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The role of dopamine in modulating the structure and function of striatal circuits

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Abstract

Dopamine (DA) is a key regulator of action selection and associative learning. The striatum has long been thought to be a major locus of DA action in this process. Although all striatal cell types express G protein-coupled receptors for DA, the effects of DA on principal medium spiny neurons (MSNs) understandably have received the most attention. In the two principal classes of MSN, DA receptor expression diverges, with striatonigral MSNs robustly expressing D_1 receptors and striatopallidal MSNs expressing D_2 receptors. In the last couple of years, our understanding of how these receptors and the intracellular signalling cascades that they couple to modulate dendritic physiology and synaptic plasticity has rapidly expanded, fuelled in large measure by the development of new optical and genetic tools. These tools also have enabled a rapid expansion of our understanding of the striatal adaptations in models of Parkinson's disease. This chapter highlights some of the major advances in these areas.

Keywords

Striatum; Dopamine; Synaptic plasticity; Dendritic excitability; Dendritic spines; Parkinson's Disease

Introduction

The dorsal striatum integrates information about sensory, motivational and motor state conveyed by cortical and thalamic neurons, facilitating the selection of actions that achieve desirable outcomes, like reward, and avoid undesirable ones. Current models of how this happens have been built upon the notion that reward prediction errors signalled by mesence phalic dopaminergic neurons innervating the striatum provide a means by which experience shapes the strength of corticostriatal synapses of principal medium spiny neurons (MSNs) and, in so doing, action selection (Cohen and Frank, 2009; Schultz, 2007; Yin and Knowlton, 2006). One of the most compelling pieces of evidence for this view comes from the inability of Parkinson's disease (PD) patients, who have lost their striatal dopaminergic innervation, to translate thought into action (Dujardin and Laurent, 2003).

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Although there is strong support for the basic tenets of these models, precisely how dopamine (DA) modulates the neural circuitry of the dorsal striatum to achieve this end has been the subject of debate. One of the experimental obstacles that has slowed physiological study is the cellular heterogeneity of the striatum and the seemingly random anatomical distribution of cell types within it. The principal neurons of the striatum are MSNs, constituting roughly 90% of all striatal neurons in most mammals (Kawaguchi, 1997). MSNs can be divided into at least two groups based on their DA receptor expression and axonal projection site: striatopallidal MSNs send their principal axonal arbor to the globus pallidus and express high levels of the D_2 DA receptor, whereas striatonigral MSNs send their principal axonal arbor to the substantia nigra and express high levels of the D_1 DA receptor (Gerfen et al., 1990). In physiological studies performed either *in vitro* or *in vivo*, these two types of MSNs have been virtually impossible to tell apart, clouding the interpretation of plasticity studies exploring the role of DA. The recent development of bacterial artificial chromosome (BAC) transgenic mice in which the expression of D_1 or D_2 receptors is reported by expression of red or green fluorescent protein (Gong et al., 2003; Shuen et al., 2008) has eliminated this problem. These studies have revealed that in mice, D_1 and D_2 MSNs differ in their intrinsic excitability and dendritic morphology (Fig. 1) (Day et al., 2008; Gertler et al., 2008). These mice have led to a flurry of discoveries about dopaminergic regulation of intrinsic excitability and striatal synaptic plasticity – providing the primary motivation for this review.

Acute dopaminergic modulation of striatal MSN excitability

D_1 receptors are positively coupled to adenylyl cyclase (type V) through G_{olf} (Herve et al., 1995). Elevation in cytosolic cAMP levels leads to the activation of protein kinase A (PKA). PKA has a variety of intracellular targets that affect cellular excitability. For example, PKA can regulate glutamate receptor trafficking via the phosphoprotein DARPP-32, the tyrosine kinase Fyn or the protein phosphatase striatal-enriched tyrosine phosphatase (STEP) (Braithwaite et al., 2006; Hallett et al., 2006; Lee et al., 2002; Scott et al., 2006; Snyder et al., 2000). Although slightly less clear, D_1 receptor activation may also directly enhance NMDA receptor currents, via L-type voltage-gated calcium channels (Blank et al., 1997; Cepeda et al., 1993; Liu et al., 2004). In addition, D_1 receptor activation has several other consequences on the milieu of conductances being integrated during cellular activity, such as reducing Na^+ channel (likely Nav1.1) conductivity and inhibiting N-type voltage-gated calcium channels (Carr et al., 2003; Kisilevsky et al., 2008; Scheuer and Catterall, 2006; Surmeier and Kitai, 1993). Such actions of D_1 receptors are consistent with the classical notion of D_1 receptor signalling as ‘excitatory’.

D_2 receptors couple to $G_{i/o}$ proteins, leading to inhibition of adenylyl cyclase through $G\alpha_i$ subunits (Stoof and Kebabian, 1984). In parallel, released $Gb\gamma$ subunits are capable of reducing Cav2 Ca^{2+} channel opening and of stimulating phospholipase Cβ isoforms, generating diacylglycerol (DAG) andprotein kinase C (PKC) activation as well as inositol trisphosphate liberation and the mobilization of intracellular Ca^{2+} stores (Hernandez-Lopez et al., 2000; Nishi et al., 1997). D_2 receptors also are capable of transactivating tyrosine kinases (Kotecha et al., 2002).

Studies of voltage-dependent channels are largely consistent with the proposition that D_2 receptors act to reduce the excitability of striatopallidal neurons and their response to glutamatergic synaptic input. Activation of D_2 receptors decreases α-amino-3-hydroxy-5-methyl-4-isoxalone propionic acid (AMPA) receptor currents in MSNs (Cepeda et al., 1993; Hernandez-Echeagaray et al., 2004) and diminishes pre-synaptic glutamate release, although it is unclear if the latter involves pre- or post-synaptically situated D_2 receptors (Bamford et al., 2004; Yin and Lovinger, 2006). D_2 receptor activation has also been shown to negatively modulate Cav1.3 Ca^{2+} channels through a calcineurin-dependent mechanism (Hernandez-Lopez et al., 2000; Olson et al., 2005), reduce opening of voltage-dependent Na^+ channels (presumably by a PKC-mediated enhancement of slow inactivation) (Surmeier and Kitai, 1993) and promote the opening of K^+ channels (Greif et al., 1995). Such actions of D_2 receptors are consistent with the classical notion of D_2 receptor signalling as ‘inhibitory’.

Given the consequences DA has on MSN excitability, post-synaptic response to glutamate and pre-synaptic glutamatergic release, it is not a large conceptual leap to assume that it may play a role in corticostriatal synaptic plasticity. Indeed, the pioneering work of Calabresi and others (1992) utilized rodent tissue slices containing cortex and striatum to demonstrate long-term depression (LTD) in striatal MSNs and pointed to the importance of DA in governing its induction. We have recently made great progress in elucidating the role of DA in both LTD and long-term potentiation (LTP) induction in striatal MSNs. This work will be a focus of the remainder of this chapter.

LTD at glutamatergic synapses on MSNs

The easiest form of synaptic plasticity to see at MSN glutamatergic synapses is LTD (Calabresi et al., 2000). Unlike the situation at many other synapses, striatal LTD induction requires pairing of post-synaptic depolarization with moderate to high-frequency afferent stimulation at physiological temperatures (Calabresi et al., 2000; Kreitzer and Malenka, 2005). Typically for the induction to be successful, post-synaptic L-type calcium channels and G_q-linked mGluR5 receptors need to be co-activated (Kreitzer and Malenka, 2005; Lovinger et al., 1993). Both L-type calcium channels and mGluR5 receptors are found near glutamatergic synapses on MSN spines, making them capable of responding to local synaptic events (Carter and Sabatini, 2004; Carter et al., 2007; Day et al., 2006; Testa et al., 1994). The interaction between these two membrane proteins in the process of LTD induction undoubtedly involves calcium. Recent work showing that prolonging the opening of L-type channels with an allosteric modulator eliminates the need to stimulate mGluR5 receptors (Adermark and Lovinger, 2007), points to shared regulation of dendritic calcium concentration. However, there is an asymmetry, as increasing mGluR5 activation by bath application of agonists does not eliminate the need for L-type calcium channel opening (Kreitzer and Malenka, 2005; Ronesi et al., 2004). This might reflect a requirement for calcium-induced calcium release (CICR) from intracellular stores in LTD induction. In many cell types, CICR depends upon calcium influx through voltage-gated calcium channels, including L-type channels (Nakamura et al., 2000). Activation of mGluR5 and the production of inositol-1,4,5-triphosphate (IP3) could serve to prime these dendritic calcium stores, boosting CICR evoked by activity-dependent calcium entry through L-type calcium

channels and thus promoting LTD induction (Berridge, 1998; Taufiq Ur et al., 2009; Wang et al., 2000).

A key event in the induction of LTD is the post-synaptic generation of endocannabinoids (ECs). ECs diffuse retrogradely to activate pre-synaptic CB1 receptors and decrease glutamate release probability. Having both pre- and post-synaptic induction criteria confers synaptic specificity on LTD expression (Singla et al., 2007). The molecular identity of the metabolic pathway leading to EC production in MSNs is still uncertain. There are two abundant striatal ECs: anandamide and 2-arachidonylglycerol (2-AG). Although previous studies have underscored the neural regulation of anandamide synthesis in the striatum (Giuffrida et al., 1999), collateral support for it has been modest (Ade and Lovinger, 2007). Recent work has provided compelling support for the proposition that 2-AG and its synthetic enzyme diacylglycerol lipase α (DAGLα) are essential (Gao et al., 2010; Lerner et al., 2010; Tanimura et al., 2010). The door is still slightly open for anandamide however. In Lerner et al.'s elegant and focused study, they found that inhibition of DAGLα was effective in preventing LTD induction only in response to moderate frequency afferent stimulation, not to higher frequency stimulation (~100 Hz). Why this would be is unclear. Both DAGLα and phospholipase D (PLD) are calcium-stimulated enzymes (Brenowitz et al., 2006). It could be that PLD requires a greater elevation in post-synaptic calcium concentration that would come with higher frequency afferent stimulation.

