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D1 and D2 dopamine-receptor modulation of striatal glutamatergic signaling in striatal medium spiny neurons

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Dopamine shapes a wide variety of psychomotor functions. This is mainly accomplished by modulating cortical and thalamic glutamatergic signals impinging upon principal medium spiny neurons (MSNs) of the striatum. Several lines of evidence suggest that dopamine D1 receptor signaling enhances dendritic excitability and glutamatergic signaling in striatonigral MSNs, whereas D2 receptor signaling exerts the opposite effect in striatopallidal MSNs. The functional antagonism between these two major striatal dopamine receptors extends to the regulation of synaptic plasticity. Recent studies, using transgenic mice in which cells express D1 and D2 receptors, have uncovered unappreciated differences between MSNs that shape glutamatergic signaling and the influence of DA on synaptic plasticity. These studies have also shown that long-term alterations in dopamine signaling produce profound and cell-type-specific reshaping of corticostriatal connectivity and function.

Introduction

Dopamine (DA) has long been known to be a crucial modulator of striatal processing of cortical and thalamic signals carried by glutamatergic synapses on the principal neurons of the striatum – medium spiny neurons (MSNs). Regulation of these neurons by DA is important for a wide array of psychomotor functions ascribed to the basal ganglia, such as habit learning and the control of serial movement [1–3]. In spite of its significance, an understanding of the physiological principles underlying MSN regulation has developed slowly. One obstacle has been the lack of homogeneity in the MSN class; there are at least two major subsets of MSN that differ in their expression of DA receptors [4,5]. These subsets cannot be readily identified on the basis of their somatodendritic morphology or electrophysiological properties. Moreover, both cell types are embedded in a rich neuronal network, involving both MSNs and interneurons, that is modulated by DA. This has made it extremely difficult to determine how DA affects MSNs directly and how it affects MSNs indirectly through synaptically coupled neurons. The recent development of mouse lines in which neurons 'report' their expression of D1 or D2 receptors by co-expressing enhanced green fluorescent protein (EGFP) promises to accelerate our pace of discovery. Another obstacle is that DA receptors are primarily found in dendrites that are inaccessible to electrodes (the principal tool of electrophysiologists), making direct study of their actions on glutamatergic signaling and dendritic excitability difficult. Optical techniques, such as two photon laser scanning microscopy (2PLSM), are enabling access to these regions, and providing fundamental new insights into their physiology and modulation by DA.

This review largely focuses on what is known about how DA modulates postsynaptic properties that influence glutamatergic synaptic events and their integration by MSNs in the dorsal striatum. Only the actions of the principal DA receptors in this region (D1 and D2 receptors) are discussed. Even with this rather narrow focus, it is impossible to summarize faithfully what has become an enormous literature in the past decade. The reader is referred to several other recent reviews [6–8]. Moreover, there is a rich literature characterizing the impact of glutamate on dopaminergic neurons and DA release that is not covered here [9,10].

The 'classical' model of DA modulation

The most widely circulated model of how DA shapes striatal activity was advanced over 15 years ago by Albin, *et al.* [3]; they posited that D1 receptors excite MSNs of the 'direct' striatonigral pathway and that D2 receptors inhibit MSNs of the 'indirect' striatopallidal pathway (Box 1). At the time, the evidence for this model was largely indirect, stemming from estimates of alterations in gene expression, glucose utilization or receptor binding, not direct measures of spiking. Later studies have proved to be largely consistent with the general principles of this model, revealing that DA activation of G-protein-coupled receptors 'excites' or 'inhibits' MSNs by modulating the gating and trafficking of voltage-dependent and ligand-gated (ionotropic) ion channels embedded in the dendritic membrane, essentially changing the way in which MSNs respond to glutamatergic signals.

Modulation of intrinsic excitability and glutamatergic signaling by D1 receptors

Striatonigral MSNs express high levels of D1 receptors [4,5]. These receptors are positively coupled to adenylyl

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Box 1. 'Direct' and 'indirect' pathways from striatal medium spiny neurons to the output nuclei of the basal ganglia

Excitatory, glutamatergic inputs to striatal neurons (Figure I) are derived from neurons in the cerebral cortex (orange arrows) and thalamus (green arrows). These target both principal medium spiny neurons contributing to the direct pathway (blue dots) and the indirect pathway (red dots). Striatonigral, 'direct' pathway medium spiny neurons project directly to neurons that interface between the basal ganglia and the rest of the brain, namely, neurons of the substantia nigra pars reticulata (SNr) and internal segment of the globus pallidus (GPi). By contrast, striatopallidal, 'indirect' pathway medium spiny neurons project axons to the external segment of the globus pallidus (GPe) or entopeduncular nucleus in rodents. GPe or entopeduncular neurons then project to the interface nuclei (SNr and GPi), in addition to the subthalamic nucleus. Adapted, with permission, from [79].

