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Dopaminergic modulation of striatal networks in health and Parkinson's disease

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Abstract

In the last couple of years, there have been significant advances in our understanding of how dopamine modulates striatal circuits underlying goal-directed behaviors and how therapeutic interventions intended to normalize disordered dopaminergic signaling can go awry. This review summarizes some of the advances in this field with a translational focus on Parkinson's disease.

Dopamine is one of the most studied neuromodulators in the nervous system. Last year, over 5000 papers were published that had dopamine as a key word. One of the most studied of the brain regions affected by dopamine is the basal ganglia; nearly 700 of the 5000 dopamine papers in 2013 had 'basal ganglia' as a keyword. The reason for this focus is relatively straightforward. Not only are the basal ganglia important to goal-directed behavior and habit formation, they are also implicated in a wide range of diseases, including Parkinson's disease (PD), Huntington's disease, schizophrenia, dystonia, attention-deficit-hyperactivity-disorder, and depression. Alterations in dopaminergic signaling are involved in most, if not all, of these disorders, making it critical to understand its normal role and how it goes awry in disease.

Dopaminergic neurons in the substantia nigra pars compacta (SNc) innervate all of the nuclei of the basal ganglia, most prominently the striatum (Fig. 1). The striatum is the largest of the basal ganglia nuclei, serving as the principal recipient of information reaching the basal ganglia. The striatal innervation is diverse but is derived primarily from cortical and thalamic regions [1]. Dopamine modulates the responsiveness of principal GABAergic spiny projection neurons (SPNs) to these inputs, as well as the strength of corticostriatal synapses. SPNs that project directly to the interface nuclei of the basal ganglia – direct pathway SPNs (dSPNs) – express primarily D₁ dopamine receptors (D1Rs), which increase intrinsic excitability and promote long-term potentiation (LTP) at glutamatergic corticostriatal synapses. SPNs that project indirectly to the interface nuclei – indirect

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pathway SPNs (iSPNs) – express primarily D₂ dopamine receptors (D₂Rs) that decrease their intrinsic excitability and promote long-term depression (LTD) at corticostriatal synapses. By inhibiting GABAergic neurons in the interface of the basal ganglia (substantia nigra pars reticulata and the internal segment of the globus pallidus), dSPNs gate thalamocortical circuits and action selection, leading it to be referred to as the ‘go’ pathway [2]. Conversely, by dis-inhibiting these same neurons, iSPNs suppress action selection making it the ‘no-go’ pathway (Fig. 1). By bi-directionally modulating these two SPN populations, dopamine is thought to not only regulate ongoing choices about what to do and not to do, but also to lay down a memory of the consequences of those choices that help guide future behavior. Several studies in the last few years have confirmed the basic features of this model [3-5]. That said, beautiful work by Costa's group [6**] has shown that dSPNs and iSPNs are concurrently active at movement initiation, suggesting that these two pathways do not simply compete for control the basal ganglia output but act in a coordinated way to promote some actions and suppress others.

In PD, this dopaminergic innervation of the striatum is lost. In the classical model, this leads to hyper-activity in iSPNs and hypo-activity in dSPNs, resulting in dis-inhibition of basal ganglia outputs and suppression of movement. Although this model has been remarkably robust, it has its limitations. One is that the spatiotemporal pattern of activity in the striatum and in other parts of the basal ganglia, which is not captured in the model, is critical to normal movement control and the motor symptoms of the disease [7]. Another major shortcoming is that it fails to account for the ability of neurons and neural circuits to adapt to sustained perturbations in activity. These homeostatic forms of plasticity are generally thought to diminish network dysfunction, but might, in certain circumstances, lead to unexpected and undesirable consequences. This short review will focus on work in the last few years that have provided new insight into the mechanisms by which dopamine regulates SPNs and how this is altered in PD states, particularly the dyskinetic state. A number of more detailed and comprehensive reviews have appeared that complement the narrow focus here [8-10].

