Review TRENDS in Neurosciences Vol.30 No.5

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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Available online 23 March 2007.

 0166-2236/$ – see front matter doi:10.1016/j.tins.2007.03.001

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

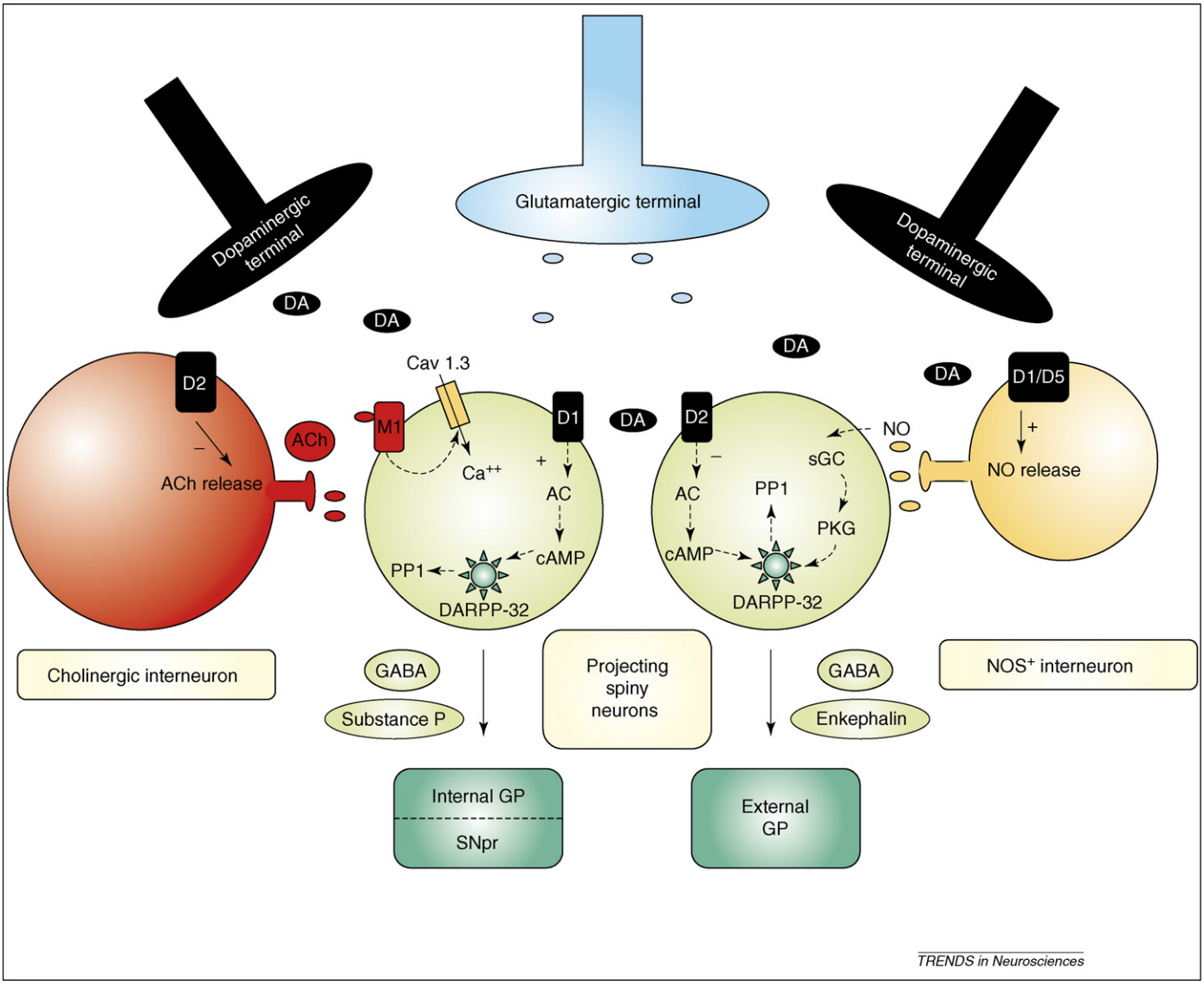

Figure 1. Dopamine (DA) receptor interaction in the induction of corticostriatal LTD. According to the prevailing opinion, D1 receptors are found predominantly in the striatonigral neurons of the 'direct pathway', whereas D2 receptors are mainly expressed by the striatopallidal neurons of the 'indirect pathway'. Because the induction of LTD requires the concomitant activation of D1 and D2 receptors, according to this hypothesis this form of synaptic plasticity should be inducible in neurons from only one of the two projection systems of the striatum. However, it is possible to hypothesize that in striatonigral neurons the activation of the D1 receptors modulates the cAMP–DARPP32–PP1 pathway, whereas the concomitant activation of D2 receptors on the cholinergic interneuron would be required to disinhibit Cav1.3 Ca^{2+} channels through the lowering of M1 receptor tone. By contrast, in D2-expressing striatopallidal neurons the activation of D1 receptors would be required to enhance NO release, which, in turn, participates in the induction phase of LTD through the cGMP pathway. Abbreviations: AC, adenylyl cyclase; Ach, acetylcholine; GP, globus pallidus; PKG, protein kinase G; sGC, soluble guanylyl cyclase.

seems to crucially influence the induction phase of LTD [35] (Figure 2).