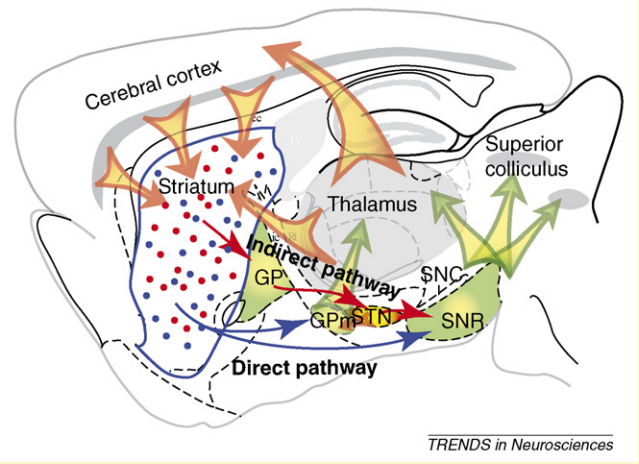

Figure I. Direct and indirect pathways in the basal ganglia. Abbreviations: SNC, substantia nigra pars compacta; SNR, substantia nigra pars reticulata; STN, subthalamic nucleus.

cyclase through G_{olf} [11]. Increases in cytosolic cAMP levels leads to the activation of protein kinase A (PKA) and phosphorylation of various intracellular targets, such as the dual function phosphoprotein DARPP-32 [12], altering cellular function.

A growing number of studies indicate that the D1–PKA cascade has direct effects on the function and trafficking of AMPA receptors and NMDA receptors. For example, D1 receptor activation of PKA enhances surface expression of both AMPA receptors and NMDA receptors [13,14]. The precise mechanisms underlying the trafficking are still unknown but the tyrosine kinase FYN and the protein phosphatase STEP (striatal-enriched phosphatase) seem to be important regulators of surface expression of glutamate receptors [15]. Trafficking and localization might also be affected by a direct interaction between D1 and NMDA receptors [16,17].

What is less clear is whether D1 receptor stimulation has rapid effects on glutamate receptor gating. Although PKA phosphorylation of the NR1 subunit is capable of enhancing NMDA receptor currents [18], the presence of this modulation in MSNs is controversial. In neurons in which the engagement of dendritic voltage-dependent ion channels has been minimized by dialyzing the cytoplasm with cesium ions, D1 receptor agonists have little or no discernible effect on AMPA-receptor-mediated or NMDA-receptor-mediated currents in the dorsal striatum [19]. However, in MSNs where this has not been done, D1 receptor stimulation rapidly enhances currents evoked by NMDA receptor stimulation [20]. The difference between these results suggests that the effect of D1 receptors on NMDA receptor currents is indirect and mediated by voltage-dependent dendritic conductances that are removed by blocking K^+ channels and clamping dendritic voltage. Indeed, blocking L-type Ca^{2+} channels, which open in the same voltage range as NMDA receptors (Mg^{2+} unblock), attenuates the D1-receptor-mediated enhancement of NMDA receptor currents [21].

This type of interaction between voltage-dependent ion channels and ionotropic receptors appears to be common in neurons. Far from the passive entities envisioned twenty years ago, neuronal dendrites are richly invested with voltage-dependent ion channels that shape synaptic responses and plasticity. Although nearly all of the studies of active dendrites to date have been in pyramidal neurons, there is evidence that similar mechanisms govern MSN dendrites [22,23]. However, unlike pyramidal neurons, the dendrites of MSNs are too small to accommodate an electrode, so indirect measures have been used to understand how DA modulates the ion channels that invest MSN dendrites. More recently, the combination of imaging (most notably 2PLSM) and patch clamp has been applied to MSN dendrites in organotypic culture and brain slices [22,23]; this approach offers a powerful alternative to conventional approaches, particularly when applied to tissue in which phenotypically homogeneous neuronal populations are fluorescently tagged.

Voltage-dependent Na^+ channels were the first well-characterized targets of the D1 receptor signaling pathway in MSNs. Voltage clamp studies showed that D1 receptor signaling led to a reduction in Na^+ channel availability without altering the voltage-dependence of fast activation or inactivation [24],confirming inferences drawn from earlier studies in tissue slices [25]. Subsequent studies have shown that PKA phosphorylation of the pore-forming subunit of the Na^+ channel promotes activity-dependent entry into a non-conducting, slow inactivated state that can be reversed only by membrane hyperpolarization [26]. It is possible that the D1 receptor modulation is mediated by phosphorylation of somatic Nav1.1 channels, because Nav1.6 channels are not efficiently phosphorylated by PKA [27]. The coupling of the D1 receptor cascade to dendritic (as opposed to somatic) Nav1.1 and/or Nav1.6 channels remains uncertain and the subcellular positioning of the scaffolding interactions necessary to bring about efficient phosphorylation of Na^+ channel subunits [27] has not been mapped in MSNs.