Size matters - Dopamine and neuronal morphology

For decades, it was thought that from the standpoint of somatodendritic anatomy and intrinsic excitability, SPNs were essentially all alike. But since the advent of bacterial artificial chromosome (BAC) transgenic mice that allow dSPNs and iSPNs to be reliably sampled, it has become apparent that there are significant differences in the intrinsic excitability of these two types of neuron as measured with somatic current injection, glutamatergic stimulation, or by measuring spike invasion into the dendrites [11-14]. Using either somatic current injection or spike invasion of dendrites to assess excitability, iSPNs are more excitable in *ex vivo* brain slices than dSPNs. But why? One obvious possibility is that this difference in intrinsic excitability counterbalances the neuromodulatory effects of dopamine. Acting through D₂Rs, dopamine tonically suppresses the activity of iSPNs and promotes LTD at excitatory glutamatergic synapses. Conversely, acting through D₁Rs, dopamine enhances the activity of dSPNs and promotes LTP at glutamatergic synapses (Fig. 1). The differences in intrinsic excitability could help make each pathway equally responsive to excitatory input *in vivo* and overall spike rate. Dendritic surface area and intrinsic

excitability could be tuned by homeostatic mechanisms designed to keep spike rate constant [15]. Chan et al. [16] showed that weeks after dopamine-depleting lesions or initiation of systemic administration of a D2R antagonist (eticlopride), the intrinsic excitability of iSPNs indeed shifted downward. In agreement, Carzola et al. [17] showed that over-expression of D2Rs increased the intrinsic excitability of SPNs. What remains to be resolved is the relationship between the dendritic anatomy and intrinsic excitability. Over-expression of D2Rs in the Carzola et al. study decreased dendritic arbor length, in agreement with the proposition that excitability and anatomy are coupled. However, one of the fundamental confounds in these experiments is that the excitability measurements have not been done *in vivo* where dopaminergic signaling is intact, but rather in *ex vivo* brain slices that create an acute parkinsonian state by washing away dopamine.

One of the other factors in this equation is synaptic connectivity. In the absence of excitatory synaptic currents, SPNs are quiescent, being dominated by inwardly rectifying Kir2 K⁺ channels [18]. As a consequence, the effect of alterations in intrinsic excitability on spiking can be compensated for by changing synaptic strength or number. One of the most prominent structural adaptations that takes place following dopamine depletion in PD models is the loss of excitatory axospinous glutamatergic synapses specifically in iSPNs [19]. In parallel, inhibitory GABAergic input to iSPNs from fast-spiking interneurons rises [20*]. Like the change in intrinsic excitability, these changes have been taken as forms of synaptic homeostatic plasticity triggered by loss of inhibitory D2R signaling. Surprisingly, with levodopa doses sufficient to induce dyskinesia, SPN spine density rises in iSPNs [21*, 22**]. Although these results fit nicely with a homeostatic model, there might be other mechanisms in play. For example, D2Rs couple through β -arrestin to intracellular signaling cascades that have functions other than to control excitability [see 23]. Fasano et al. [24] have shown that chronic activation of either D1R or D2R increases the number of spines in young SPNs, independently of any obvious homeostatic pressure. More recently, Carzola et al. [25] have added another dimension to this evolving story, showing that neuroleptic treatment and D2R over-expression bidirectionally regulate the size of dSPN functional axon collaterals in the globus pallidus. How this change is brought about is still unclear but it provides another example of structural plasticity triggered by perturbations in dopamine signaling. New pharmacogenetic tools that allow non-invasive cell-type specific modulation of excitability and intracellular signaling over extended periods of time should have a major impact [26-28].

Listening to what you're told – dopamine and synapses

SPNs in the dorsal striatum are innervated by cortical and thalamic glutamatergic neurons. The cortical innervation is the predominant one, forming axospinous synapses throughout the SPN dendritic tree. The pattern and strength of these synaptic connections is widely thought to embody memories of past experience, serving to guide future action selection. One of the best-documented effects of dopamine is to modulate the strength of these synapses.

The rules by which dopamine influences synaptic strength are still hotly debated. In the last few years, several important studies have helped create some clarity.

One of the most reproducible observations is that D2R signaling promotes the induction of LTD at corticostriatal synapses. It is widely agreed upon that D2R-dependent LTD is induced postsynaptically and expressed presynaptically. Postsynaptically, mGluR5 activation and opening of L-type Ca^{2+} channels are necessary for the production of endocannabinoids (eCB) that act at presynaptic CB1 receptors to diminish glutamate release [29] (Fig. 2). This eCB-dependent form of LTD (eCB-LTD) is seen in the majority of SPNs [30,31], not just half as predicted by the restricted expression of D2Rs in iSPNs. How then does LTD get induced in dSPNs? In agreement with earlier work [30], Tozzi et al. [32*] have shown that the D2R-dependence of LTD induced by high frequency electrical stimulation (HFS) is indirect, reflecting the influence of cholinergic interneurons (ChIs). ChIs express D2Rs that slow their discharge rate and diminish acetylcholine (ACh) release [33]. Reduced ACh release and M1 muscarinic receptor signaling in dSPNs appears to be permissive for LTD induction. Although there are suggestions [30,34], precisely why is not clear. One complication in these experiments (as in the vast majority of this literature) is the reliance upon HFS in which there undoubtedly is current spread to the striatum, leading not only to the activation of striatal dopaminergic and cholinergic fibers but an undetermined array of other cellular elements. Another is lack of receptor subtype-specific muscarinic antagonists used in these studies.