One still unresolved question about the induction of striatal LTD is whether activation of D_2 receptors is necessary. Activation of D_2 receptors is a potent stimulus for anandamide production (Giuffrida et al., 1999). However, recent work showing the sufficiency of L-type channel opening in EC-dependent LTD (Adermark and Lovinger, 2007), makes it clear that D_2 receptors play a modulatory – not obligatory – role. The real issue is the role of D_2 receptors in LTD induction using synaptic stimulation. Attempts to address this question using BAC mice have consistently found that in D_2 receptor expressing striatopallidal MSNs, D_2 receptor activation seems to be necessary (Kreitzer and Malenka, 2007; Shen et al., 2008; Wang et al., 2006). This could be due to the need to suppress A2a adenosine receptor signalling that could impede efficient EC synthesis and LTD induction (Fuxe et al., 2007a, 2007b; Shen et al., 2008). Indeed, Lerner et al. demonstrate quite convincingly that antagonism of A2a receptors promotes EC-dependent LTD induction in striatopallidal MSNs (Lerner et al., 2010).

Is EC-dependent LTD inducible in the other major population of MSNs that do not express D_2 receptors – the D_1 receptor dominated striatonigral MSNs? Kreitzer and Malenka (2007) reported that LTD was not inducible in these MSNs using a minimal local stimulation. This result was confirmed subsequently (Fig. 2) (Shen et al., 2008). However, using macroelectrode stimulation, EC-dependent LTD is readily inducible in identified D_1 MSNs (Wang et al., 2006), consistent with the high probability of MSN LTD induction seen in previous work (Calabresi et al., 2007). Thus, the stimulation paradigm seems critical to LTD induction in D_1 MSNs. Why? The problem with these induction protocols is that the type of axon and cell activated by the electrical stimulus is poorly controlled. With intra-striatal stimulation or with nominal white matter stimulation in coronal brain slices, glutamatergic afferent fibres, dopaminergic fibres and fibres intrinsic to the striatum are all activated,

producing a mixture of neuromodulators that makes the interpretation of results less than straightforward. In Kreitzer and Malenka's case, minimal local stimulation of both dopaminergic and glutamatergic fibres appears to be critical to the LTD induction failure, as blocking D_1 receptors unmasked a robust EC-dependent LTD in D_1 MSNs (Shen et al., 2008), establishing a clear parallel to the A2a receptor phenomenon described by Lerner et al. (Lerner et al., 2010). This kind of complication also appears to be responsible for the apparent D_2 receptor dependence of LTD induction in D_1 MSNs using macroelectrodes that more effectively activate cholinergic interneuron axons (Wang et al., 2006).

The neuromodulator mixture created by non-specific electrical stimulation could also be a factor in slice studies implicating nitric oxide (NO) signalling in LTD induction (Calabresi et al., 1999). The principal sources of NO in the striatum are NO synthase expressing interneurons and endothelial cells. Experiments by Sergeeva et al. (2007) implicate both neuronal and endothelial sources of NO in LTD. Calcium entry and stimulation by NO in both cell types presumably occur in response to elevation in extracellular glutamate. In nitric oxide synthase (NOS) interneurons, N-methyl-D-aspartate (NMDA) receptors are necessary for NOS activation (Ondracek et al., 2008). However, this creates a problem in that LTD induction in the dorsal striatum of adult rodents is not NMDA receptor dependent. Recent work by Sergeeva's group has shown that there is a developmental dependence to the signalling mechanisms responsible for NO production and LTD, with engagement of NMDA receptor-stimulated NO production being necessary for EC-dependent LTD induction only in juvenile rodents (Chepkova et al., 2009). This suggests that endothelial cells play a more pivotal role in the adult dorsal striatum. Another interesting aspect of the NO story is where it is acting. MSNs express very high levels of NO-stimulated soluble guanylyl cyclase and protein kinase G (Ariano, 1983). But these cells appear not to be the target of NO in LTD. Rather, it appears that the site of NO action is downstream of CB1 receptor activation, in the pre-synaptic terminal (Sergeeva et al., 2007). How this relates to Lovinger's evidence implicating pre-synaptic gene expression in the expression of LTD is unclear.

The lack of specificity in activating inputs to MSNs during the induction of plasticity also raises questions about the type of glutamatergic synapse being affected by EC-dependent LTD. Studies using nominal white matter or cortical stimulation in a coronal brain slices typically assume that the glutamatergic fibres being stimulated are of cortical origin, but very few of these fibres are left intact in this preparation (Kawaguchi et al., 1989). The thalamic glutamatergic 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 (Smith et al., 2009; Wilson, 2004). As a consequence, it is not really known whether EC-dependent LTD is present at corticostriatal or thalamostriatal synapses or both. The localization of CB1 receptors on corticostriatal terminals, but not thalamostriatal terminals (Uchigashima et al., 2007), is consistent with the hypothesis that LTD is a corticostriatal phenomenon, but more definitive studies are needed. Cutting brain slices in planes that preserve cortical and/or thalamic connectivity is one way to sort this out (Ding et al., 2008; Kawaguchi et al., 1989; Smeal et al., 2007). But these approaches have limitations given the highly convergent nature of the glutamatergic input to MSNs (Wilson, 2004). Optogenetic approaches offer a powerful alternative strategy (Zhang

et al., 2006) that would allow glutamatergic inputs from various cortical and thalamic regions to be dissected.

LTP at glutamatergic synapses on MSNs

Less is known about the mechanisms controlling induction and expression of LTP at glutamatergic synapses. Most of the work describing LTP at glutamatergic synapses has been done with sharp electrodes (either *in vivo* or *in vitro*), not with patch-clamp electrodes in brain slices that afford greater experimental control and definition of the cellular and molecular determinants of induction. However, there have been a number of studies using these approaches in the last few years that have made progress in characterizing LTP mechanisms.

Previous studies have argued that LTP induced in MSNs by pairing high-frequency stimulation of glutamatergic inputs, and post-synaptic depolarization depends upon co-activation of D_1 DA and NMDA receptors (Calabresi et al., 2007). The involvement of NMDA receptors in LTP induction is not controversial. What is controversial is the involvement of D_1 receptors. Robust expression of these receptors is only found in striatonigral MSNs, roughly half of the MSN population, making it difficult to understand how LTP induction could be universally dependent on them unless some rather complicated, indirect mechanism was involved. Again, the advent of BAC transgenic mice has provided a tool to sort this issue out. Using perforated patch recordings to preserve the intracellular milieu controlling the induction of synaptic plasticity, our group found that the induction of LTP at glutamatergic synapses was dependent on D_1 DA receptors only in striatonigral MSNs, not in D_2 receptor expressing striatopallidal MSNs (Fig. 2) (Flajolet et al., 2008; Shen et al., 2008). In D_2 MSNs, LTP induction required activation of A2a adenosine receptors. These receptors are robustly expressed in striatopallidal MSNs and have a very similar intracellular signalling linkage to that of D_1 receptors; that is, they positively couple to adenylyl cyclase and PKA. Acting through PKA, D_1 and A2a receptor activation leads to the phosphorylation of DARPP-32 and a variety of other signalling molecules, including MAPKs, linked to synaptic plasticity (Sweatt, 2004).

The nature of the co-operativity between NMDA receptors and D_1/A2a receptor signalling in the induction of LTP remains to be resolved. This interaction governs the timing dependence of spike timing-dependent plasticity (STDP) (Pawlak and Kerr, 2008; Shen et al., 2008). For example, when D_2 receptors in striatopallidal MSNs were blocked and A2a receptors were stimulated, pairing a short burst of post-synaptic spikes with an excitatory post synaptic potential (EPSP) 10 ms later led to LTP induction, whereas with normal G protein-coupled receptor stimulation this protocol invariably produced LTD. In contrast, in striatonigral MSNs, pairing post-synaptic spiking with a trailing pre-synaptic volley only produced LTD in the absence of D_1 receptor stimulation, suggesting that PKA signalling could abrogate LTD induction. Reversing the order of stimulation gave LTP only when D_1 receptors were stimulated and yielded LTD otherwise, arguing that PKA signalling not only could shut down LTD induction, but was also necessary for LTP induction. Conceptually similar results have been reported in other cell types (Seol et al., 2007; Tzounopoulos et al., 2007), leading to the notion that LTD and LTP induction are governed by ‘opponent

processes' that interact at synaptic sites to determine the sign of synaptic plasticity. Altered activation of these processes could be responsible for 'anti-Hebbian' plasticity reported in the striatum (Fino et al., 2005). How these opponent processes interact with one another and the cellular mechanisms underlying changes in synaptic strength remains to be determined. Given the evidence that PKA signalling can potentiate NMDA receptor currents (Blank et al., 1997; Colwell and Levine, 1995), it is tempting to think that A2a and D_1 receptors promote LTP induction in this way. Molecules like regulator of calmodulin signalling (RCS), whose affinity for calmodulin and negative regulation of calcium signalling is dramatically elevated by PKA phosphorylation, could also contribute to the opponent interaction (Xia and Storm, 2005). The proposition that there is an LTD 'cancelling' signal arising from D_1 or A2a receptors but which requires some measure of co-operativity from NMDA receptor signalling (and CaMKII) would appear to be an economical solution to the plasticity problem, as it makes little sense to allow both processes to proceed independently. Another potential mediator of this interaction is STEP (Braithwaite et al., 2006). Activation of STEP promotes the endocytosis of both NMDA and AMPA receptors and is inactivated by PKA phosphorylation (Tashev et al., 2009; Zhang et al., 2008). Calcium activation of STEP also shortens ERK1/2 and Fyn kinase signalling, establishing a connection to striatal LTP (Dunah et al., 2004; Flajolet et al., 2008; Nguyen et al., 2002; Paul et al., 2003; Pelkey et al., 2002).

The nature of this interaction also has implications for the distal reward problem (Sutton and Barto, 1981). The change in DA release produced by the consequences of action selection occurs later in time than the pre- and post-synaptic activity that produced the action. In theoretical treatments of this issue, there are two strategies for dealing with this temporal delay or distal reward. One way is to have temporally co-incident pre- and post-synaptic activity create an eligibility trace (perhaps expressed as elevated CAMKII or calcineurin) that subsequently can be acted on by an outcome-dependent signal, in this case DA. However, if DA receptor signalling changes the impact of patterned synaptic stimulation on intracellular signalling cascades controlling the induction of plasticity, it is difficult to see how this could work. An alternative approach is to have repeating/reverberating activity or have the outcome event trigger a fictive replay of the action selection (Drew et al., 2006; Genovesio et al., 2006; Tsujimoto and Sawaguchi, 2004). As the corticostriatal pathway is the first leg of a multi-synaptic loop between the cortex, basal ganglia, thalamus and again cortex (Alexander and Crutcher, 1990), it is not hard to imagine how such an approach may work.