When the somatic membrane potential is held for several hundred milliseconds near the up-state (~ -60 mV; Box 2) [28], D1 receptor stimulation has a different effect from that when it is held at nominal down-state potentials (~ -80 mV). At this up-state membrane potential, the electrophysiological phenotype of the MSN is transformed, as the constellation of ion channels governing activity is re-configured. Perhaps the most marked change is the closure or inactivation of Kir2, Kv1 and Kv4 K^+ channels that oppose the depolarizing influences of

Box 2. Up- and down-states in medium spiny neurons

In the absence of convergent glutamatergic input, the membrane potential of medium spiny neurons (MSNs) resides close to the potassium equilibrium potential (~−85 mV). This is called the down-state. In response to strong glutamatergic input, medium spiny neurons depolarize to a second preferred membrane potential around −55 mV, near spike threshold. This is called the up-state. Redrawn, with permission, from [28] (Figure I).

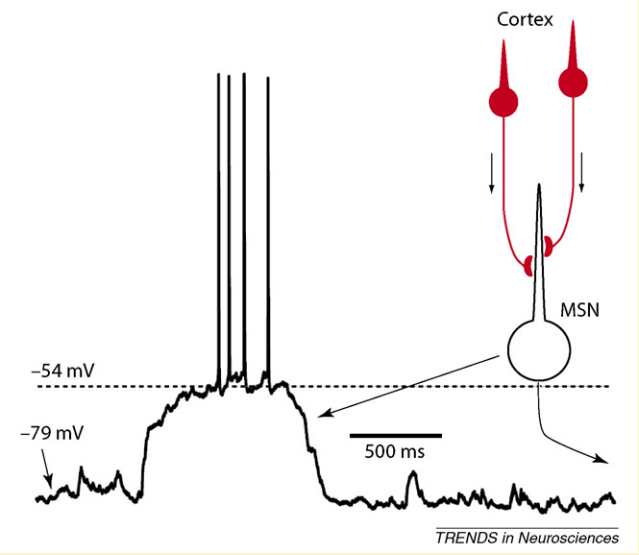

Figure I. Up- and down-states in medium spiny neurons.

glutamate receptors. In this state, D1 receptor stimulation increases (rather than reduces) the response to intrasomatic current injection [29]. The augmented response is attributable in part to enhanced opening of L-type Ca^{2+} channels following PKA phosphorylation [30,31]. L-type channels with a pore-forming Cav1.3 subunit are probably major targets of this modulation; these channels have a voltage threshold near −60 mV and are anchored near glutamatergic synapses in spines through a scaffolding interaction with the protein SH3 and multiple ankyrin repeat domain (SHANK) [32]. Enhanced opening of these channels and NMDA receptors [20,33–35] accounts for the ability of D1 receptor stimulation to promote synaptically driven plateau potentials of MSNs (resembling up-states *in vivo*) in corticostriatal slices [36], as in cortical pyramidal neurons [37]. D1 receptor stimulation also reduces opening of Cav2 Ca^{2+} channels that couple to small conductance Ca^{2+}-activated K^+ channels (SK) [38], potentially further augmenting dendritic electrogenesis.

Taken together, these results indicate that D1 receptor signaling through PKA increases the responsiveness of striatonigral neurons to sustained synaptic release of glutamate, generating up-states, but reduces the response to transient or uncoordinated glutamate release that fails to depolarize significantly the dendritic membrane for more than a few tens of milliseconds from the down-state.

Modulation of intrinsic excitability and glutamatergic signaling by D2 receptors

Expression of D2 receptors is high in striatopallidal MSNs. D2 receptors couple to $G_{i/o}$ proteins, leading to inhibition of adenylyl cyclase through $G\alpha_i$ subunits [39]. In parallel, released $G\beta\gamma$ subunits are capable of reducing Cav2 Ca^{2+} channel opening and of stimulating phospholipase Cβ isoforms, generating diacylglycerol (DAG) and protein kinase C (PKC) activation as well as inositol (1,4,5)-trisphosphate (IP_3) liberation and the mobilization of intracellular Ca^{2+} stores [40,41]. D2 receptors are also capable of transactivating tyrosine kinases [42].

