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Neuromodulatory control of striatal plasticity and behavior

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Excitatory synapses onto projection neurons in the striatum, the input nucleus of the basal ganglia, play a key role in regulating basal ganglia circuit function and are a major site of long-term synaptic plasticity. Here, we review the mechanisms and regulation of both long-term potentiation and long-term depression at these synapses. In particular, we highlight the role that neuromodulators play in determining the strength and direction of plasticity, which ultimately shapes the balance of activity in basal ganglia circuits and regulates motor behavior.

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Introduction

The basal ganglia are a network of subcortical brain nuclei important for action selection and motor learning [1–4]. Our understanding of basal ganglia circuit function has long been dominated by the classic Albin-DeLong model, based on the clinical manifestations of Parkinson's and Huntington's Diseases. In this model, information flows through the basal ganglia in two parallel circuits – the direct and the indirect pathways – which diverge from the main input nucleus of the basal ganglia, the striatum, and converge again in the output nuclei of the basal ganglia. The Albin-DeLong model postulates that increased activity of the direct pathway facilitates movement, whereas increased activity of the indirect pathway inhibits movement. While this is an oversimplification of the complex basal ganglia circuit (for review see [5]), recent tests of the model have lent support to its general structure. Using viral-mediated cell-type-specific expression of channelrhodopsin-2, our lab demonstrated that firing rates of direct-pathway and indirect-pathway medium spiny neurons (MSNs), the projection neurons of the striatum, control different aspects of movement in the directions predicted by the Albin-DeLong model [6]. Further evidence for this hypothesis comes from experiments that selectively lesioned indirect-pathway MSNs, a manipulation that led to dramatic increases in locomotor behavior [7].

Given that the firing rates of direct-pathway and indirect-pathway MSNs directly influence movement, it is important to ask what physiological mechanisms regulate MSN firing rates. In order to fire any spikes at all, MSNs rely on excitatory input from cortex and thalamus [8]. Therefore, modulation of excitatory synaptic input strength should be particularly effective at modulating MSN firing rates. Indeed, plasticity at excitatory synapses onto MSNs is involved in motor skill acquisition [9,10], and is disrupted in animal models of movement disorders, including Parkinson's disease and dystonia [11••,12••,13–16].

Although synaptic plasticity at excitatory inputs to MSNs has been studied extensively, the detailed mechanisms underlying its expression and regulation remain unknown. Fortunately, our understanding of plasticity in the striatum has benefitted greatly from the recent generation and use of BAC transgenic lines that allow easy identification of MSNs of the direct and indirect pathways [17,18]. The BAC reporter lines rely on the differential expression of G-protein-coupled receptors (GPCRs) in the two types of MSNs: indirect-pathway neurons selectively express G_i-coupled dopamine D2 and G_s-coupled adenosine A2A receptors, whereas direct-pathway neurons selectively express G_i-coupled muscarinic acetylcholine M4 receptors and G_s-coupled dopamine D1 receptors. Thus, fluorescent proteins expressed from the promoters of these receptors selectively label either the indirect or the direct pathway. Differential expression of these G_i and G_s-coupled GPCRs by the two MSN subtypes is not just an experimentally useful coincidence, but reflects important differences in the way that the neuromodulators dopamine, adenosine, and acetylcholine control plasticity in the two pathways. Understanding the molecular mechanisms that regulate LTP and LTD in the striatum is crucial because it will allow us to better understand the circuit-level mechanisms that underlie action selection and motor learning by the basal ganglia circuit. Furthermore, understanding the mechanisms by which dopamine, adenosine, and acetylcholine control striatal plasticity and basal ganglia circuit function will aid the search for new treatments for Parkinson's disease and other basal ganglia disorders.

Indirect-pathway LTD

In indirect-pathway MSNs, long-term depression (LTD) of excitatory inputs occurs in response to high frequency

(100 Hz) stimulation paired with postsynaptic depolarization, or in response to negative spike timing (i.e. synaptic stimulation delivered shortly after the MSN spikes) [11••,12••,19–21]. The mechanisms underlying indirect-pathway LTD appear to be similar using both protocols. LTD is induced postsynaptically by activation of G_q-coupled mGluRs and L-type calcium channels, which together lead to the mobilization of endocannabinoids [11••,12••,22–24]. Endocannabinoids then travel retrogradely across the synaptic cleft and activate presynaptic CB1 receptors [22,25]. Prolonged activation of CB1 receptors (several minutes) leads to presynaptic expression of LTD as a decrease in release probability [26]. Successful induction of indirect-pathway LTD requires activation of dopamine D2 receptors, but also lack of activation of postsynaptic adenosine A2A receptors [12••,27•]. Thus, by regulating the activation of these GPCRs, dopamine and adenosine gate LTD induction in indirect-pathway MSNs.

