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Striatal synapses, circuits, and Parkinsons disease

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The striatum is a hub in the basal ganglia circuitry controlling goal directed actions and habits. The loss of its dopaminergic (DAergic) innervation in Parkinsons 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.

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Introduction

PD is a progressive neurodegenerative disorder characterized 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 ~90% 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 $G_{s/olf}$-coupled D1 receptors (D1Rs) while iSPNs express $G_{i/o}$-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 Parkinsons 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. intratelencephalic 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 levodopa [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

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