In iSPNs, the mechanisms are clearer. In a beautiful piece of detective work, Lerner and Kreitzer [35*] showed that by inhibiting adenylyl cyclase (AC), D2R signaling diminished protein kinase A (PKA) stimulation of RGS4, disinhibiting mGluR1/5-mediated eCB production and LTD. This mechanism also explained at least in part the ability of A2a adenosine receptors, which are positively coupled to AC in iSPNs, to blunt LTD induction, as suggested by spike-timing-dependent plasticity (STDP) work [36] (Fig. 2).

Another modulator of eCB production is Ca^{2+} -calmodulin-dependent kinase II (CaMKII). Colbran's group [37*] has revealed that CaMKII, which is implicated in most forms of LTP, suppresses striatal eCB production by diacylglycerol lipase- α . Ca^{2+} entry through NMDA receptors (NMDARs) leads to CaMKII phosphorylation. Therefore, PKA regulation of Ca^{2+} entry through NMDARs [38*] could be an efficient means of turning on and off eCB production (Fig. 2). Certainly work by Higley and Sabatini [39] showing D2R suppression of Ca^{2+} entry through NMDARs in iSPNs is consistent with this sort of a mechanism.

Are there similar mechanisms in dSPNs that directly regulate LTD induction? An obvious candidate would be the M4 muscarinic receptor, which is highly expressed in dSPNs and coupled to G_i proteins [40-42]. Are there forms of LTD in the striatum that don't depend upon eCBs? Both opioids and serotonin induce a presynaptic form of LTD at corticostriatal synapses that is eCB-independent [43,44] (Fig. 1). Is there a postsynaptically expressed form of LTD in SPNs?

Although difficult to induce in *ex vivo* brain slices, there is little doubt that the corticostriatal synapse, like all other glutamatergic synapses that have been studied in depth, undergoes LTP in the right circumstances [36,45,46]. In SPNs, like other neurons, activation of NMDARs is necessary for LTP induction. But this isn't enough for SPNs. In dSPNs, LTP requires the co-activation of D1Rs that positively couple to AC and PKA. Recently, two

important linkages between D1Rs and NMDARs have been established. First, work by Zukin's group shows that PKA phosphorylation of the GluN2B subunit increases its Ca^{2+} permeability, providing a novel explanation for the ability of D1R signaling to promote LTP induction [38]. This mechanism extends to iSPNs where A2aRs (which are positively coupled to AC) increase NMDAR Ca^{2+} influx [39] (Fig. 2). How phosphorylation of a cytoplasmic residue alters ionic selectivity without changing channel conductance remains to be determined.

D1Rs also regulate the subcellular distribution of NMDARs. In a technical tour-de-force of cultured hippocampal neurons, Ladepeche et al. [47] demonstrated that D1Rs form reversible aggregates with NMDARs in the extrasynaptic space; stimulation of D1Rs promoted dissociation of these clusters, leading to movement of NMDARs into the synaptic region where they could promote LTP induction. This finding is consistent with earlier work in cultured striatal neurons showing that NMDARs could act as a trap for readily diffusible D1Rs [48]. However, whether this happens in mature SPNs remains to be determined. In ventral SPNs, D1R stimulation reportedly decreases, rather than increases, synaptic NMDARs [49].

Yet another linkage between D1Rs and NMDARs is provided by an intriguing study showing that D1R-triggered phosphorylation of mGluR5 promotes its isomerization and its ability to increase NMDAR currents [50]. This Pin1-mediated prolyl-isomerization required Homer 1a to disrupt the normal scaffolding of mGluR5.

Does timing matter?

