reside within dSPNs and be associated with aberrant synaptic plasticity [25,26]. But this new work suggests that adaptations in iSPNs are also involved in the pathophysiology underlying LID. It remains to be determined whether this re-wiring is an accurate re-establishment of prior circuits and whether this re-wiring is critical to the emergence of dyskinesia, but the new data highlights the importance of functional interdependence between iSPN and dSPN circuits and the complications that arise when the balance between the two is perturbed.

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

Bidirectional synaptic plasticity at corticostriatal glutamatergic synapses has long been suggested to be the cellular basis for goal-directed and habitual learning [27]. Among the various forms of plasticity reported, the presynaptically-expressed, endocannabinoid (eCB)-dependent LTD is best understood: it is mediated by presynaptic CB1 eCB receptors (CB1Rs) and it is also dependent upon postsynaptic activation of mGluR5. In iSPNs, D2R activation, through $G_{i/o}$ signaling, inhibits RGS4 signaling and disinhibits mGluR5-mediated eCB production [28]. Is there a parallel $G_{i/o}$ signaling pathway in dSPNs for LTD induction? $G_{i/o}$-coupled muscarinic M4 receptor (M4R) may play such a role [29]. Shen *et al.* [30**] have demonstrated that activation of M4R signaling, either by a positive allosteric modulator of M4R or by chemogenetic activation of ChIs, facilitates LTD induction in dSPNs through suppression of RGS4 — establishing a clear mechanistic parallel to the situation in iSPNs. Just like D2Rs [31], M4R also inhibited NMDAR-mediated Ca^{2+} influx and thereby suppressed LTP induction [30**]. Therefore, similar mechanisms exist in iSPNs and dSPNs:

M4R and D2R promote LTD and suppress LTP induction, whereas D1R and A2aR facilitate LTP and inhibit LTD induction.

How does bidirectional synaptic plasticity change in the PD state? There seems to be two phases in animal models of PD. In the acute phase (<1 week of DA depletion), bidirectional plasticity is disrupted in a cell type-specific manner: LTD is lost in iSPNs due to absence of D2R signaling, whereas LTP is impaired in dSPNs due to lack of D1R activation [21,32]; but LTP in iSPNs and LTD in dSPNs are still robust [21]. However, in the chronic phase (>3 to 4 weeks), no long-term synaptic plasticity can be induced [30**,33,34]. Why? One possible scenario is that synaptic mechanisms for LTP in iSPNs and LTD in dSPNs, rather than being impaired, have actually been saturated. This is consistent with the observation that unitary synaptic response is enhanced in iSPNs and reduced in dSPNs at about three weeks after DA depletion [15*].

Does levodopa completely normalize impaired synaptic plasticity in PD? Unlikely, considering the fact that DA operates on at least two timescales: tonic and phasic. The leading model posits that tonic DA enables certain forms of movement whereas phasic DA signals reward and facilitates goal-directed and habitual movement [35]. This model was recently revised by an elegant study by Howe *et al.* [36**]. Using two-photon imaging of the activity of DAergic axons in the dorsal striatum of moving mice, they showed that phasic DA, depending on the origin of DAergic axons, could signal either locomotion or reward. Phasic DA accomplishes these ends by activating both D1Rs and, as recently found, D2Rs [37]. In addition to gating circuitry, this phasic activation may be crucial for properly sculpted synaptic plasticity. In ventral striatum, two recent studies have revealed a critical time window of phasic DA (<1 to 2 s) for synaptic plasticity induction [38**,39]. 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.

Levodopa administration in parkinsonian mice is capable of restoring LTP in dSPNs and LTD in iSPNs [30**], 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 [40]; 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 [40] also prevents iSPNs from responding to patterned activity appropriately [30**]. In this state, spike-timing-dependent plasticity (STDP) protocols that normally induce Hebbian LTP induce LTD in iSPNs. Because DA signaling, and the changes in synaptic strength it brings about, are no longer governed by the outcome of behavior, it is easy to imagine that synaptic strengths become randomized, leading to purposeless, ‘random’ movement or dyskinesia [30**,34]. In dSPNs, M4R activation and $G_{i/o}$ signaling, suppressed aberrant LTP and alleviated dyskinetic movements [30**]. By contrast, chemogenetic activation of G_s signaling in dSPNs (mimicking ON-state signaling) aggravated dyskinesia [41]. Several other strategies of normalizing aberrant plasticity also improved behavior, further implicating striatal synaptic plasticity in the disease mechanisms [42,43].