Dendritic excitability and synaptic plasticity

Although most of the induction protocols that have been used to study striatal plasticity are decidedly unphysiological, involving sustained, strong depolarization and/or high-frequency synaptic stimulation that induces dendritic depolarization, they do make the necessity of post-synaptic depolarization clear. In a physiological setting, what types of depolarization are likely to gate induction? One possibility is that spikes generated in the axon initial segment (AIS) propagate into dendritic regions where synapses are formed. Recent work has shown that STDP is present in MSNs (Fino et al., 2005; Pawlak and Kerr, 2008; Shen et al., 2008). But there are reasons to believe that this type of plasticity is relevant for only a subset

of the synapses formed on MSNs. MSN dendrites are several hundred microns long, thin and modestly branched. Their initial 20–30 μm are largely devoid of spines and glutamatergic synapses. Glutamatergic synapse and spine density peak near 50 μm from the soma and then modestly decline with distance (Wilson, 2004). Because of their geometry and ion channel expression, AIS generated spikes rapidly decline in amplitude as they invade MSN dendrites (as judged by their ability to open voltage-dependent calcium channels), producing only a modest depolarization 80–100 μm from the soma. This is less than half the way to the dendritic tips (Day et al., 2008), arguing that a large portion of the synaptic surface area is not normally accessible to somatic feedback about the outcome of aggregate synaptic activity. High-frequency, repetitive somatic spiking improves dendritic invasion, but distal (>100 μm) synapses remain relatively inaccessible.

In the more distal dendritic regions, what controls plasticity? The situation in MSNs might be very similar to that found in deep layer pyramidal neurons where somatically generated bAPs do not invade the apical dendritic tuft (Golding et al., 2002). In this region, convergent synaptic stimulation is capable of producing a local calcium spike or plateau potential that produces a strong enough depolarization to open L-type calcium channels, to unblock NMDA receptors and promote plasticity. *In vivo*, convergent synaptic inputs to MSNs can trigger plateau potentials called up-states (Wilson and Kawaguchi, 1996). Although transitions from the resting down-state to the up-state have all the hallmarks of an active, regenerative process (e.g. stereotyped transition kinetics, a narrow range of up-state potentials), transitions are very difficult to manipulate with a sharp electrode impaling the somatic region (Wilson and Kawaguchi, 1996). This suggests that the site of up-state generation is in distal dendritic regions that cannot be easily manipulated. If this were the case, distal dendrites should have ionic conductances that could support a plateau. Calcium imaging using two-photon laser scanning microscopy (2PLSM) has shown that there is robust expression of both low-threshold Cav3 and Cav1 channels in MSN dendrites (Carter and Sabatini, 2004; Carter et al., 2007; Day et al., 2008), a result that has been confirmed using cell-type-specific gene profiling (Day et al., 2006) (unpublished observations). The rich investment of MSN dendrites with strongly rectifying Kir2 K^+ channels also creates a favourable biophysical condition for plateau potential generation.

The question is how the plateaus or up-states are normally generated. Based on the sparse connectivity between individual cortical axons and MSNs (Kincaid et al., 1998; Wilson, 2004), modelling studies have concluded that several hundred pyramidal neurons need to be near simultaneously active for a sufficient amount of current to be injected into dendrites for an up-state to be generated (Stern et al., 1997; Wilson, 2004). These studies have assumed that MSN dendrites are passive. However, if dendrites are not passive but active, then the convergence requirements could be dramatically different. Although glutamate uncaging experiments at proximal spines have not revealed regenerative processes (Carter et al., 2007), the situation could be different at more distal locations. If this is the case, spatial convergence of glutamatergic inputs onto a distal dendrite could induce a local plateau potential capable of pulling the rest of the cell into the up-state, fundamentally altering the impact of synaptic input on other dendrites. This is a way in which spatially convergent excitatory input to one dendrite could gate synaptic input to another. The lack of temporal

correlation between up-state transitions and EPSP-driven spike generation is consistent with a scenario like this one (Stern et al., 1998). If this were how MSNs operated, it would fundamentally change our models of striatal information processing.

In vivo studies of striatal synaptic plasticity have provided an important counterpoint to the perspectives based on reduced *in vitro* preparations. The pioneering work of (Charpier and Deniau, 1997) demonstrated that with more intact input, LTP was readily inducible in MSNs, contrary to the prevailing model. More recently, Stoetzner et al. have shown that the sign of synaptic plasticity in MSNs is influenced by anaesthetic and presumably the degree of cortical synchronization in corticostriatal projections (Stoetzner et al., 2010). In particular, they show that in barbiturate anaesthetized rats, 5 Hz stimulation of motor cortex evokes LTP in the striatum, but that in awake animals the same stimulation induced LTD. A challenge facing the field is how to bridge these observations. Because glutamatergic connections are sparse, it is virtually impossible to reliably stimulate a collection of synapses onto a particular MSN dendrite with an electrode in a brain slice. Optogenetic techniques might provide a feasible alternative strategy. Another strategy would be to employ two-photon laser uncaging (2PLU) of glutamate at visualized synaptic sites (Carter and Sabatini, 2004). These tools are becoming more widely available and should allow the regenerative capacity of MSN dendrites to be tested soon. If it turns out to be the case that up-states are locally generated in dendrites, then it also becomes feasible to characterize their role in the induction of synaptic plasticity. Up-states could be sufficient, as in the apical tuft of pyramidal neurons, or they could simply be necessary by promoting back-propagation of spikes into the distal dendrites (Kerr and Plenz, 2002).

Homeostatic plasticity in PD models

Sorting out how DA regulates synaptic plasticity in striatal MSNs has obvious implications for disease states that are triggered by alterations in the function of dopaminergic neurons. Second in prominence among DA-dependent disorders only to drug abuse, PD is a common neurodegenerative disorder whose motor symptoms are attributable largely to the loss of dopaminergic neurons innervating the dorsal striatum. In the prevailing model, the excitability of the two major populations of MSNs shifts in opposite directions following DA depleting lesions, creating an ‘imbalance’ in the regulation of the motor thalamus favouring suppression of movement (Albin et al., 1989; Wichmann and DeLong, 1996). In particular, D_2 receptor expressing striatopallidal MSNs spike more, whereas D_1 receptor expressing striatonigral MSNs spike less in the PD state. The mechanisms underlying this shift were not known at the time the model was formulated, but have widely been assumed to reflect changes in intrinsic excitability that accompanied loss of inhibitory D_2 receptor signalling and excitatory D_1 receptor signalling. Indeed, studies by our group and others have found electrophysiological support for this view (Mallet et al., 2006; Surmeier et al., 2007).

What about synaptic remodelling? Several studies have suggested that in the absence of DA, synaptic plasticity is lost, essentially ‘freezing’ the striatal circuit in its pre-depleted state (Calabresi et al., 2007; Kreitzer and Malenka, 2007). However, recent studies of defined MSN populations have shown that although DA is necessary for plasticity to be bidirectional

and Hebbian, it is not necessary for the induction of plasticity *per se* (Shen et al., 2008). Following DA depletion, pairing pre-synaptic and post-synaptic activity – regardless of which came first – induced LTP in D_2 MSNs and LTD in D_1 MSNs. This result adds a new dimension to the prevailing model by showing that activity-dependent changes in synaptic strength parallel those of intrinsic excitability following DA depletion. Work *in vivo* examining the responsiveness of anti-dromically identified MSNs to cortical stimulation following unilateral lesions of the striatal dopaminergic innervation is consistent with this broader model (Mallet et al., 2006).

But this poses a problem. Neurons are homeo-static; sustained perturbations in synaptic or intrinsic properties that make neurons spike more or less than their set-point engage homeostatic mechanisms that attempt to bring activity back to the desired level (Marder and Goaillard, 2006; Turrigiano, 1999). One of the most common mechanisms of homeostatic plasticity is to alter synaptic strength or to scale synapses. In striatopallidal MSNs, the elevation in activity following DA depletion triggers a dramatic down-regulation of glutamatergic synapses formed on spines (Fig. 3) (Day et al., 2006). This can be viewed as a form of homeostatic plasticity. Like scaling seen in other cell types, the synaptic modification depends upon calcium entry through voltage-dependent L-type calcium channels that presumably report activity levels.

In an attempt to better characterize the homeo-static mechanisms controlling synapse density in MSNs, striatum from transgenic mice expressing a D_2 receptor reporter construct was co-cultured with wild-type cerebral cortex. In these co-cultures, MSN dendrites develop nearly normal spine density with pre-synaptic glutamatergic terminals (Fig. 4) (Segal et al., 2003; Tian et al., 2010). Sustained (>3 h) depolarization induced a pruning of glutamatergic synapses and spines in striatopallidal MSNs. This pruning was antagonized by dihydropyridines, implicating L-type calcium channels as with DA depletion (Fig. 4) (Day et al., 2006; Neely et al., 2007; Segal et al., 2003). However, unlike the situation *in vivo*, L-type channels with a Cav1.3 pore-forming subunit were not necessary, but rather ones with a Cav1.2 subunit. It could be that this reflects some abnormality in the cultured MSNs. But it seems more likely that this difference is a reflection of local and global mechanisms underlying spine pruning. *In vivo*, low-threshold Cav1.3 channels are located near glutamatergic synapses where they are capable of being activated by synaptic depolarization. Their activation could be important to effective propagation of synaptic depolarization to the soma. Thus, eliminating or antagonizing Cav1.3 channels should attenuate the synaptic consequences of DA depletion, mitigating the homeostatic drive. High-threshold Cav1.2 channels appear to be largely somatic where they report spiking (or strong depolarization). In our experiments, by bath application of elevated potassium, the normal dendritic synaptic mechanisms were bypassed and somatic Cav1.2 channels directly activated. These channels have been implicated in other forms of homeostatic synaptic plasticity induced by global alterations in excitability or synaptic activity (Turrigiano, 1999).