The most likely downstream mediator of D2 and A2A receptor signaling is cAMP. D2 and A2A receptors are oppositely coupled to cAMP accumulation, just as they are to LTD induction. Additionally, adenylyl cyclase 5 knockout mice have impaired indirect-pathway LTD and the mechanism of LTD impairment is upstream of G_q-coupled mGluRs [28•]. We do not, however, understand the mechanism of D2 and A2A receptor modulation of LTD downstream of cAMP. Is PKA involved? If so, what are its relevant substrates? Mapping out the convergent signaling cascades of D2, A2A, and mGlu receptors as well as L-type calcium channels remains an important area of research.

Indirect-pathway LTP

Long-term potentiation (LTP) was first observed at excitatory synapses onto MSNs using sharp electrodes and an extracellular solution containing 0 mM Mg^{2+} [29]. Under these conditions, LTP is induced by high-frequency stimulation. More recently, LTP has been elicited in the presence of physiological Mg^{2+} concentrations using perforated patch recordings and positive spike timing (i.e. synaptic stimulation delivered shortly before the MSN is induced to spike) [12••,30]. LTP is postsynaptically expressed and depends on postsynaptic NMDA receptor activation [10,12••,29,31]. Two recent studies also indicate that the neurotrophic factors FGF and BDNF promote LTP in MSNs, probably through enhancement of NMDA currents [31,32].

In indirect-pathway MSNs specifically, LTP requires A2A receptor activation as well as a lack of activation of D2 receptors, since a D2 agonist can convert the spike-timing dependent LTP into LTD [12••,31]. Thus, D2 and A2A receptors gate LTP induction as well as LTD induction. High dopamine levels and low adenosine levels will shift plasticity induction in indirect-pathway MSNs towards LTD. By contrast, low dopamine levels and high adenosine levels will promote LTP in indirect-pathway MSNs.

As with LTD, it is not known how D2 and A2A receptors are able to modulate LTP. However, some clues exist. Since sharp electrodes or perforated patch recordings are required to observe LTP, diffusible signaling molecules are probably involved. Additionally, it was recently shown that D2 and A2A receptors oppositely modulate NMDA receptor signaling through PKA [33•]. It is not yet clear, however, whether postsynaptic PKA is in fact involved in LTP and, if so, what the relevant substrates of PKA are for this process.

Direct-pathway LTD

LTD in direct-pathway MSNs is not as well studied as it is in indirect-pathway MSNs, but the literature suggests that its mechanisms, involving postsynaptic G_q-coupled mGluRs and L-type calcium channels and presynaptic CB1 receptors, are similar. LTD in direct-pathway MSNs is blocked by a CB1 receptor antagonist as well as by a G_q-coupled mGluR antagonist [12••]. Additionally, LTD induced by pharmacological activation of L-type calcium channels has been observed in both direct-pathway and indirect-pathway MSNs [24].

Although the mechanisms of LTD at excitatory synapses onto direct-pathway MSNs are probably similar to those in indirect-pathway MSNs, the activation of mGluRs and L-type calcium channel signaling, and therefore LTD itself, may be gated by different neuromodulator receptors. Direct-pathway MSNs do not express D2 and A2A receptors, but they do express a complementary pair of G_s-coupled and G_i-coupled receptors: dopamine D1 and acetylcholine M4 receptors [34]. Using a spike-timing dependent induction protocol, Shen *et al.* observed LTD in direct-pathway MSNs when D1 receptors were blocked [12••]. This finding may explain why earlier studies of striatal LTD [11••] failed to observe LTD at direct-pathway synapses: if dopamine release is stimulated by an intrastriatal stimulating electrode, this dopamine can activate D1 receptors and block direct-pathway LTD. D1 receptors may thus act similarly to A2A receptors in the indirect pathway, whereas M4 receptors could act similarly to D2 receptors in the indirect pathway. The role of M4 receptors in LTD has not yet been explored experimentally, but M4 is an attractive candidate for a G_i-coupled D2-analog in the direct pathway [35].

Direct-pathway LTP

The only existing study of LTP in identified direct-pathway MSNs to date showed that LTP can be induced at direct-pathway synapses by positive spike timing using perforated-patch whole-cell recordings [12••]. This LTP required NMDA receptors, just as it did in indirect-pathway MSNs, but also depended on activation of D1

receptors. An older study using sharp electrodes also found that D1 receptors are required for LTP [36]. Thus, in LTP as in LTD, D1 receptors appear to act analogously to A2A receptors in the indirect pathway, implying that cAMP/PKA signaling is probably required to initiate LTP induction in direct-pathway MSNs.