As with D1 receptor signaling, there are several studies showing that D2 receptor signaling alters glutamate receptor function in dorsal striatal MSNs. Activation of D2 receptors decreases AMPA receptor currents of MSNs recorded in tissue slices [20]. Subsequent studies, using acutely isolated neurons and voltage clamp techniques, support a direct action on dendritic AMPA receptors [43]. D2 receptor signaling leads to dephosphorylation of S845 of GluR1 subunit, which should promote trafficking of AMPA receptors out of the synaptic membrane [44]. D2 receptor stimulation also diminishes presynaptic release of glutamate [45]; however, it is not clear whether this is mediated by presynaptically or postsynaptically positioned D2 receptors [46].

Studies of voltage-dependent channels are largely consistent with the proposition that D2 receptors act to reduce the excitability of striatopallidal neurons and their response to glutamatergic synaptic input. D2-receptor-mediated mobilization of intracellular Ca^{2+} leads to negative modulation of Cav1.3 Ca^{2+} channels through a calcineurin-dependent mechanism [32,40]. D2 receptor activation also reduces opening of voltage-dependent Na^+ channels, presumably by a PKC-mediated enhancement of slow inactivation [24]. In addition, D2 receptors promote the opening of K^+ channels [47]. This coordinated modulation of ion channels provides a mechanistic foundation for the ability of D2 receptor agonists to reduce the responsiveness of MSNs in slices at up-state membrane potentials [40]. The dopaminergic modulation of intrinsic and glutamatergic synaptic channels in striatal medium spiny neurons is summarized in Table 1.

The indirect players – striatal interneurons

While considering how DA influences MSN activity, it is impossible to ignore the contribution of interneurons. Most, if not all, of the three types of striatal interneuron express DA receptors [48]. Reviewing this literature is beyond the scope of this article, but a few comments are needed particularly in the context of D2 receptor signaling. The best characterized of the interneurons is the giant, aspiny cholinergic interneuron. In primates, cholinergic interneurons are important determinants of associative and motor learning [49], which are presumably mediated by alterations in the strength of MSN glutamatergic synapses. D2 receptor signaling diminishes acetylcholine (ACh) release both by reducing autonomous interneuron spiking and by inhibiting Ca^{2+} entry necessary for exocytosis [50,51]. ACh has a plethora of intrastriatal targets, including DA terminals [52], glutamatergic terminals [53] and MSNs [53,54]. Although the physiological functions of ACh are multifaceted, its postsynaptic effects on MSNs largely serve to enhance excitability and responsiveness to glutamatergic input. Thus, by reducing ACh release, D2

Table 1. Dopamine modulation of intrinsic and glutamatergic synaptic channels in striatal MSNs

Receptor	Channel	Modulation[a]	Refs
D1	Nav1	↓ Peak current; negative shift of voltage-dependent inactivation	24
	Cav1.2 and Cav1.3	↑ Peak current	30,31
	Cav2	↓ Peak current	38
	NMDA	↑ Peak current; ↑ subunit trafficking	14,20,21,33–35
	GluR1	↑ Surface expression	13,15
D2	Nav1	Negative shift of voltage-dependent inactivation; ↑ slow inactivation	24,26
	Cav1.2 and Cav1.3	↓ Peak current	32,40
	Cav2	↓ Peak current	50
	Kir3	↑ Channel opening	47
	AMPA and GluR1	↓ Peak current; ↓ surface expression	15,20,21

[a]↑ indicates an increase in channel activity; ↓ indicates a decrease in channel activity.

receptors complement their direct effects on MSNs, lowering cellular excitability. The D1 and D2 receptor signaling mechanisms outlined here are summarized in Figure 1.

Long-term depression of glutamatergic synaptic transmission

One of the most commonly described functions of DA in the dorsal striatum is to control the induction of plasticity at glutamatergic synapses. Long-term depression (LTD) at corticostriatal synapses has generated the most work. When postsynaptic depolarization is paired with high frequency stimulation (HFS) of glutamatergic fibers, LTD of synaptic transmission is seen in almost all MSNs. Unlike LTD induced by low frequency stimulation in the ventral striatum [55], LTD induction in the dorsal striatum is not NMDA dependent. There is general agreement that this form of LTD (HFS-LTD) is induced postsynaptically and is dependent upon activation of Cav1.3 L-type Ca^{2+} channels, mGluR1 and mGluR5 receptors and the generation of endocannabinoids (ECs). ECs exert their effect presynaptically, acting at CB_1 receptors, which are necessary for LTD expression [56–58]. There is also general agreement that activation of D2 receptors is necessary for LTD induction. Whether this dependence is direct or indirect is controversial. If postsynaptic D2 receptors are necessary, only D2-receptor-expressing striatopallidal neurons should express HFS-LTD. This clearly is not the case. This has been definitively shown recently using BAC transgenic mice in which D1 and D2 receptor expressing MSNs are labeled with EGFP [59]. In coronal slices, D2 receptor antagonists as well as L-type channel and CB_1 receptor antagonists block HFS-LTD induction in both types of MSN.