In MSNs, calcium entry through Cav1.2 L-type calcium channels triggered a signalling cascade that led to a transcriptionally dependent spine pruning. The first step in this cascade was activation of the calcium-dependent protein phosphatase calcineurin. Calcineurin dephosphorylates myocyte enhancer factor 2 (MEF2) (Flavell et al., 2006), increasing its

transcriptional activity. As in other neurons (Flavell et al., 2006; Shalizi et al., 2006), MEF2 up-regulation increased the expression of two genes linked to synaptic remodelling – Nur77 and Arc (Fig. 5). These experiments establish a translational framework within which adaptations in striatal synapses that are linked to the symptoms of PD can be explored.

There are other recently described network adaptations relevant to homeostatic plasticity in PD models. For example, although feed-forward inhibition through fast spiking GABAergic interneurons does not appear to be directly altered, low-threshold GABAergic interneurons do elevate their input to at least a subset of MSNs in PD models (Dehorter et al., 2009; Mallet et al., 2005). Recurrent collateral inhibition between MSNs, which is normally strongest between D_2 MSNs, is almost abolished following DA depletion (Taverna et al., 2008). These adaptations in conjunction with enhanced striatopallidal MSN excitability are likely to contribute to the transmission of beta band activity from the cortex through the striatum to the globus pallidus (Murer et al., 2002).

A major gap in the existing literature is a description of the intrinsic changes in MSN excitability following prolonged DA depletion. All the work with identified cell types has relied on short-term (~<1 week) DA depletions (e.g. Day et al., 2006; Kreitzer and Malenka, 2007), but there clearly are slower adaptations that take 3–4 weeks to stabilize. Given the robust differences in the anatomy and intrinsic physiology of striatonigral and striatopallidal MSNs that exist in the normal striatum (Gertler et al., 2008), it is easy to conjecture that these resting differences are due to differential regulation of basal excitability by DA. If that were true, losing DA could trigger homeostatic processes that make MSNs much more alike.

Concluding remarks

In the last few years, our understanding of the mechanisms controlling synaptic plasticity in the corticostriatal circuits has significantly deepened. Although DA is the central player in the induction of plasticity at corticostriatal synapses on principal MSNs, other acetylcholine, adenosine and NO have joined the drama. However, much remains to be done. How the relatively sparse but functionally important interneuron populations contribute to plasticity remains to be clearly defined, although there are a number of recent advances in this area (Gittis et al., 2010; Higley et al., 2009; Martella et al., 2009). The development of transgenic mice expressing Cre in select neuronal populations (and the growing stable of mice with floxed genes) should propel this effort forward and allow a molecular dissection of these mechanisms in coming years. The growing application of optical approaches, like 2PLSM and 2PLU, also promises to yield insights into synaptic integration and plasticity not achievable with any other approach. Coupling these new tools with optogenetic strategies for activating microcircuits relevant to action selection should prove to be a watershed for basal ganglia and motor systems research. These approaches should allow us to gain a better grasp of basal ganglia pathophysiology in disease states – like PD, Huntington's disease and drug abuse – and in so doing develop a new generation of therapeutics.

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Abbreviations

2-AG	2-arachidonylglycerol
2PLSM	2 photon laser scanning microscopy
2PLU	2 photon laser uncaging
AIS	axon initial segment
BAC	bacterial artificial chromosome
DA	dopamine
DAG	diacylglycerol
DAGLα	diacylglycerol lipase α
EC	endocannabinoid
GPCR	G protein-coupled receptor
IP3	inositol 1,4,5-trisphosphate
LTD	long-term depression
LTP	long-term potentiation
MEF2	myocyte enhancer factor 2
MSN	medium spiny neurons
NO	nitric oxide
PKA	protein kinase A
PKC	protein kinase C
PLD	phospholipase D
RCS	regulator of calmodulin signalling
STDP	spike timing-dependent plasticity
STEP	striatal-enriched tyrosine phosphatase

References

Ade KK, Lovinger DM. Anandamide regulates postnatal development of long-term synaptic plasticity in the rat dorsolateral striatum. Journal of Neuroscience. 2007; 27:2403–2409. [PubMed: 17329438]

Adermark L, Lovinger DM. Combined activation of L-type Ca2+ channels and synaptic transmission is sufficient to induce striatal long-term depression. Journal of Neuroscience. 2007; 27:6781–6787. [PubMed: 17581965]

Albin RL, Young AB, Penney JB. The functional anatomy of basal ganglia disorders. Trends in Neurosciences. 1989; 12:366–375. [PubMed: 2479133]

Alexander GE, Crutcher MD. Functional architecture of basal ganglia circuits: Neural substrates of parallel processing. Trends in Neurosciences. 1990; 13:266–271. [PubMed: 1695401]

Ariano MA. Distribution of components of the guanosine 3',5'-phosphate system in rat caudate-putamen. Neuroscience. 1983; 10:707–723. [PubMed: 6139769]

Bamford NS, Zhang H, Schmitz Y, Wu NP, Cepeda C, Levine MS, et al. Heterosynaptic dopamine neuro-transmission selects sets of corticostriatal terminals. Neuron. 2004; 42:653–663. [PubMed: 15157425]

Berridge MJ. Neuronal calcium signaling. Neuron. 1998; 21:13–26. [PubMed: 9697848]

Blank T, Nijholt I, Teichert U, Kugler H, Behrsing H, Fienberg A, et al. The phosphoprotein DARPP-32 mediates cAMP-dependent potentiation of striatal N-methyl-D-aspartate responses. Proceedings of the National Academy of Sciences of the United States of America. 1997; 94:14859–14864. [PubMed: 9405704]

Braithwaite SP, Paul S, Nairn AC, Lombroso PJ. Synaptic plasticity: One STEP at a time. Trends in Neurosciences. 2006; 29:452–458. [PubMed: 16806510]

Brenowitz SD, Best AR, Regehr WG. Sustained elevation of dendritic calcium evokes widespread endocannabinoid release and suppression of synapses onto cerebellar Purkinje cells. Journal of Neuroscience. 2006; 26:6841–6850. [PubMed: 16793891]

Calabresi P, Centonze D, Gubellini P, Marfia GA, Pisani A, Sancesario G, et al. Synaptic transmission in the striatum: From plasticity to neurodegeneration. Progress in Neurobiology. 2000; 61:231–265. [PubMed: 10727775]

Calabresi P, Gubellini P, Centonze D, Sancesario G, Morello M, Giorgi M, et al. A critical role of the nitric oxide/cGMP pathway in corticostriatal long-term depression. Journal of Neuroscience. 1999; 19:2489–2499. [PubMed: 10087063]

Calabresi P, Maj R, Pisani A, Mercuri NB, Bernardi G. Long-term synaptic depression in the striatum: Physiological and pharmacological characterization. Journal of Neuroscience. 1992; 12:4224–4233. [PubMed: 1359031]

Calabresi P, Picconi B, Tozzi A, Di Filippo M. Dopamine-mediated regulation of corticostriatal synaptic plasticity. Trends in Neurosciences. 2007; 30:211–219. [PubMed: 17367873]

Carr DB, Day M, Cantrell AR, Held J, Scheuer T, Catterall WA, et al. Transmitter modulation of slow, activity-dependent alterations in sodium channel availability endows neurons with a novel form of cellular plasticity. Neuron. 2003; 39:793–806. [PubMed: 12948446]

Carter AG, Sabatini BL. State-dependent calcium signaling in dendritic spines of striatal medium spiny neurons. Neuron. 2004; 44:483–493. [PubMed: 15504328]

Carter AG, Soler-Llavina GJ, Sabatini BL. Timing and location of synaptic inputs determine modes of subthreshold integration in striatal medium spiny neurons. Journal of Neuroscience. 2007; 27:8967–8977. [PubMed: 17699678]

Cepeda C, Buchwald NA, Levine MS. Neuromodulatory actions of dopamine in the neostriatum are dependent upon the excitatory amino acid receptor subtypes activated. Proceedings of the National Academy of Sciences of the United States of America. 1993; 90:9576–9580. [PubMed: 7692449]

Charpier S, Deniau JM. *In vivo* activity-dependent plasticity at cortico-striatal connections: Evidence for physiological long-term potentiation. Proceedings of the National Academy of Sciences of the United States of America. 1997; 94:7036–7040. [PubMed: 9192687]

Chepkova AN, Fleischer W, Kazmierczak T, Doreulee N, Haas HL, Sergeeva OA. Developmental alterations of DHPG-induced long-term depression of corticostriatal synaptic transmission: Switch from NMDA receptor-dependent towards CB1 receptor-dependent plasticity. Pflugers Archive. 2009; 459:131–141. [PubMed: 19701770]

Cohen MX, Frank MJ. Neurocomputational models of basal ganglia function in learning, memory and choice. Behavioural Brain Research. 2009; 199:141–156. [PubMed: 18950662]

Colwell CS, Levine MS. Excitatory synaptic transmission in neostriatal neurons: Regulation by cyclic AMP-dependent mechanisms. Journal of Neuroscience. 1995; 15:1704–1713. [PubMed: 7891129]

Day M, Wang Z, Ding J, An X, Ingham CA, Shering AF, et al. Selective elimination of glutamatergic synapses on striatopallidal neurons in Parkinson disease models. Nature Neuroscience. 2006; 9:251–259.

Day M, Wokosin D, Plotkin JL, Tian X, Surmeier DJ. Differential excitability and modulation of striatal medium spiny neuron dendrites. Journal of Neuroscience. 2008; 28:11603–11614. [PubMed: 18987196]

Dehorter N, Guigoni C, Lopez C, Hirsch J, Eusebio A, Ben-Ari Y, et al. Dopamine-deprived striatal GABAergic interneurons burst and generate repetitive gigantic IPSCs in medium spiny neurons. Journal of Neuroscience. 2009; 29:7776–7787. [PubMed: 19535589]

Ding J, Peterson JD, Surmeier DJ. Corticostriatal and thalamostriatal synapses have distinctive properties. Journal of Neuroscience. 2008; 28:6483–6492. [PubMed: 18562619]

Drew TW, McCollough AW, Vogel EK. Event-related potential measures of visual working memory. Clinical EEG and Neuroscience. 2006; 37:286–291. [PubMed: 17073166]

Dujardin K, Laurent B. Dysfunction of the human memory systems: Role of the dopaminergic transmission. Current Opinion in Neurology. 2003; 16(Suppl. 2):S11–S16. [PubMed: 15129845]

Dunah AW, Sirianni AC, Fienberg AA, Bastia E, Schwarzschild MA, Standaert DG. Dopamine D1-dependent trafficking of striatal N-methyl-D-aspartate glutamate receptors requires Fyn protein tyrosine kinase but not DARPP-32. Molecular Pharmacology. 2004; 65:121–129. [PubMed: 14722243]

Fino E, Glowinski J, Venance L. Bidirectional activity-dependent plasticity at corticostriatal synapses. Journal of Neuroscience. 2005; 25:11279–11287. [PubMed: 16339023]

Flajolet M, Wang Z, Futter M, Shen W, Nuangchamnong N, Bendor J, et al. FGF acts as a co-transmitter through adenosine A(2a) receptor to regulate synaptic plasticity. Nature Neuroscience. 2008; 11:1402–1409.

