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Dopamine-mediated regulation of corticostriatal synaptic plasticity

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The striatum represents the main input into the basal ganglia. Neurons projecting from the striatum receive a large convergence of afferents from all areas of the cortex and transmit neural information to the basal ganglia output structures. Corticostriatal transmission is essential in the regulation of voluntary movement, in addition to behavioural control, cognitive function and reward mechanisms. Long-term potentiation (LTP) and long-term depression (LTD), the two main forms of synaptic plasticity, are both represented at corticostriatal synapses and strongly depend on the activation of dopamine receptors. Here, we discuss possible feedforward and feedback mechanisms by which striatal interneurons, in association with striatal spiny neurons and endogenous dopamine, influence the formation and maintenance of both LTP and LTD. We also propose a model in which the spontaneous membrane oscillations of neurons projecting from the striatum (named 'up' and 'down' states), in addition to the pattern of release of endogenous dopamine, bias the synapse towards preferential induction of LTP or LTD. Finally, we discuss how endogenous dopamine crucially influences changes in synaptic plasticity induced by pathological stimuli, such as energy deprivation.

Introduction

The striatum represents the main input into the basal ganglia; neurons projecting from the striatum receive a large convergence of afferents from all areas of the cortex, which has a crucial integrative and computational role, leading to the acquisition of motor and cognitive action sequences [1,2].

Medium GABA-containing spiny neurons represent the main (>95%) neuronal population of the striatum and modulate the output signals of the basal ganglia through interaction with three major subclasses of interneurons: fast-spiking, parvalbumin-containing, GABA-releasing interneurons; low-threshold spike (LTS), NADPH diaphorase- and somatostatin-positive interneurons; and large cholinergic aspiny interneurons [3,4]. Cortical inputs reach GABA-releasing neurons that output from the striatum, on which they exert a powerful glutamate-mediated excitatory influence. Dopaminergic afferents from the substantia nigra pars compacta (SNpc) converge with these cortical signals, supporting the role of the striatum in the processing of reward signals that depends on the association of dopamine-mediated transmission and sensory cues from cortical areas [2,5].

Long-lasting, activity-dependent synaptic changes are thought to underlie the ability of the brain to translate experiences into memories and seem to represent the cellular model underlying learning and memory processes.

The two 'classic' forms of long-term synaptic plasticity, long-term potentiation (LTP) and long-term depression (LTD), are widely expressed at excitatory synapses throughout the brain and have both been described at corticostriatal connections, at which they might underlie motor-skill learning, cognitive performance and reward mechanisms [2,6,7]. Dopamine influences the physiological processes of the striatum through several mechanisms, including the modulation of various voltage-gated currents. The induction of synaptic plasticity in the striatum requires interaction between dopamine and other neurotransmitters, including glutamate primarily [functioning at both ionotropic (NMDA and AMPA) and metabotropic receptors] and also acetylcholine, nitric oxide (NO) and endogenous cannabinoids (ECBs). Dopamine, functioning at dopamine D1-like (D1 and D5) and D2-like (D2, D3 and D4) receptors crucially influences both the induction and the reversal of neuroplasticity at corticostriatal synapses.

The requirement of dopamine for the induction of striatal LTP and LTD makes these two forms of synaptic plasticity unique in comparison with long-term synaptic changes in other brain areas. In fact, although endogenous dopamine is required for the maintenance and modulation of hippocampal plastic changes [8], it does not seem to be implicated in their induction. Conversely, in the striatum, a certain level of endogenous dopamine seems to be required for the induction of both LTP and LTD.

In recent years, significant progress has been made in the field of synaptic plasticity, including elucidation of the role of dopamine in its regulation. Nevertheless, several questions about dopamine-mediated control of corticostriatal neuroplasticity are still unanswered. How does the pattern of dopamine release from the SNpc preferentially induce LTD or LTP? How do the two different classes of dopamine receptors cooperate to induce these forms of neuronal plasticity? How do various pathological conditions associated with acute and neurodegenerative diseases affect dopamine-dependent corticostriatal synaptic plasticity? Finally, do these forms of dopamine-dependent

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plasticity represent the neuronal correlate of reward processes?

An old question: is dopamine excitatory or inhibitory?

The precise mechanism by which dopamine regulates the physiological activity of striatal target cells is not completely understood. *In vivo*, pioneering electrophysiological studies have suggested both excitatory [9] and inhibitory actions [10] of dopamine on striatal neurons. The first *in vitro* studies showed that both D1 and D2 receptors modulate multiple voltage-dependent currents in medium spiny neurons that project from the striatum.