There are two theories to explain why D2-receptor-dependent HFS-LTD is detectable in both types of MSN. One theory is that HFS-LTD induction is regulated by cholinergic interneurons acting through ubiquitously expressed M1 muscarinic receptors [60]. Our group has argued that the D2 receptor dependence of LTD stems from the need to lower M1 receptor activity during HFS-LTD induction. This requirement presumably stems from the

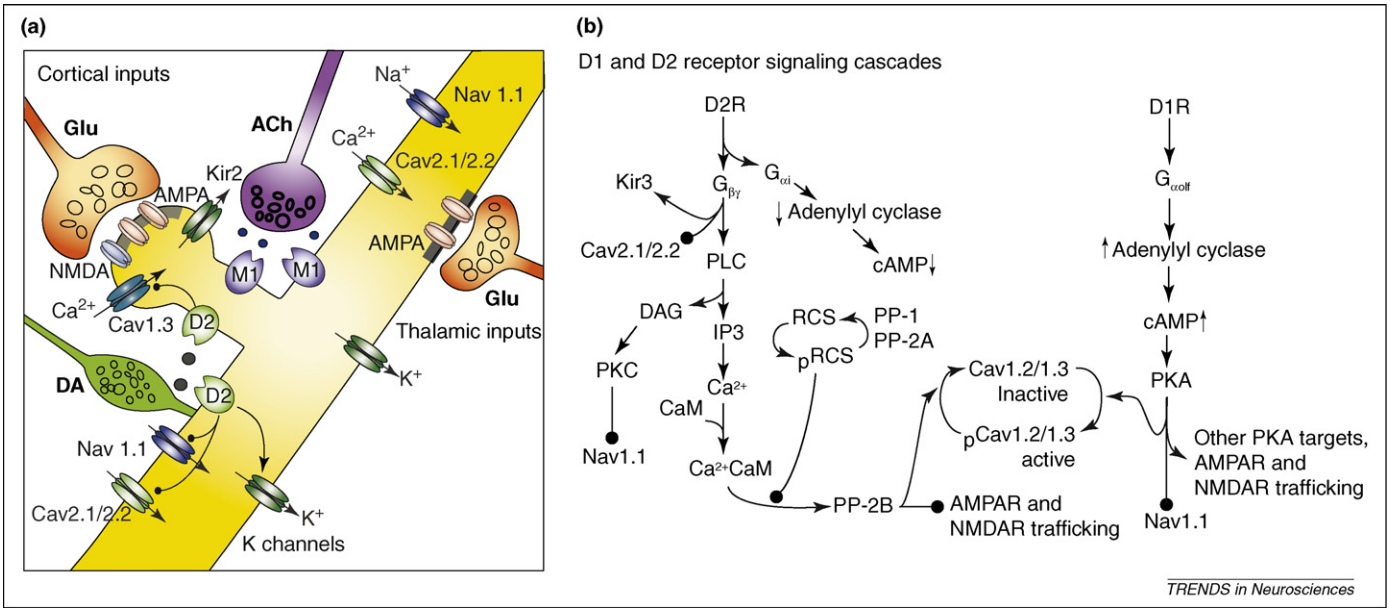

Figure 1. Dopaminergic signaling affecting the integration of glutamatergic signaling in MSNs. **(a)** Schematic representation of a striatopallidal MSN dendrite and spine. DA and muscarinic receptor activation modulates intrinsic excitability by altering the gating of Ca^{2+}, Na^+ and K^+ channels. **(b)** Signal transduction pathways mediating the effects of D1 receptors in striatonigral MSNs and D2 receptors in striatopallidal MSNs. Abbreviations: ACh, acetylcholine; AMPAR, AMPA receptor; DA, dopamine; DAG, 1,2-diacylglycerol; D1R, dopamine D1 receptor; D2R, dopamine D2 receptor; Glu, glutamate; IP3, inositol 1,4,5 trisphosphate; NMDAR, NMDA receptor; PKA, protein kinase A; PKC, protein kinase C; PLC, phospholipase C; PP-2B, protein phosphatase 2B; RCS, regulator of calmodulin signaling.