Long-term potentiation: a parallel, but opposite, form of synaptic plasticity

Similar to LTD, LTP is considered a cellular-level model of learning and is crucial for the storage and retrieval of neural information in several brain areas [36]. In the striatum, LTP was initially revealed by removing Mg^{2+} ions from the external medium [37]. By deinactivating NMDA receptor channels, this experimental condition revealed a component of the excitatory postsynaptic potential (EPSP) that was potentiated by repetitive, tetanic activation of corticostriatal fibres and that was NMDA-dependent [37]. Moreover, *in vivo* intracellular recordings showed that repetitive activation of cortical inputs induced striatal LTP if combined with postsynaptic depolarization [38]. Similar to LTD, the induction of LTP at corticostriatal synapses was blocked by unilateral dopamine denervation using 6-OHDA [39]. Nevertheless, whereas D1 and D2 receptors interact synergistically to enable formation of LTD, they seem to operate in opposition during the induction phase of LTP [39]. Corticostriatal LTP is blocked by D1 and D5 receptor antagonists [40,41] and lost in mice lacking the D1 receptor [35]. By contrast, activation of D2 receptors normally exerts a negative control on the formation of NMDA-dependent LTP. LTP is significantly enhanced either by using the D2 receptor antagonist L-sulpiride or in mice lacking D2 receptors, whereas the D2-selective receptor agonist quinpirole not only blocks LTP, but also reveals LTD when the repetitive stimulation of corticostriatal terminals is applied in Mg^{2+}-free extracellular medium [22].