A very basic question – relevant to both LTD and LTP – is how the timing of dopaminergic signals affects the induction of synaptic plasticity. Phasic spiking in SNc dopaminergic neurons is evoked by salient stimuli or reward. This activity increases striatal dopamine concentration, leading to activation of D1Rs on dSPNs [51]. The timing of this release and the kinetics of the cellular response to release must be important to form striatal associations between behavior and its outcomes. Because D1Rs are GPCRs that engage intracellular signaling cascades, the temporal parameters of the cellular response are not obvious. Recent work has taken a major step toward filling this gap. Using optical biosensors for cyclic adenosine monophosphate (cAMP) production by AC and its activation of PKA, Castro et al. [52] demonstrated that SPNs respond to phasic dopamine signals rapidly and for a prolonged period. Nominally brief (<1 sec) stimulation of D1Rs by uncaging dopamine produced a rapid, near maximal elevation in PKA activity that lasted over a minute. Moreover, the response in SPNs was more rapid and robust than that in cortical neurons – a difference attributed to higher phosphodiesterase expression in cortical neurons. The availability of caged dopamine – either NPEC-dopamine (used by Castro et al.) or RubiDOPA [53] – make a whole range of experiments mimicking *in vivo* signaling possible.

What does this tell us about how dopamine shapes action selection? One thing it tells us is that phasic dopamine release creates a minute-long window in which dSPN activity should be enhanced and LTP induction enabled. This could be very important for laying down habits that involve ‘chunking’ a group of actions in a sequence. In a maze running task,

Graybiel's group [54] found that striatal dopamine levels increased as the goal was approached, possibly in anticipation of reward, rather than only at the start and end of the task. This rising dopaminergic signal during an action sequence could lead to strengthening of the synaptic connections between cortical neurons coding those actions and dSPN microcircuits associated with that sequence.

Cholinergic interneurons: unexpected drivers of dopamine release

For decades, dopamine and ACh have thought to subserve opposing roles in regulation of the striatal circuitry. This view was initially based upon clinical observation [55], but found plenty of preclinical support [see for example 31]. Recent work has made it clear that this model is too simple. The first hint of this complication came from work examining the response of ChIs to thalamic stimulation (their principal excitatory input) showing that phasic ChI activation triggered a dopamine dependent pause [56]. But how? Two recent studies [57*,58*] demonstrated that optogenetic activation of a population of ChIs triggered phasic dopamine release from terminals. This was mediated by Ca^{2+} permeable nicotinic receptors, presumably on the dopaminergic terminals. Moreover, this mechanism could short-circuit DA release evoked by electrical stimulation of DA axons. Threfell et al. also demonstrated that optical stimulation of thalamic projections to ChIs could mimic the effect of direct activation of ChIs, raising the possibility that the thalamic intralaminar nuclei can control DA release—a situation they are well-positioned to do, given their sensitivity to salient stimuli [59] (Fig. 1).

There are many implications of this finding. One is for transplant therapies in late stage PD patients. One of the enduring concerns about this approach is that because dopaminergic neurons are transplanted into the striatum, rather than the mesencephalon, they lack the normal innervation that drives their response to internal or external events. If transplanted neurons are innervated by striatal ChIs, which are intact in PD patients, they could retain at least a significant part of this regulation.

What goes wrong in L-DOPA induced dyskinesia?

The principal symptomatic therapy for PD patients is L-3,4-dihydroxyphenylalanine (LDOPA) – the precursor for dopamine. In later stage PD patients, as the dose needed to achieve symptomatic benefit rises, L-DOPA commonly induces involuntary movements or dyskinesia. The mechanisms underlying L-DOPA-induced dyskinesia (LID) have been avidly pursued in the hope of developing a palliative treatment. A commonly held view is that LID is primarily a consequence of excessive activation of D1R signaling in dSPNs during the transient elevation in striatal dopamine concentration caused by oral delivery of the drug [60,61]. This induces a host of changes in dSPNs, including hyper-activation of extracellular signal related kinase (ERK) and mammalian target of rapamycin complex 1 (mTORC1). Rhes (Ras homolog enriched in the striatum) is an important part of the mechanism activating mTORC1 in LID [62]. These signaling adaptations lead to broad changes in gene transcription and translation. Using the BAC-TRAP approach [63], Heiman et al. [64] have shown how remarkably complex these changes in dSPN gene expression are. Although it has been widely assumed that sensitized D1R signaling was necessary for these

adaptations with chronic L-DOPA treatment, work by Alcacer et al. [65] has questioned this proposition, pointing to the probable importance of NMDAR signaling through Ras [66-68].