need to minimize M1 receptor inhibition of L-type Ca^{2+} channels involved in induction. As noted above, cholinergic interneurons robustly express D2 receptors and their activation potently reduces interneuron activity and ACh release. The other theory is that D2 receptor dependent HFS-LTD in D1 MSNs is essentially a 'spill-over' artifact of the induction paradigm when using macroelectrodes to activate glutamatergic synapses [61]. In this scenario, ECs produced in striatopallidal neurons during the induction protocol diffuse to neighboring glutamatergic terminals synapsing on striatonigral MSNs, inducing LTD. Using local microstimulation, Kreitzer and Malenka [61] did not see HFS-LTD in nominal striatonigral MSNs (these were identified not by a D1 BAC mouse but with an M4 BAC mouse). Activation of D2 receptors is a very potent stimulus for EC production [62] and the ability of D2 receptors to activate phospholipase C (PLC) [40] certainly is consistent with a direct involvement in EC production. However, this theory demands that presynaptic CB_1 receptor activation is sufficient for LTD induction – a point of contention [63]. Moreover, it is puzzling that presynaptic CB_1 receptors located on terminals forming synapses on striatonigral neurons appear to be just as potent in inducing short-term inhibition and LTD as those found on terminals forming synapses on striatopallidal neurons.

Another topic germane to this issue is the heterogeneity of the glutamatergic synapses formed on MSNs. Most reviews have focused almost entirely on the cortical innervation of MSNs, leaving the thalamic input to a virtual footnote (Box 1). Studies using nominal white matter or cortical stimulation coronal brain slices typically assume that the glutamatergic fibers being stimulated are of cortical origin but very few of these fibers are left intact in this preparation [64]. The thalamic innervation of MSNs is similar in magnitude to that of the cerebral cortex, perhaps constituting as much as 40% of the total glutamatergic input to MSNs, terminating on both shafts and spines [65]. Anatomical studies indicate that the intralaminar nuclei target primarily striatonigral neurons in the primate striatum; however, this might not be the case in rodents [66], in which 'motor' nuclei [ventroanterior (VA) and ventrolateral (VL) nuclei] project primarily to striatopallidal neurons [65,67]. This apparent dichotomy between motor and 'associative' inputs is consistent with recent studies suggesting that input to striatopallidal neurons comes largely from pyramidal neurons contributing to descending motor control circuits, whereas the input to striatonigral neurons comes from neurons with axons that are largely intra-telencephalic [68]. None of the studies to date examining synaptic plasticity has used preparations that allow cortical or thalamic inputs to be activated selectively or their modulation by DA to be examined.

Long-term potentiation of glutamatergic synaptic transmission

Much less is known about the mechanisms that control induction of long-term potentiation (LTP) than for LTD. Studies in tissue slices have indicated that LTP induced by HFS of corticostriatal glutamatergic inputs (HFS-LTP) depends upon co-activation of D1 and NMDA receptors [69,70]. As noted above, D1 receptor stimulation enhances NMDA receptor currents both directly and indirectly by enhancing L-type Ca^{2+} channels located nearby [21,31], although 'boosting' by L-type channels appears not to be necessary for LTP induction [71]. There was some question about the physiological relevance of LTP in MSNs, but this issue has been resolved by the demonstration that it is readily inducible *in vivo* [72]. The discrepancy presumably stemmed from the difficulty in depolarizing MSN dendrites sufficiently to overcome Mg^{2+} block of NMDA receptors with focal stimulation in a brain slice. How HFS-LTP is expressed has not been carefully examined. As with HFS-LTD, the dependence of a nominally widespread form of synaptic plasticity upon a receptor with restricted distribution is puzzling. BAC transgenic mice in which D1 and D2 receptor expressing MSNs are labeled should be helpful in resolving this issue.

The role of dendritic ion channels in the induction and expression of synaptic plasticity

How does dendritic excitability – and dopaminergic modulation of this excitability – affect the induction and expression of plasticity at glutamatergic synapses? The majority of the studies that have shaped thinking in the field have relied upon recordings from neurons filled with K^+ and Na^+ channel blockers (Cs^+ and QX-314), effectively removing postsynaptic excitability from the plasticity equation. This has been a valuable, simplifying manipulation but it does not mimic the situation *in vivo*. A major challenge in the years to come will be to move beyond this simplification. One way of linking naturally occurring activity patterns to synaptic plasticity is to examine how pairing somatically generated spikes and short bursts of synaptic activity alter synaptic strength [73]. Spike-timing dependent plasticity (STDP) of this sort depends upon back-propagating action potentials (bAPs) that serve to depolarize synaptic regions before, during or after glutamate release. Fino *et al.* [74] reported a form of STDP at corticostriatal synapses. Nothing is known about how DA regulates this form of plasticity. The abundance of DA receptors on dendritic shafts [75,76] certainly creates an opportunity for them to regulate the propagation of bAPs (and STDP) in MSNs; these non-synaptic DA receptors might also modulate synaptically driven up- and down-state transitions in MSNs and plasticity that could be triggered by sustained dendritic Ca^{2+} influx [77].