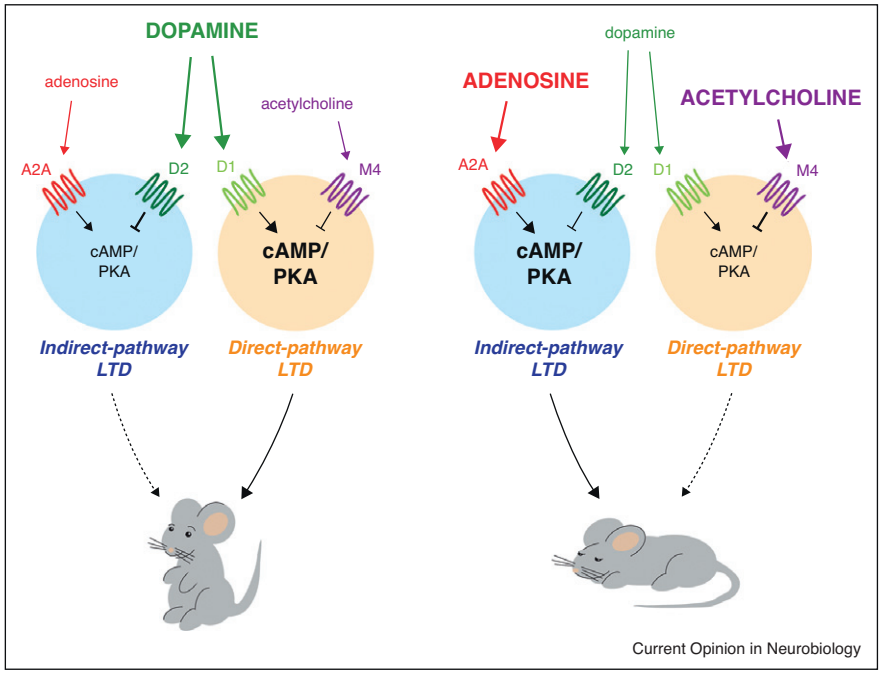
Striatal neuromodulators transduce behavioral states into appropriate patterns of motor behavior

An important theme that emerges from the body of data summarized above is that the relative levels of neuromodulators present in the striatum at any given time determines whether excitatory glutamatergic signaling causes synapses in the striatum to increase or decrease in strength. Indeed, the behavioral state of an animal can influence the direction of striatal plasticity observed [37]. This suggests that one important role of striatal neuromodulators is to transduce salient environmental cues or changes in internal state into appropriate patterns of motor behavior (Figure 1). Release of the most widely studied striatal neuromodulator, dopamine, occurs in response to a variety of stimuli on a wide range of timescales (from milliseconds to hours) [38]. While reward-related signals are generally fast, slower modulation of striatal dopamine occurs in response to internal states such as uncertainty, curiosity, hunger, aggression, and fatigue [38].

Hunger, an extremely ethologically relevant internal state, increases dopamine levels [39,40]. High dopamine levels will cause a weakening of indirect-pathway synapses and strengthening of direct-pathway synapses, leading to increased locomotor behavior required to forage for food. By contrast, a sated animal would have lower dopamine levels that would cause LTP of indirect-pathway synapses and LTD of direct-pathway synapses, leading to more immobility, enabling the animal to digest food and store energy.

As another example, consider the role of adenosine in the CNS. It is hypothesized to provide a readout of overall metabolic load (though its exact mechanisms of release in the striatum are unclear) [41]. Increased levels of adenosine, perhaps associated with prolonged wakefulness, would lead to activation of striatal A2A receptors on indirect-pathway MSNs. This in turn would promote LTP and inhibit LTD at excitatory afferent synapses, leading to an overall increase in indirect-pathway MSN activity and a reduction in locomotor activity, enabling the animal to sleep or conserve energy.

Figure 1



Regulation of synaptic plasticity and behavioral state by striatal neuromodulators. Left, when the levels of dopamine are high relative to adenosine and acetylcholine, cAMP/PKA activity is low in indirect-pathway MSNs, biasing excitatory synapses onto those cells towards LTD. Meanwhile, cAMP/PKA activity is high in direct-pathway MSNs, biasing excitatory synapses onto those cells towards LTP. Indirect-pathway LTD and direct pathway LTP are proposed to cause an active, motivated behavioral state. Right, when the levels of dopamine are low relative to adenosine and acetylcholine, cAMP/PKA activity is high in indirect-pathway MSNs, biasing excitatory synapses onto those cells towards LTP. Meanwhile, cAMP/PKA activity is low in direct-pathway MSNs, biasing excitatory synapses onto those cells towards LTD. Indirect-pathway LTP and direct pathway LTD are proposed to induce an inactive, apathetic behavioral state.