Flavell SW, Cowan CW, Kim TK, Greer PL, Lin Y, Paradis S, et al. Activity-dependent regulation of MEF2 transcription factors suppresses excitatory synapse number. Science. 2006; 311:1008–1012. [PubMed: 16484497]

Fuxe K, Ferre S, Genedani S, Franco R, Agnati LF. Adenosine receptor-dopamine receptor interactions in the basal ganglia and their relevance for brain function. Physiology & Behavior. 2007a; 92:210–217. [PubMed: 17572452]

Fuxe K, Marcellino D, Genedani S, Agnati L. Adenosine A(2a) receptors, dopamine D(2) receptors and their interactions in Parkinson's disease. Movement Disorders. 2007b; 22:1990–2017. [PubMed: 17618524]

Gao Y, Vasilyev DV, Goncalves MB, Howell FV, Hobbs C, Reisenberg M, et al. Loss of retrograde endocannabinoid signaling and reduced adult neurogenesis in diacylglycerol lipase knock-out mice. Journal of Neuroscience. 2010; 30:2017–2024. [PubMed: 20147530]

Genovesio A, Tsujimoto S, Wise SP. Neuronal activity related to elapsed time in prefrontal cortex. Journal of Neurophysiology. 2006; 95:3281–3285. [PubMed: 16421197]

Gerfen CR, Engber TM, Mahan LC, Susel Z, Chase TN, Monsma FJ Jr. et al. D1 and D2 dopamine receptor-regulated gene expression of striatonigral and striatopallidal neurons. Science. 1990; 250:1429–1432. [PubMed: 2147780]

Gertler TS, Chan CS, Surmeier DJ. Dichotomous anatomical properties of adult striatal medium spiny neurons. Journal of Neuroscience. 2008; 28:10814–10824. [PubMed: 18945889]

Gittis AH, Nelson AB, Thwin MT, Palop JJ, Kreitzer AC. Distinct roles of GABAergic inter-neurons in the regulation of striatal output pathways. Journal of Neuroscience. 2010; 30:2223–2234. [PubMed: 20147549]

Giuffrida A, Parsons LH, Kerr TM, Rodriguez de Fonseca F, Navarro M, Piomelli D. Dopamine activation of endogenous cannabinoid signaling in dorsal striatum. Nature Neuroscience. 1999; 2:358–363.

Golding NL, Staff NP, Spruston N. Dendritic spikes as a mechanism for cooperative long-term potentiation. Nature. 2002; 418:326–331. [PubMed: 12124625]

Gong S, Zheng C, Doughty ML, Losos K, Didkovsky N, Schambra UB, et al. A gene expression atlas of the central nervous system based on bacterial artificial chromosomes. Nature. 2003; 425:917–925. [PubMed: 14586460]

Greif GJ, Lin YJ, Liu JC, Freedman JE. Dopamine-modulated potassium channels on rat striatal neurons: Specific activation and cellular expression. Journal of Neuroscience. 1995; 15:4533–4544. [PubMed: 7790922]

Hallett PJ, Spoelgen R, Hyman BT, Standaert DG, Dunah AW. Dopamine D1 activation potentiates striatal NMDA receptors by tyrosine phosphorylation-dependent subunit trafficking. Journal of Neuroscience. 2006; 26:4690–4700. [PubMed: 16641250]

Hernandez-Echeagaray E, Starling AJ, Cepeda C, Levine MS. Modulation of AMPA currents by D2 dopamine receptors in striatal medium-sized spiny neurons: Are dendrites necessary? European Journal of Neuroscience. 2004; 19:2455–2463. [PubMed: 15128399]

Hernandez-Lopez S, Tkatch T, Perez-Garci E, Galarraga E, Bargas J, Hamm H, et al. D2 dopamine receptors in striatal medium spiny neurons reduce L-type ca2+ currents and excitability via a novel PLC[beta]1-IP3-calcineurin-signaling cascade. Journal of Neuroscience. 2000; 20:8987–8995. [PubMed: 11124974]

Herve D, Rogard M, Levi-Strauss M. Molecular analysis of the multiple golf alpha subunit mRNAs in the rat brain. Brain Research Molecular Brain Research. 1995; 32:125–134. [PubMed: 7494450]

Higley MJ, Soler-Llavina GJ, Sabatini BL. Cholinergic modulation of multivesicular release regulates striatal synaptic potency and integration. Nature Neuroscience. 2009; 12:1121–1128.

Kawaguchi Y. Neostriatal cell subtypes and their functional roles. Neuroscience Research. 1997; 27:1–8. [PubMed: 9089693]

Kawaguchi Y, Wilson CJ, Emson PC. Intracellular recording of identified neostriatal patch and matrix spiny cells in a slice preparation preserving cortical inputs. Journal of Neurophysiology. 1989; 62:1052–1068. [PubMed: 2585039]

Kerr JN, Plenz D. Dendritic calcium encodes striatal neuron output during up-states. Journal of Neuroscience. 2002; 22:1499–1512. [PubMed: 11880480]

Kincaid AE, Zheng T, Wilson CJ. Connectivity and convergence of single corticostriatal axons. Journal of Neuroscience. 1998; 18:4722–4731. [PubMed: 9614246]

Kisilevsky AE, Mulligan SJ, Altier C, Iftinca MC, Varela D, Tai C, et al. D1 receptors physically interact with N-type calcium channels to regulate channel distribution and dendritic calcium entry. Neuron. 2008; 58:557–570. [PubMed: 18498737]

Kotecha SA, Oak JN, Jackson MF, Perez Y, Orser BA, Van Tol HH, et al. A D2 class dopamine receptor transactivates a receptor tyrosine kinase to inhibit NMDA receptor transmission. Neuron. 2002; 35:1111–1122. [PubMed: 12354400]

Kreitzer AC, Malenka RC. Dopamine modulation of state-dependent endocannabinoid release and long-term depression in the striatum. Journal of Neuroscience. 2005; 25:10537–10545. [PubMed: 16280591]

Kreitzer AC, Malenka RC. Endocannabinoid-mediated rescue of striatal LTD and motor deficits in Parkinson's disease models. Nature. 2007; 445:643–647. [PubMed: 17287809]

Lee FJ, Xue S, Pei L, Vukusic B, Chery N, Wang Y, et al. Dual regulation of NMDA receptor functions by direct protein-protein interactions with the dopamine D1 receptor. Cell. 2002; 111:219–230. [PubMed: 12408866]

Lerner TN, Horne EA, Stella N, Kreitzer AC. Endocannabinoid signaling mediates psychomotor activation by adenosine A2A antagonists. Journal of Neuroscience. 2010; 30:2160–2164. [PubMed: 20147543]

Liu JC, DeFazio RA, Espinosa-Jeffrey A, Cepeda C, de Vellis J, Levine MS. Calcium modulates dopamine potentiation of N-methyl-D-aspartate responses: Electrophysiological and imaging evidence. Journal of Neuroscience Research. 2004; 76:315–322. [PubMed: 15079860]

Lovinger DM, Tyler EC, Merritt A. Short- and long-term synaptic depression in rat neostriatum. Journal of Neurophysiology. 1993; 70:1937–1949. [PubMed: 7905031]

Mallet N, Ballion B, Le Moine C, Gonon F. Cortical inputs and GABA interneurons imbalance projection neurons in the striatum of Parkinsonian rats. Journal of Neuroscience. 2006; 26:3875–3884. [PubMed: 16597742]

Mallet N, Le Moine C, Charpier S, Gonon F. Feedforward inhibition of projection neurons by fast-spiking GABA interneurons in the rat striatum *in vivo*. Journal of Neuroscience. 2005; 25:3857–3869. [PubMed: 15829638]

Marder E, Goaillard JM. Variability, compensation and homeostasis in neuron and network function. Nature Reviews. Neuroscience. 2006; 7:563–574.

Martella G, Tassone A, Sciamanna G, Platania P, Cuomo D, Viscomi MT, et al. Impairment of bidirectional synaptic plasticity in the striatum of a mouse model of DYT1 dystonia: Role of endogenous acetylcholine. Brain. 2009; 132:2336–2349. [PubMed: 19641103]

Murer MG, Tseng KY, Kasanetz F, Belluscio M, Riquelme LA. Brain oscillations, medium spiny neurons, and dopamine. Cellular and Molecular Neurobiology. 2002; 22:611–632. [PubMed: 12585682]

Nakamura T, Nakamura K, Lasser-Ross N, Barbara JG, Sandler VM, Ross WN. Inositol 1,4,5-trisphosphate (IP3)-mediated ca2+ release evoked by metabotropic agonists and backpropagating action potentials in hippocampal CA1 pyramidal neurons. Journal of Neuroscience. 2000; 20:8365–8376. [PubMed: 11069943]

Neely MD, Schmidt DE, Deutch AY. Cortical regulation of dopamine depletion-induced dendritic spine loss in striatal medium spiny neurons. Neuroscience. 2007; 149:457–464. [PubMed: 17888581]

Nguyen TH, Liu J, Lombroso PJ. Striatal enriched phosphatase 61 dephosphorylates Fyn at phosphotyrosine 420. The Journal of Biological Chemistry. 2002; 277:24274–24279. [PubMed: 11983687]

Nishi A, Snyder GL, Greengard P. Bidirectional regulation of DARPP-32 phosphorylation by dopamine. Journal of Neuroscience. 1997; 17:8147–8155. [PubMed: 9334390]

Olson PA, Tkatch T, Hernandez-Lopez S, Ulrich S, Ilijic E, Mugnaini E, et al. G-protein-coupled receptor modulation of striatal CaV1.3 L-Type Ca2+ channels is dependent on a shank-binding domain. Journal of Neuroscience. 2005; 25:1050–1062. [PubMed: 15689540]

Ondracek JM, Dec A, Hoque KE, Lim SA, Rasouli G, Indorkar RP, et al. Feed-forward excitation of striatal neuron activity by frontal cortical activation of nitric oxide signaling *in vivo*. European Journal of Neuroscience. 2008; 27:1739–1754. [PubMed: 18371082]

Paul S, Nairn AC, Wang P, Lombroso PJ. NMDA-mediated activation of the tyrosine phosphatase STEP regulates the duration of ERK signaling. Nature Neuroscience. 2003; 6:34–42.