Concluding remarks

Although we are still some way from a secure grasp of how DA affects the activity of striatal circuits, there are some tentative conclusions that can be drawn. Acting principally through D2 receptors, DA reduces glutamate release as well as the postsynaptic responsiveness of striatopallidal MSNs to released glutamate. This short-term modulation is complemented by D2-receptor-dependent promotion of long-term depression of glutamatergic synaptic transmission. Our grasp of how DA modulates striatonigral MSNs is less secure. Acting principally at postsynaptic D1 receptors in striatonigral MSNs, DA appears to depress weak, asynchronous synaptic signals but to augment the response to strong, coordinated glutamatergic input,

promoting NMDA receptor opening and up-state transitions. In addition, D1 receptor signaling facilitates long-term potentiation of glutamatergic signaling, enhancing network connections that are consistently active during important environmental events that trigger phasic DA release.

What this means for striatal function is far from clear. Alterations in dopaminergic signaling can have profound effects on cognitive and motor function, and are implicated in disorders such as schizophrenia, dystonia, Tourette's syndrome, drug abuse and Parkinson's disease (Box 3). One possible role of striatally released DA is to promote cortically driven action selection. This conjecture is based upon the popular model asserting that activity in striatopallidal MSNs and the indirect pathway serves to suppress action, whereas activity in striatonigral MSNs serves to

Box 3. Dopaminergic modulation of glutamatergic signaling in Parkinson's disease

The relationship between DA and glutamate in Parkinson's disease (PD) has long been the subject of speculation. Since the debut of the now 'classical' model nearly twenty years ago, there have been few direct tests of its predictions and very little hard data generated on how the physiology of MSNs adapts to DA depletion, largely because it has been difficult to distinguish striatonigral and striatopallidal neurons. BAC transgenic mice in which these MSN populations are labeled have changed that situation. The first study of DA depletion using these animals revealed a stark asymmetry between striatopallidal and striatonigral MSNs in their response to the loss of DA [80]. DA depletion led to the loss of glutamatergic synapses and spines of striatopallidal MSNs (Figure Ib). By contrast, DA depletion had no discernible morphological or physiological effect on synaptic function in neighboring striatonigral MSNs. In parallel with the elimination of glutamatergic synaptic contacts, the dendritic trees of striatopallidal neurons shrank, indicating that the overall loss in glutamatergic synaptic input was even more profound. Unlike other adaptations in PD models [81], the extent of the loss did not appear to be significantly different one month after DA depletion, indicating that the regulatory processes controlling synapse elimination are complete within days and dependent upon the loss of DA, not the death of dopaminergic neurons. Although spine and glutamatergic synapse loss after DA depletion had been seen in animal models of PD and in PD patients [82–84], the speed, selectivity and magnitude of the loss was not expected.

Some of the participants in the synaptic pruning have been identified. Genetic deletion or pharmacological blockade of L-type Cav1.3 Ca^{2+} channels prevents the loss of spines and synapses after DA depletion. As noted above, these channels are strategically positioned at spiny glutamatergic synapses [32]. L-type channels contribute to the rise in intraspine Ca^{2+} concentration particularly in response to back-propagating action potentials (bAPs) [22]. DA depletion, by eliminating the D2 receptor 'brake' on somatodendritic excitability [85], could enhance intraspine Ca^{2+} entry. Falling DA levels also increase interneuron ACh release and M1 muscarinic receptor activity in striatopallidal MSNs, further increasing dendritic responsiveness to glutamatergic input (W. Shen and D. Surmeier, unpublished) [86]. Thus, by increasing dendritic excitability and Ca^{2+} entry associated with excitatory glutamatergic input, DA depletion appears to trigger a homeostatic mechanism aimed at normalizing activity (measured by Ca^{2+} entry). As in other neurons [87], this aim is accomplished by reducing the principal source of excitatory drive - glutamatergic synapses. Because striatopallidal medium spiny neurons depend upon temporally convergent glutamatergic synaptic inputs from motor command centers [88], the loss of a substantial portion of this input should profoundly disrupt movement-related, patterned activity and in so doing limit their ability to control the emergence of synchronous bursting in the pallido–subthalamic circuit. The failure to control the pallido–subthalamic circuit should lead to unwanted movements and the cardinal symptom of PD – the inability to translate thought into efficient movement.