Compared to the well-characterized eCB signaling, the role of nitric oxide (NO)/cGMP signaling in striatal synaptic plasticity was less clear. This is surprising given the robust expression of NO signaling proteins in the striatum [44,45]. Striatal NO was first documented by Calabresi *et al.*: tetanic stimulation of corticostriatal afferents induced LTD in SPNs that was dependent on NO, cGMP and postsynaptic protein kinase G [46]. Since then, NO had been considered a permissive modulator of the canonical eCB-LTD [47]. But this idea has recently been challenged [48]. Using two-photon glutamate uncaging (which bypasses any potential presynaptic effect), Rafalovich *et al.* showed that a cGMP analog persistently decreased uncaging-evoked glutamatergic responses, suggesting that cGMP-dependent LTD is a novel, post- synaptically expressed form of LTD. The apparent occlusion of presynaptic eCB-LTD by NO-LTD is not due to shared signaling pathway, but rather results from NO inhibition of L-type calcium current required for eCB-LTD induction. Moreover, optogenetic activation of PLTSIs, which have dense expression of NO synthase, led to a robust NO-LTD, suggesting that NO is a physiological modulator of synaptic strength at both corticostriatal and thalamostriatal synapses, contrasting it again with eCB-LTD [49]. Nevertheless, very little is known about how NO-LTD is regulated in SPNs. For example, among the various types of phosphodiesterases expressed by SPNs, which ones negatively modulate NO-LTD?

In PD models, both up-regulation and down-regulation of the NO/cGMP signaling pathway have been reported [50–52]. Why there is a discrepancy is unclear. In agreement with those arguing that NO signaling is down- regulated, cGMP-dependent LTD appears to be absent in parkinsonian animals [53]. Is this caused by firstly, the lack of D1R activation required for NO production in DA- depleted striatum [54], secondly, the loss of NOS-expressing interneurons [55], or thirdly, a combination of both? Even more puzzling is the role of NO signaling in LID: treatments that suppress or elevate cGMP levels have both been reported to be effective in ameliorating dyskinetic behaviors [53,56,57].

SPN collateral inhibition re-emerges

SPNs have robust recurrent axonal collaterals [58,59] that form GABAergic synapses with the dendrites of neigh- boring SPNs and interneurons [60–63]. Initially, it was thought that these synapses were of little functional importance [59]. But paired recordings from iSPNs and dSPNs using D1 and D2 BAC transgenic mice suggested that these recurrent connections were potentially significant and follow certain rules. First, recurrent synapses emanating from iSPNs are more frequently found and are on average more potent than those emanating from dSPNs [62,64]. A corollary of this rule is that connections are not uniformly distributed, with dSPN-to-iSPN being the least frequent pair. Second, the density of collateral synapses is moderate: the coupling probability of adjacent SPN pairs (<50 mm) is roughly 30–50%, and each pre- synaptic SPN makes 2–5 GABAergic synapses with its target neuron [62,64,65]. Third, recurrent collateral synapses are subject to DA modulation, the direction of which depends on the type of presynaptic DA receptors. D1R activation increases GABA release while D2R activation decreases it [64–68]. One caveat is that most of these studies relied heavily on bath application of chemicals and thus could not rule out indirect effects, considering the diverse distribution of DA receptors in the striatum.

Collateral synapses are targeted largely to distal dendrites [8•,59,69]. What is the physiological function of these 'remote' synapses? In particular, how does dendritic inhibition shape local excitatory inputs and regenerative events that exist in distal dendrites? There are theoretical answers [70,71], but little experimental evidence. This is because it is difficult to study dendritic integration with a somatic electrode while the fine dendrites of SPNs forbid dendritic patch recording. Moreover, it is almost impossible to selectively manipulate collateral synapses without affecting other connections in the striatum. The latter problem was recently circumvented by using a combination of novel genetic, optogenetic and chemogenetic techniques [72,73]. Dobbs *et al.* found that lateral inhibition, evoked by optogenetically activating a cohort of iSPNs, strongly reduced intrinsic excitability of postsynaptic dSPNs in nucleus accumbens. Consistent with earlier pharmacological studies, this lateral inhibition is reduced by D2R agonist or cocaine in control mice, but not in knockout mice where D2R is selectively deleted in iSPNs (iMSN-Drd2KO). Interestingly, cocaine-induced locomotion is also diminished in iMSN-Drd2KO mice, but rescued by chemogenetic activation of G_i signaling in iSPNs. Although it is not possible to exclude dendritic mechanisms with the approaches used, this work shows that cocaine-induced locomotion is gated by DA modulation of collateral transmission [72]. Consistent with this model, selective deletion of D2R from iSPNs alone increased GABAergic transmission presumably in part at collateral connections, decreased firing of both iSPNs and dSPNs, and caused hypokinesia [73]. Although much remains to be done, these recent studies have given us new insights into the functional relevance of the collateral transmission from iSPNs to dSPNs.