Pawlak V, Kerr JN. Dopamine receptor activation is required for corticostriatal spike-timing-dependent plasticity. Journal of Neuroscience. 2008; 28:2435–2446. [PubMed: 18322089]

Pelkey KA, Askalan R, Paul S, Kalia LV, Nguyen TH, Pitcher GM, et al. Tyrosine phosphatase STEP is a tonic brake on induction of long-term potentiation. Neuron. 2002; 34:127–138. [PubMed: 11931747]

Ronesi J, Gerdeman GL, Lovinger DM. Disruption of endocannabinoid release and striatal long-term depression by postsynaptic blockade of endocannabinoid membrane transport. Journal of Neuroscience. 2004; 24:1673–1679. [PubMed: 14973237]

Scheuer T, Catterall WA. Control of neuronal excitability by phosphorylation and dephosphorylation of sodium channels. Biochemical Society Transactions. 2006; 34:1299–1302. [PubMed: 17073806]

Schultz W. Multiple dopamine functions at different time courses. Annual Review of Neuroscience. 2007; 30:259–288.

Scott L, Zelenin S, Malmersjo S, Kowalewski JM, Markus EZ, Nairn AC, et al. Allosteric changes of the NMDA receptor trap diffusible dopamine 1 receptors in spines. Proceedings of the National Academy of Sciences of the United States of America. 2006; 103:762–767. [PubMed: 16407151]

Segal M, Greenberger V, Korkotian E. Formation of dendritic spines in cultured striatal neurons depends on excitatory afferent activity. European Journal of Neuroscience. 2003; 17:2573–2585. [PubMed: 12823464]

Seol GH, Ziburkus J, Huang S, Song L, Kim IT, Takamiya K, et al. Neuromodulators control the polarity of spike-timing-dependent synaptic plasticity. Neuron. 2007; 55:919–929. [PubMed: 17880895]

Sergeeva OA, Doreulee N, Chepkova AN, Kazmierczak T, Haas HL. Long-term depression of corticostriatal synaptic transmission by DHPG depends on endocannabinoid release and nitric oxide synthesis. European Journal of Neuroscience. 2007; 26:1889–1894. [PubMed: 17868368]

Shalizi A, Gaudilliere B, Yuan Z, Stegmuller J, Shirogane T, Ge Q, et al. A calcium-regulated MEF2 sumoylation switch controls postsynaptic differentiation. Science. 2006; 311:1012–1017. [PubMed: 16484498]

Shen W, Flajolet M, Greengard P, Surmeier DJ. Dichotomous dopaminergic control of striatal synaptic plasticity. Science. 2008; 321:848–851. [PubMed: 18687967]

Shuen JA, Chen M, Gloss B, Calakos N. Drd1atdTomato BAC transgenic mice for simultaneous visualization of medium spiny neurons in the direct and indirect pathways of the basal ganglia. Journal of Neuroscience. 2008; 28:2681–2685. [PubMed: 18337395]

Singla S, Kreitzer AC, Malenka RC. Mechanisms for synapse specificity during striatal long-term depression. Journal of Neuroscience. 2007; 27:5260–5264. [PubMed: 17494712]

Smeal RM, Gaspar RC, Keefe KA, Wilcox KS. A rat brain slice preparation for characterizing both thalamostriatal and corticostriatal afferents. Journal of Neuroscience Methods. 2007; 159:224–235. [PubMed: 16899300]

Smith Y, Villalba RM, Raju DV. Striatal spine plasticity in Parkinson's disease: Pathological or not? Parkinsonism & Related Disorders. 2009; 15(Suppl. 3):S156–S161. [PubMed: 20082980]

Snyder GL, Allen PB, Fienberg AA, Valle CG, Huganir RL, Nairn AC, et al. Regulation of phosphorylation of the GluR1 AMPA receptor in the neostriatum by dopamine and psychostimulants *in vivo*. Journal of Neuroscience. 2000; 20:4480–4488. [PubMed: 10844017]

Stern EA, Jaeger D, Wilson CJ. Membrane potential synchrony of simultaneously recorded striatal spiny neurons *in vivo*. Nature. 1998; 394:475–478. [PubMed: 9697769]

Stern EA, Kincaid AE, Wilson CJ. Spontaneous subthreshold membrane potential fluctuations and action potential variability of rat corticostriatal and striatal neurons *in vivo*. Journal of Neurophysiology. 1997; 77:1697–1715. [PubMed: 9114230]

Stoetzner CR, Pettibone JR, Berke JD. State-dependent plasticity of the corticostriatal pathway. Neuroscience. 2010; 165:1013–1018. [PubMed: 19932155]

Stoof JC, Kebabian JW. Two dopamine receptors: Biochemistry, physiology and pharmacology. Life Sciences. 1984; 35:2281–2296. [PubMed: 6390056]

Surmeier DJ, Kitai ST. D1 and D2 dopamine receptor modulation of sodium and potassium currents in rat neostriatal neurons. Progress in Brain Research. 1993; 99:309–324. [PubMed: 7906427]

Surmeier DJ, Ding J, Day M, Wang Z, Shen W. D1 and D2 dopamine-receptor modulation of striatal glutamatergic signaling in striatal medium spiny neurons. Trends in Neurosciences. 2007; 30:228–235. [PubMed: 17408758]

Sutton RS, Barto AG. Toward a modern theory of adaptive networks: Expectation and prediction. Psychological Review. 1981; 88:135–170. [PubMed: 7291377]

Sweatt JD. Mitogen-activated protein kinases in synaptic plasticity and memory. Current Opinion in Neurobiology. 2004; 14:311–317. [PubMed: 15194111]

Tanimura A, Yamazaki M, Hashimotodani Y, Uchigashima M, Kawata S, Abe M, et al. The endocannabinoid 2-arachidonoylglycerol produced by diacylglycerol lipase alpha mediates retrograde suppression of synaptic transmission. Neuron. 2010; 65:320–327. [PubMed: 20159446]

Tashev R, Moura PJ, Venkitaramani DV, Prosperetti C, Centonze D, Paul S, et al. A substrate trapping mutant form of striatal-enriched protein tyrosine phosphatase prevents amphetamine-induced stereotypes and long-term potentiation in the striatum. Biological Psychiatry. 2009; 65:637–645. [PubMed: 19026408]

Taufiq Ur R, Skupin A, Falcke M, Taylor CW. Clustering of InsP3 receptors by InsP3 retunes their regulation by InsP3 and Ca2+. Nature. 2009; 458:655–659. [PubMed: 19348050]

Taverna S, Ilijic E, Surmeier DJ. Recurrent collateral connections of striatal medium spiny neurons are disrupted in models of Parkinson's disease. Journal of Neuroscience. 2008; 28:5504–5512. [PubMed: 18495884]

Testa CM, Standaert DG, Young AB, Penney JB Jr. Metabotropic glutamate receptor mRNA expression in the basal ganglia of the rat. Journal of Neuroscience. 1994; 14:3005–3018. [PubMed: 8182455]

Tian X, Kai L, Hockberger PE, Wokosin DL, Surmeier DJ. MEF-2 regulates activity-dependent spine loss in striatopallidal medium spiny neurons. Molecular and Cellular Neuroscience. 2010; 44(1): 94–108. [PubMed: 20197093]

Tsujimoto S, Sawaguchi T. Neuronal representation of response-outcome in the primate prefrontal cortex. Cerebral Cortex. 2004; 14:47–55. [PubMed: 14654456]

Turrigiano GG. Homeostatic plasticity in neuronal networks: The more things change, the more they stay the same. Trends in Neurosciences. 1999; 22:221–227. [PubMed: 10322495]

Tzounopoulos T, Rubio ME, Keen JE, Trussell LO. Coactivation of pre- and postsynaptic signaling mechanisms determines cell-specific spike-timing-dependent plasticity. Neuron. 2007; 54:291–301. [PubMed: 17442249]

Uchigashima M, Narushima M, Fukaya M, Katona I, Kano M, Watanabe M. Subcellular arrangement of molecules for 2-arachidonoyl-glycerol-mediated retrograde signaling and its physiological contribution to synaptic modulation in the striatum. Journal of Neuroscience. 2007; 27:3663–3676. [PubMed: 17409230]

Wang SS, Denk W, Hausser M. Coincidence detection in single dendritic spines mediated by calcium release. Nature Neuroscience. 2000; 3:1266–1273.

Wang Z, Kai L, Day M, Ronesi J, Yin HH, Ding J, et al. Dopaminergic control of corticostriatal long-term synaptic depression in medium spiny neurons is mediated by cholinergic interneurons. Neuron. 2006; 50:443–452. [PubMed: 16675398]

Wichmann T, DeLong MR. Functional and pathophysiological models of the basal ganglia. Current Opinion in Neurobiology. 1996; 6:751–758. [PubMed: 9000030]

Wilson, CJ. Basal ganglia.. In: Shepherd, GM., editor. The synaptic organization of the brain. Vol. 5. Oxford UP; Oxford: 2004. p. 361-414.

Wilson CJ, Kawaguchi Y. The origins of two-state spontaneous membrane potential fluctuations of neostriatal spiny neurons. Journal of Neuroscience. 1996; 16:2397–2410. [PubMed: 8601819]

Xia Z, Storm DR. The role of calmodulin as a signal integrator for synaptic plasticity. Nature Reviews Neuroscience. 2005; 6:267–276.

Yin HH, Knowlton BJ. The role of the basal ganglia in habit formation. Nature Reviews Neuroscience. 2006; 7:464–476.