Dopamine, through its interaction with D1 receptors, can induce reversible inhibition of Na^+-mediated action-potential discharges in striatal neurons and reduce excitatory transmission in the striatum in a voltage-dependent manner; this latter effect is evident at depolarized levels of the membrane potential and absent at hyperpolarized values [11,12]. Dopamine also modulates high-voltage-activated Ca^{2+} currents, reversibly reducing N- and P-type Ca^{2+} currents and enhancing L-type currents in striatal neurons through a protein kinase A (PKA)-mediated mechanism [13]. By contrast, the activation of D2-like receptors suppresses transmembrane Ca^{2+} currents through L-type Ca^{2+} channels [14] and modulates K^+ currents [15]. An inhibitory effect of D2 receptor stimulation is evident after the upregulation of D2 receptors that follows catecholamine depletion or receptor supersensitivity secondary to chronic treatment with dopamine receptor antagonists [16,17].

Dopamine also has a crucial role in regulation of the filtering functions of the intrastriatal circuit by functioning on the intrinsic striatal interneuronal network [18].

All the current data support the hypothesis that dopamine probably exerts multiple actions on the physiological activity of striatal neurons, both inhibiting and enhancing neuronal evoked activity, depending on the level of membrane depolarization and physiological state of the neuron.

The discovery of long-term depression

Since the beginning of the 1990s, pioneering *in vitro* studies of long-term activity-dependent modification at glutamatergic corticostriatal synapses have demonstrated that high-frequency stimulation (HFS) of corticostriatal fibres using a train of pulses at 100 Hz, in association with postsynaptic neuron firing, consistently induced LTD of glutamatergic synaptic transmission onto striatal-output neurons [19–21]. This form of synaptic plasticity was not affected by bath application of NMDA receptor antagonists but was significantly reduced by glutamate metabotropic receptor antagonists [19]. A crucial role of dopaminergic signalling in the induction of striatal LTD has been demonstrated since the first description of LTD [19]. Both D1 and D2 receptor antagonists blocked LTD, which was also absent in slices obtained from rats in which the nigrostriatal dopaminergic system was lesioned by unilateral nigral injection of 6-hydroxydopamine (6-OHDA) [19]. In dopamine-depleted slices, it was possible to restore the induction of LTD by co-administration of a D1 and D2 receptor agonist, suggesting that D1 and D2 receptors interact synergistically in the striatum to enable formation of LTD [19] (Figure 1). A few years later, a crucial role for D2 receptors in the regulation of the mechanisms underlying the direction of long-term changes in synaptic efficacy was demonstrated in the striatum by recordings from D2 receptor-null mice [22]. Mice lacking D2 receptors failed to show LTD after tetanic stimulation of corticostriatal fibres. In fact, mutant mice synapses showed LTP, even with the presence of Mg^{2+} ions in the cell medium, a condition that is known to inactivate NMDA glutamate receptors [22]. Interestingly, LTD is absent also in genetic models of early-onset familial parkinsonism, such as in mice lacking the *DJ-1* gene, an established cause of autosomal recessive early-onset Parkinson's disease (PD) in humans [23]. *DJ-1*-null mice show a normal number of dopaminergic neurons in the substantia nigra but a remarkable reduction of the evoked dopamine overflow in the striatum, primarily as a result of increased reuptake and a failure to express LTD after repeated synaptic stimulation [24].

Possible feedforward and feedback mechanisms in long-term depression

A crucial synaptic balance between dopamine and acetylcholine exists in the striatum, and acetylcholine seems to be a key mediator of dopamine-dependent striatal plasticity and learning [25]. Dopamine release is strongly modulated by the activation of nicotinic receptors located on dopaminergic nerve terminals in the striatum [26], and activation of nicotinic receptors, during synaptic activation by HFS, seems to interact with the dopaminergic actions that lead to striatal LTD [27]. Accordingly, a crucial role in the dopaminergic control of corticostriatal induction of LTD has been suggested for large striatal cholinergic interneurons. It has been hypothesized that the dependence of LTD on D2 receptors could reflect lowering of muscarinic M1 acetylcholine receptor activity mediated by the effect of dopamine functioning at D2 receptors on striatal cholinergic interneurons [28]. According to the author's hypothesis, because M1 receptor activation reduces the activity-dependent opening of subunit 1.3 forming L-type voltage-gated Ca^{2+} channels (Cav1.3 Ca^{2+} channels), leading to reduced ECB synthesis, lowering M1 receptor tone would promote the induction of LTD by disinhibiting Cav1.3 Ca^{2+} channels [28] (Figure 2).

A crucial role in the induction of corticostriatal LTD has also been suggested for the postsynaptic synthesis and release of ECBs [29]. D2 receptor activation has been linked to ECB release [30,31] and enhanced ECB release by dopamine seems to be essential for eliciting ECB-induced LTD [32]. Furthermore, the D2 receptor antagonist sulpiride can completely block state-dependent ECB-induced LTD, whereas quinpirole, a D2 receptor agonist, enhances its magnitude [32] (Figure 2).

Dopamine also seems to have a role in the modulation of the feedforward control exerted by the NO–cGMP pathway on corticostriatal LTD [33]. In fact, neuronal nitric oxide synthase (NOS) is activated *in vivo* by burst firing of nigrostriatal dopamine cells through a D1 and D5 receptor-dependent mechanism [34], and stimulation of D1 and D5 receptors located on striatal NO-producing interneurons leads to the release of NO from these cells and