Is collateral transmission altered in PD? Taverna *et al.* found that collateral connectivity was profoundly reduced in two mouse models of PD [62], in agreement with work by Flores-Barrera *et al.* [20]. This may result, at least in part, from impaired NO signaling in parkinsonian animals [52]. However, a recent report did not find any significant change in collateral transmission in a genetic model of PD [64]. The discrepancy might result from variations in the extent and duration of DA depletion between PD models. The modulation by DA and short-term synaptic plasticity of collateral transmission also seem to be altered in PD models [64,74]. What is still unclear is how the changes in lateral inhibition contribute to the dysfunctional striatal signal processing in PD and LID.

The contribution of thalamostriatal circuits in PD

Compared to our understanding of the corticostriatal system, our understanding of the thalamostriatal system has just started to expand. The growing consensus is that thalamostriatal inputs are highly heterogeneous in anatomical organizations, synaptic properties, and behavioral functions [75]. For example, the striatum receives glutamatergic afferents from a variety of thalamic nuclei [11,12], the best characterized of which is the parafascicular thalamic nuclei (PF) in rodents (or center median/ PF nuclei in primates) [76]. Non-PF thalamic projections make synaptic contacts mostly on dendritic spines of SPNs ('axospinous') like the corticostriatal inputs, but PF axons largely synapse on dendritic shafts ('axoshaft'). Because of the high input impedance of dendritic spines, axospinous synapses facilitate the strong local depolarization necessary to engage the mechanisms governing synaptic plasticity [77]. These mechanisms may be absent at axoshaft PF

synapses. Perhaps to compensate for this anatomical feature, PF synapses have a robust complement of NMDAR-type glutamate receptors [78]. The significance of these unique properties of PF synapses is unclear but could be related to the poly-sensory, alerting nature of the information relayed by PF [79]. Furthermore, PF — but not non-PF nuclei — also projects to striatal interneurons [80–82]. This is best understood for ChIs, which in turn exert a wide range of effects on striatal circuitry [83–86].

Substantial neuronal loss is found in intralaminar thalamic nuclei in both PD patients [87] and MPTP-treated mon- keys [88]. However, little was known about the role of thalamostriatal circuit in the symptoms of PD. Recently, Parker *et al.* [89**] have suggested that thalamic excitation of dSPNs is selectively reduced in parkinsonian mice as a consequence of altered plasticity mechanisms at this synapse, contributing to the imbalance in excitability of iSPNs and dSPNs. The authors showed that chemo- genetic inhibition of thalamic neurons alleviated motor deficits in DA-depleted mice, clearly implicating thalamostriatal circuits in PD pathophysiology. As intriguing as this study is, there are several important questions that remain unanswered. First, given the heterogeneity of the thalamostriatal circuitry, it is not clear whether the changes in SPN connectivity apply to all thalamic synapses. Second, given the richness of the thalamostriatal connectivity with striatal interneurons and the importance of interneurons in modulating synaptic strength, it is not clear whether they are playing a role in the thalamostriatal phenotype. Undoubtedly, given the tools available to regulate interneuron activity, these questions will be answered in the near future.

Conclusions

In the last couple of years, there has been considerable progress toward understanding not just the normative function of striatal circuits, but how they change in PD and following treatment with levodopa. Several new themes have emerged. One is homeostatic plasticity and its role in mitigating network pathophysiology in the early stages of the disease. Another continuing theme is the importance of aberrant, DA-dependent synaptic plasticity in driving the network dysfunction in both PD and LID. A third is the contribution of thalamostriatal circuits to striatal and ultimately basal ganglia dysfunction. How these cellular and network adaptations dictate behavior remains unanswered, but the rapid evolution of *in vivo* recording techniques that can be applied to awake, unanesthetized animals is sure to provide new insights in the near future. Although it was believed for decades that direct and indirect pathways had opposing effects on behavioral output, a rapidly growing body of evidence suggests that this model is oversimplified — coordinated activity and spatiotemporal organization of neuronal ensembles of both pathways are critical to behavior [90*,91–93]. It would be invaluable to determine how these additional dimensions are altered in parkinsonian state.

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