Yin HH, Lovinger DM. Frequency-specific and D2 receptor-mediated inhibition of glutamate release by retrograde endocannabinoid signaling. Proceedings of the National Academy of Sciences of the United States of America. 2006; 103:8251–8256. [PubMed: 16698932]

Zhang Y, Venkitaramani DV, Gladding CM, Kurup P, Molnar E, Collingridge GL, et al. The tyrosine phosphatase STEP mediates AMPA receptor endocytosis after metabotropic glutamate receptor stimulation. Journal of Neuroscience. 2008; 28:10561–10566. [PubMed: 18923032]

Zhang F, Wang LP, Boyden ES, Deisseroth K. Channelrhodopsin-2 and optical control of excitable cells. Nature Methods. 2006; 3:785–792. [PubMed: 16990810]

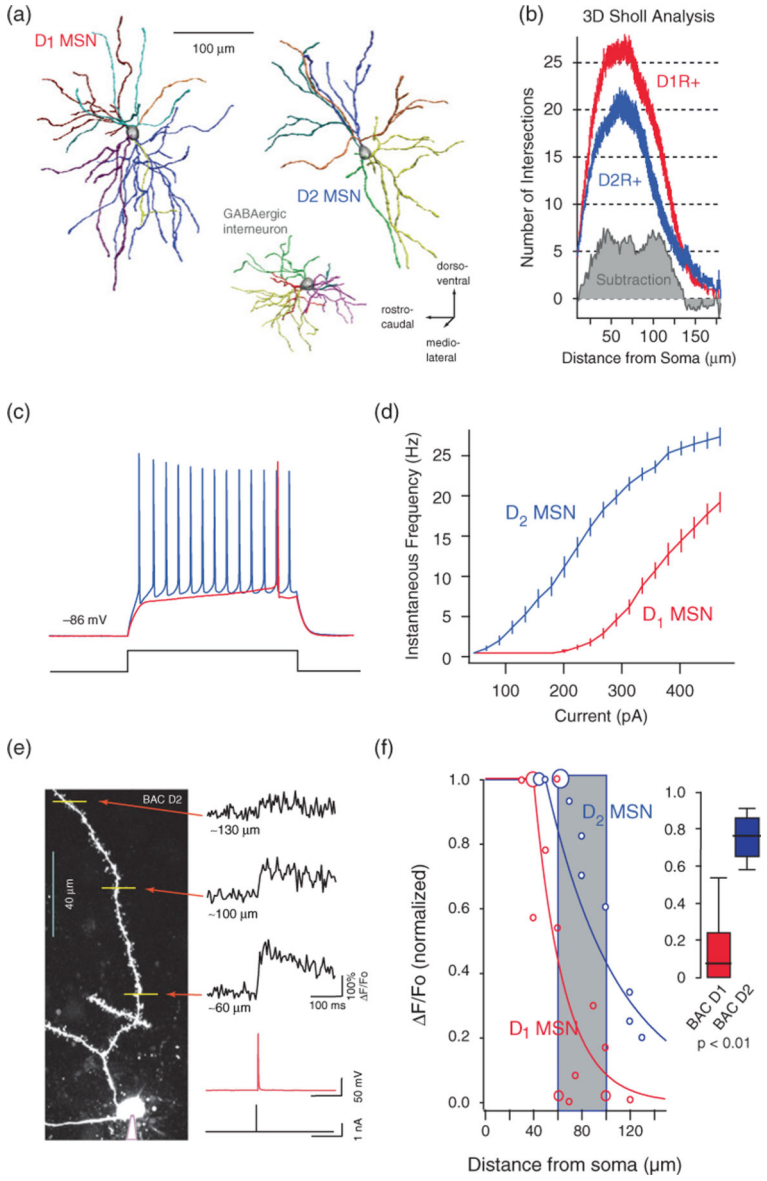

Fig. 1.

D_1 and D_2 MSNs are differentially excitable. (a) Reconstructions of biocytin-filled D_1 and D_2 MSNs. Striatal neurons from P35–P45 BAC transgenic mice were biocytin filled, imaged and reconstructed in three dimensions. A GABAergic interneuron is included for comparison. (b) Analysis of anatomical differences between reconstructed D_1 and D_2 MSNs. A three-dimensional Sholl analysis of biocytin filled and reconstructed neurons from P35–P45 BAC transgenic mice. Data are shown as mean (±SEM) number of intersections at 1 µm eccentricities from the soma for 15 D_1 and 16 D_2 MSNs. D1 MSNs have a more highly branched dendritic tree, as indicated by the increased number of intersections and positive subtracted area (grey shading). (c) Membrane responses to intra-somatic current injection reveal divergence in excitability of D_1 and D_2 MSNs (d) The higher excitability in the D2 MSN population is illustrated in an F–I plot. (e) Maximum intensity projection image of a D_2 MSN using 2PLSM (left) loaded with Alexa Fluor 568 and Fluo-4. Somatic APs

were induced and corresponding spine calcium transients were measured at three distances from the soma (line scans indicated by yellow lines) and shown to the right. (f) The decrementation of somatic AP-induced dendritic calcium transients along a dendrite is compared between D_1 (n = 11) and D_2 (n = 6) MSNs. The data show bAP invasion into MSN dendrites degrades faster in D_1 vs. D_2 MSNs (Mann–Whitney rank sum test). Figure modified from Day et al. (2008) and Gertler et al. (2008).

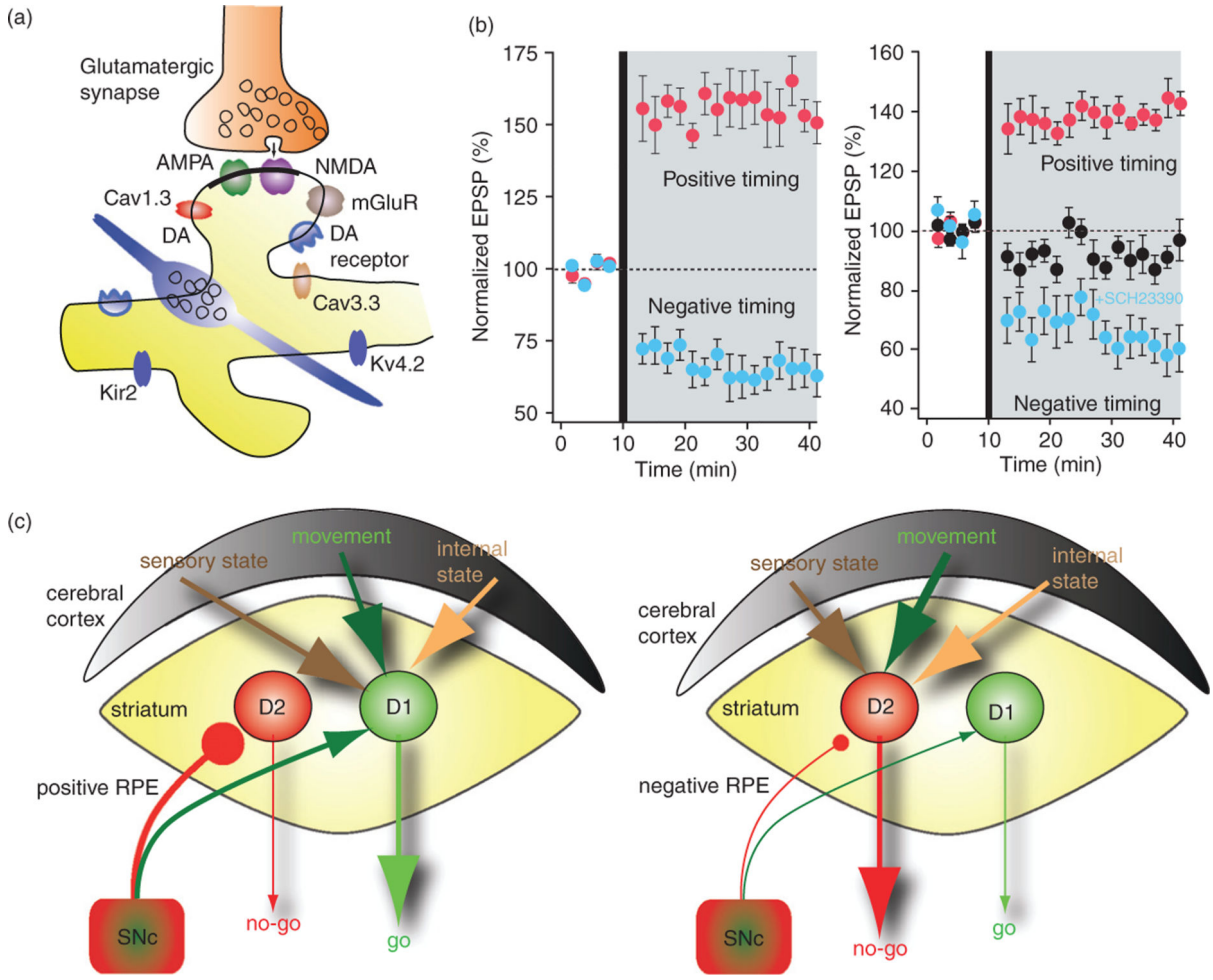

Fig. 2.

STDP in D_1 and D_2 MSNs. (a) Model of a typical MSN dendritic spine, showing glutamatergic and dopaminergic inputs. (b) (Left) Positive spike timing (theta burst patterns of pre- and post-synaptic stimulation, pre-synaptic stimulation at –5 ms) produces LTP and negative spike timing (pre-synaptic stimulation at +10 ms) produces LTD in D_2 MSNs. (Right) Positive spike timing produces LTP, whereas negative timing does not induce plastic changes in D_1 MSNs. When D_1 receptors are blocked by SCH23390, however, negative timing induced LTD is unmasked. (c) Model showing the behavioural consequences of differential corticostriatal STDP on D_2 and D_1 MSNs. Figure modified from Shen et al. (2008).