The changes in striatal physiology associated with LID have been more difficult to ascertain. What has been asserted is that in the dyskinetic state, corticostriatal LTP in dSPNs cannot be reversed and LTD is impaired, leading to an aberrant strengthening of cortical excitation of dSPNs and inappropriate action selection [60,61]. This view is derived from electrophysiological examination of SPNs in *ex vivo* brain slices shortly after the last dose of L-DOPA when striatal dopamine levels should be high and D1R stimulation sustained ('on-state'). Indeed, in the normal striatum, both depotentiation and LTD require D1R stimulation be terminated [36,69], which is not likely in the on-state, even in the absence of any pathological alteration in regulation of synaptic plasticity. Picconi et al. [70*] have posited that inhibition of a phosphodiesterase (PDE) degrading cyclic guanosine monophosphate (cGMP) restores LTD and diminishes LID in animal models. Although intriguing, there are a host of unanswered questions about this result. Perhaps the most fundamental is the nature of the LTD 'rescued' by PDE inhibition, as it is nominally dependent upon nitric oxide (NO) signaling originating in striatal interneurons, not eCB production by SPNs. The relationship between NO triggered LTD and eCB-LTD has never been satisfactorily delineated. Moreover, the proposition that striatal NO signaling is impaired in LID is controversial [71,72].

Although the involvement of dSPNs in LID mice has been clearly documented, the role of iSPNs is less clear [7]. The demonstration that the dramatic loss of axospinous synapses in iSPNs following dopamine-depleting lesion is reversed with the induction of LID [21,22], strongly suggests that iSPNs do play a role. But it isn't obvious whether this network alteration promotes dyskinesia or is an attempt to mitigate symptoms. At the outset, it needs to be determined whether the re-establishment of connections in an adult leads to restoration of functional synapses and normal activity patterns – something not assayed for in either of the anatomical studies conducted to date.

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Highlights

- Spiny projection neurons do not just differ in their expression of dopamine receptors.
- The signaling mechanisms controlling synaptic plasticity are diverse.
- Cholinergic interneurons play an unexpected role in dopamine release.
- Aberrant synaptic plasticity is central to levodopa-induced dyskinesia.

Figure 1.

Circuit diagram depicting basal ganglia circuitry and forms of presynaptic LTD and postsynaptic LTP. The blue blowout to the left of the circuit diagram highlights features of D1 receptor expressing dSPNs (top) and D2 receptor expressing iSPNs (bottom) with dSPNs having larger dendritic arbors than iSPNs. Both dSPNs and iSPNs receive glutamatergic input from the cortex and thalamus; cortical innervation is primarily axospinous and thalamic axodendritic as depicted, albeit not exclusively.

Figure 2.

Schematic depicting hypothesized pathways mediating synaptic plasticity in striatal SPNs. Signal transduction pathways mediating the effects of activation of G_s -coupled D1R/A2aR, G_i -coupled M4R/D2R, G_q -coupled mGluR5, and tyrosine kinase TrkB receptor. Note that high PKA activity inhibits G_q -coupled mGluR5 signaling via RGS4. This inhibition effectively prevents the mobilization of both 2-AG and AEA [35**]. Activation of CaMKII suppresses striatal DGLα activity [37*]. Elevating cAMP/PKA signaling promotes NMDAR-mediated Ca^{2+} permeability [38*]. Black arrowheads depict positive regulation and black circles depict negative regulation. Abbreviations: 2-AG, 2-Arachidonoylglycerol; A2aR, adenosine receptor 2a; AC5, adenylyl cyclase 5; AEA, anandamide; Akt, Protein Kinase B; CaMKII, Ca^{2+} /calmodulin-dependent protein kinase II; cAMP, 3'-5'-cyclic adenosine monophosphate; DAG, 1,2-diacylglycerol; D1R, dopamine D1 receptor; D2R, dopamine D2 receptor; ERK, extracellular signal-regulated kinase; M4R, muscarinic receptor 4; NMDAR, N-methyl-D-aspartate receptor; MEK, mitogen-activated protein kinase kinase; mGluR5, metabotropic glutamate receptor 5; NMDA receptor; PI3K, phosphatidylinositol 3-kinases; PIP_2 , Phosphatidylinositol 4,5-bisphosphate; PKA, protein kinase A; PLCβ, phospholipase Cβ; PLD, phospholipase D; RGS4, regulator of G-protein signaling 4; Src, Src-family kinases; TrkB, tropomyosin related kinase B receptor.