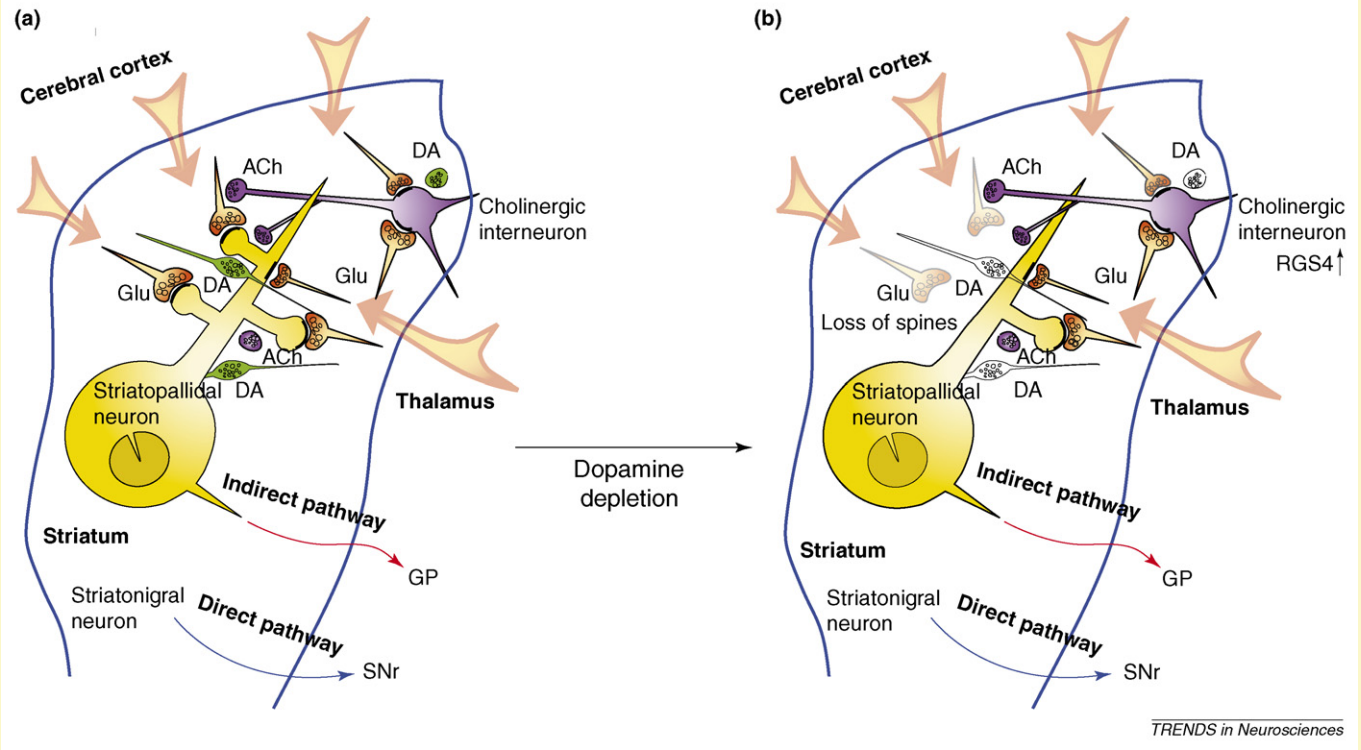

Figure I. Schematic representation summarizing the change in morphology and synaptic connectivity of striatopallidal D2 receptor expressing MSNs following dopamine depletion. Depletion increases the excitability of striatopallidal MSNs and presumably decreases the excitability of striatonigral MSNs [85]. Abbreviations: ACh, acetylcholine; DA, dopamine; Glu, glutamate; GP, globus pallidus; RGS4, regulator of G-protein signalling 4; SNr, substantia nigra pars reticulata.

promote action [78]. Basal striatal DA levels produced by autonomous activity in substantia nigra pars compacta (SNc) DA neurons should act primarily at high affinity D2 receptors expressed by striatopallidal MSNs, preventing them from responding too readily to uncoordinated cortical activity. When SNc DA neurons transiently spike at high frequency in response to environmental cues, low affinity D1 receptors should be activated, transiently enhancing the responsiveness of striatonigral MSNs to properly coordinated cortical 'action commands'; in parallel, this burst of DA cell activity will suppress tonic activity in cholinergic interneurons, potentially synergizing with postsynaptic D2 receptors on striatopallidal MSNs to prevent cortical glutamatergic signals shared with striatonigral MSNs from generating a state-transition, spiking and inappropriate action suppression. In this way, DA might gate the responsiveness of striatal output pathways to shared cortical glutamatergic action commands, preventing co-activation of incompatible action programs.

Acknowledgments

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