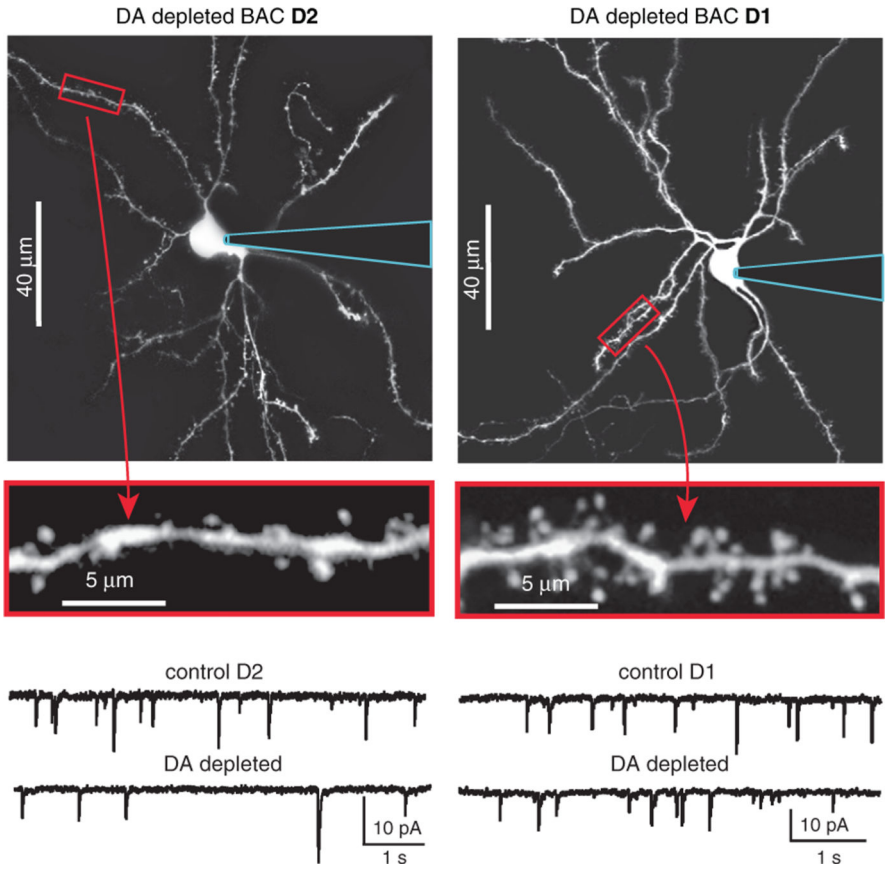

Fig. 3.

Dopamine depletion causes a reduction in spine density in D_2 MSNs but not D_1 MSNs. Alexa 594 loaded D_2 (left) and D_1(right) MSNs 5 days after dopamine depletion (reserpine). High-power images of spines indicated by red boxes are shown below. After dopamine depletion spine density is significantly decreased in D_2 MSNs, but appears normal in D_1 MSNs. mEPSC traces taken from control and dopamine depleted MSNs (bottom) show that following dopamine depletion mEPSC frequency is decreased in D_2 MSNs but unaltered in D_1 MSNs, correlating with the observed change in spine density. Figure modified from Day et al. (2006).

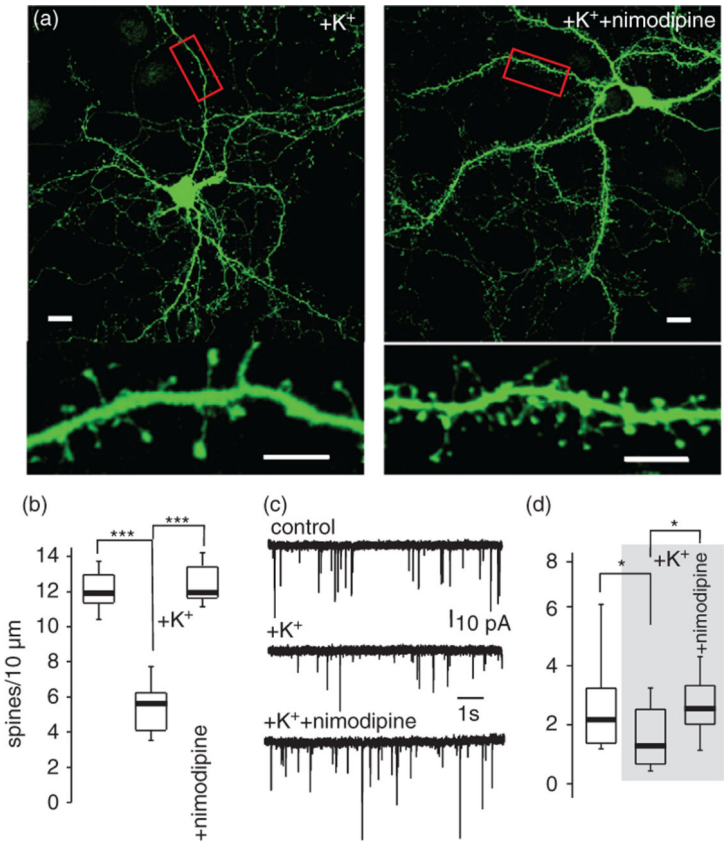

Fig. 4.

L-type Ca^{2+} channels are necessary for spine and synapse elimination. (a) Images of D_2 MSNs in corticostriatal co-cultures treated with 35 mM KCl and ionotropic receptor blockers for 24 h, in absence or presence of 10 μM nimodipine. Bar, upper panels 10 μm; lower panels, 5 μm. (b) Quantification of spine density showing that nimodipine blocked the membrane depolarization-induced spine loss (control, median = 11.9, n = 15; $+K^+$, median = 5.6, n = 18; $+K^+$+nimodipine, median = 11.9, n = 13). (c) Examples of mEPSCs recording from the D_2 MSNs treated as in (a). (d) Box plot showing membrane depolarization resulted in reduction of mEPSC frequency (control, median = 2.17, n = 19; $+K^+$, median = 1.29, n = 14), which was blocked by nimodipine ($+K^+$+nimodipine, median = 2.92, n = 18). * p < 0.05, *** p < 0.001, Mann–Whitney rank sum test. Figure taken from Tian et al. (2010).

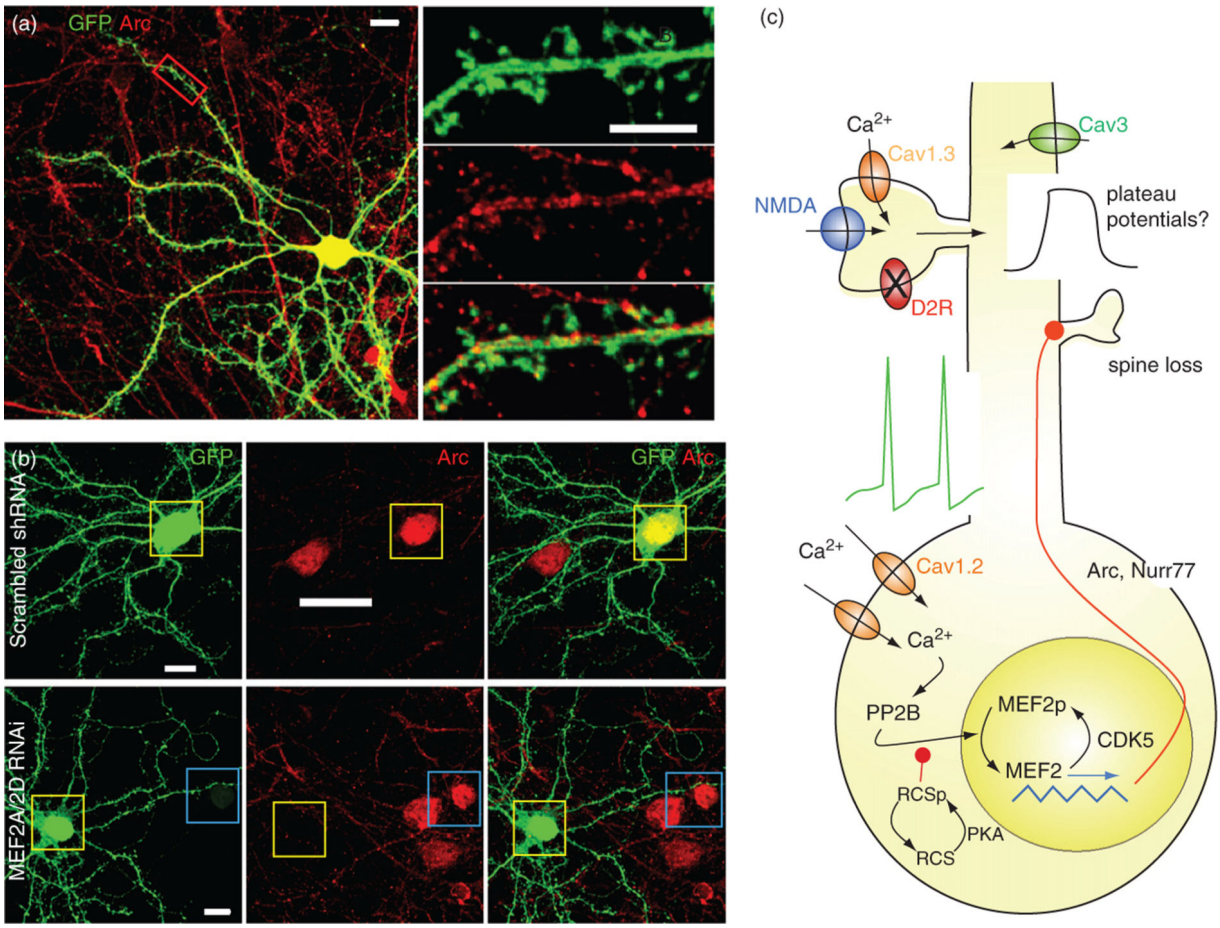

Fig. 5.

Membrane depolarization induces MEF2-dependent Arc expression. (a) A D_2 MSN in a corticostriatal co-culture treated with 35 mM KCl and ionotropic receptor blockers for 2 h and stained with anti-GFP and anti-Arc antibodies. High-magnification images (right panels) show Arc expression in dendrites. (b) Images of D_2 MSNs in corticostriatal co-cultures transfected with indicated shRNAs and depolarized for 2 h. Transfected cells are shown in yellow squares, an untransfected cell is shown in a blue square. (c) Model showing the cellular signaling that mediates the spine loss in D_2 MSNs. Scale bars: low-magnification images, 10 μm; high-magnification images 5 μm. Figure taken from Tian et al. (2010).