In healthy animals, variations in the levels of striatal neuromodulators will lead to motivated or apathetic states within the normal range of the animal's behavior. However, persistently high striatal dopamine may cause hyperactivity and dyskinesias whereas persistently low dopamine, as in Parkinson's disease, causes immobility. An important assumption of this scheme is that 'long-term' plasticity in the striatum may only last for minutes to hours, or until it is reversed by an opposing form of synaptic plasticity (an issue that is discussed in the next section of this review). This is in contrast to long-term plasticity in motor cortex, which is associated with motor memories that can last for the lifetime of the organism [42,43]. In fact, motor memory may be initially shaped by the basal ganglia but ultimately consolidated in motor cortex.

LTD and LTP: opponent processes?

Functionally, LTD and LTP are opponent processes, but are the induction of LTD and the induction of LTP linked mechanistically? An attractive hypothesis that emerges from the body of data summarized above is that cAMP/PKA signaling links the two processes by oppositely modulating them. Enhanced PKA activity increases NMDA receptor signaling and therefore should promote LTP. Low PKA activity (or at least low cAMP) biases MSNs towards LTD. Testing of this hypothesis awaits future experiments. In the meantime, however, it also begs the question: what are the targets of PKA at excitatory synapses onto MSNs? How could PKA influence both G_q-coupled mGluR and L-type calcium channel signaling (for LTD) and NMDA receptor signaling (for LTP)?

There are many possible targets for PKA. For LTP, one possibility is that PKA phosphorylates NMDA receptors directly to activate them. Other possible targets include the striatal-enriched phosphatases STEP46 and STEP61, and DARPP-32, all of which are expressed by MSNs and contain known PKA phosphorylation sites [44,45]. PKA phosphorylation causes DARPP-32 to inhibit PP1. Inhibition of PP1, in turn, increases the phosphorylation of NMDA and AMPA receptors, activating them [46]. PKA phosphorylation, as well as inhibition of PP1, also regulates STEP activity. Postsynaptic STEP and DARPP-32 signaling might be especially important for LTP since LTP is postsynaptically expressed. In agreement with this view, a mutant substrate-trapping form of STEP prevents LTP but not LTD [47•] and the loss of DARPP-32 prevents LTP in both direct-pathway and indirect-pathway MSNs [48•].

For LTD, the possible targets of PKA (postsynaptically) must be involved in the mGluR or L-type calcium channel signaling pathways that lead to endocannabinoid production. One group found that D1 receptor agonists potentiated G_q signaling in a PKA-dependent manner in HEK cells [49]. PKA might be able to regulate G_q signaling by phosphorylating it directly, or by phosphorylating some downstream components of the signaling pathway such as PLCβ or IP_3 receptors, or by phosphorylating Regulators of G-protein Signaling (RGSs) or G-protein-coupled Receptor Kinases (GRKs). Others have found that D1 receptor agonists can enhance L-type calcium channel currents via cAMP/PKA signaling [50,51], raising the possibility that L-type calcium channels could be a direct or indirect target of PKA modulation.

The issue of whether LTD and LTP are mechanistically linked also raises another crucial unanswered question in the field. How can LTD and LTP act as opponent processes if the former is expressed presynaptically while the latter is expressed postsynaptically? By undergoing LTD, and then later LTP, a MSN synapse would not return to its original state, but would end up with a low presynaptic release probability but a robust ability to detect and respond to release events postsynaptically. Do all MSN excitatory synapses eventually become 'locked' in this state? If so, synaptogenesis would be required to support continued plasticity (and, presumably, motor learning) in adulthood and the hypothesis put forth in the previous section would be invalid. Alternatively, there might be homeostatic resetting mechanisms for MSN synapse strength. Such resetting mechanisms might be active – de-potentiation/de-depression mechanisms – or passive – slow resetting caused by constant cycling of cellular components. De-potentiation of MSN synapses has been observed using low-frequency stimulation (1–2 Hz) and involves apparently postsynaptic mechanisms including signaling by DARPP-32, PP1, and STEP [31,47,52,53]. De-depression of endocannabinoid-mediated LTD has not, to our knowledge, been demonstrated. Evidence for passive resetting of MSN synapse strength is also scant, but passive resetting cannot yet be excluded as a possibility. The solution to the question of how MSNs maintain their ability to undergo plasticity will be crucial to our understanding of how the basal ganglia support action selection and learning processes.

Conclusion

Our understanding of striatal plasticity has advanced rapidly in the past few years. With the advent of BAC transgenic mice that allow identification of direct-pathway and indirect-pathway MSNs both *in vitro* and *in vivo*, the field has finally begun to come into focus. Recordings from different populations of striatal MSNs have demonstrated distinct forms of synaptic plasticity at their excitatory inputs, which are differentially regulated by neuromodulators. These striatal neuromodulators may represent a key interface between the state of an animal and its motor behavior, enabling an animal to adjust its

activity patterns in accordance with an ever changing internal and external environment.

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