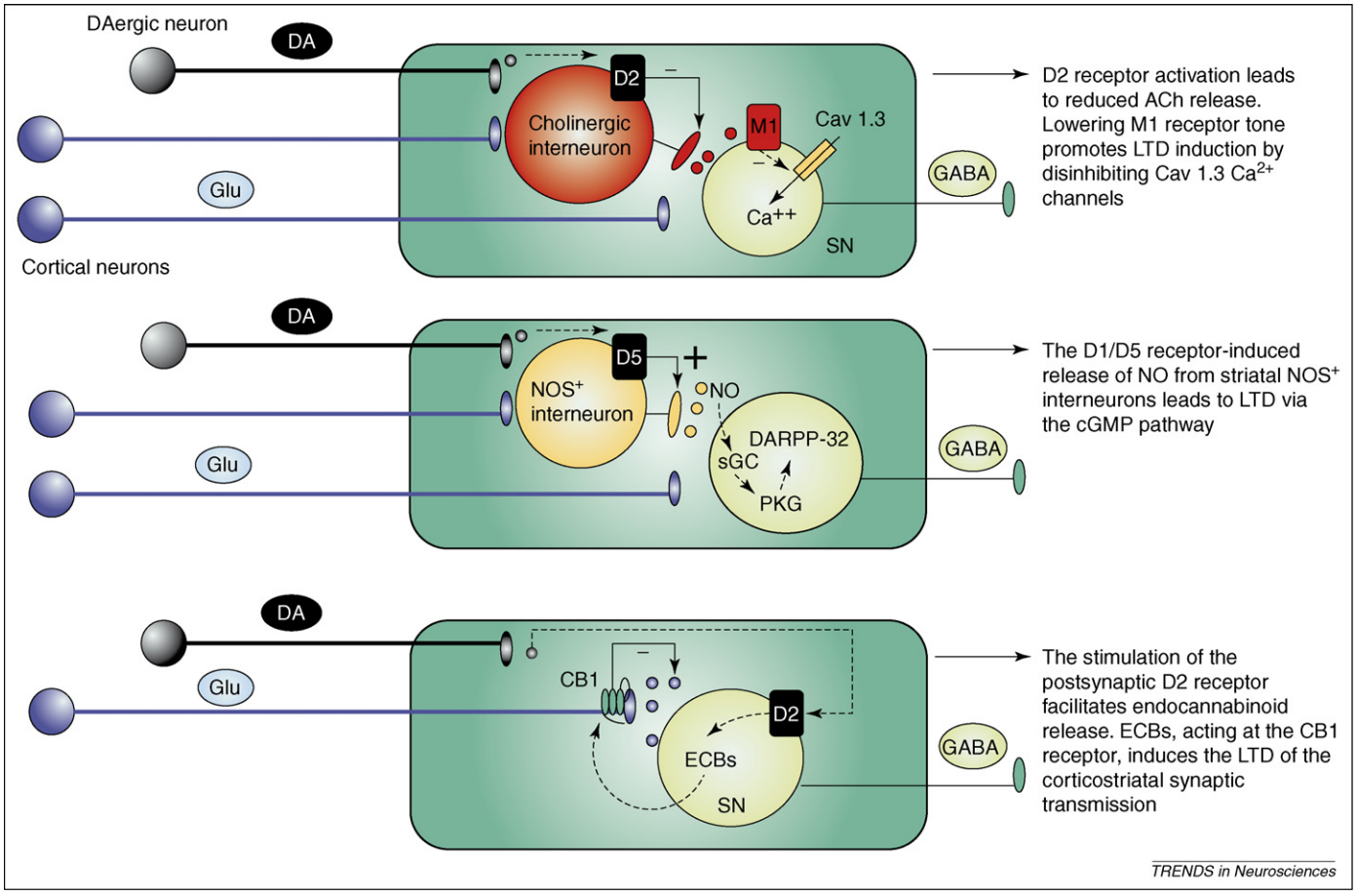

Figure 2. Dopamine (DA) controls corticostriatal LTD through feedforward and feedback mechanisms. DA not only controls the induction phase of LTD by functioning at the D1 and D2 receptors located on projecting GABA-releasing neurons, but the neurotransmitter also crucially influences the modulation of LTD by other neurotransmitters. In particular, DA influences the modulatory action exerted by cholinergic interneurons, NO-releasing, NOS-positive interneurons and the ECB system. Abbreviations: CB1, cannabinoid receptor 1; Glu, glutamate; M1, muscarinic M1 acetylcholine receptor; PKG, protein kinase G; SN, spiny neuron.

As described for LTD, a crucial synaptic balance between dopamine and acetylcholine seems to exist in the striatum. Large striatal cholinergic interneurons provide an essential integrative role within the intrinsic neuronal circuit in which they operate [42] and endogenous acetylcholine influences dopamine concentrations by functioning on presynaptic nicotinic receptors [26]. Interestingly, dopamine, through its activation of D5 receptors, is required for the induction of an NMDA-independent LTP described in cholinergic interneurons [43]. Therefore, striatal cholinergic interneurons also seem to actively participate in the memory process by undergoing long-term dopamine-dependent changes in synaptic efficacy. Moreover, striatal cholinergic interneurons and dopaminergic neurons show opposite, but co-incident, reward-related activities [5,44], suggesting that dopamine could potentially interfere with the acquisition of behavioural responses to reward-related stimuli, thereby affecting synaptic plasticity at the synapses of both projecting spiny neurons and cholinergic interneurons.

In the striatum, stimulation of D1 and D2 receptors triggers opposite effects on the intracellular levels of cAMP, stimulating and inhibiting adenylyl cyclase activity, respectively [45]. The intracellular levels of cAMP modulate the activity of cAMP-dependent PKA. A major substrate for PKA in spiny neurons is the dopamine- and cAMP-regulated phosphoprotein 32 kDa (DARPP32), which, in turn, functions as a potent inhibitor of protein phosphatase 1 (PP1). PP1 regulates the functional activity of many physiological effectors, including NMDA and AMPA glutamate receptors [45]. Interestingly, both LTP and LTD are abolished after the genetic disruption of DARPP32 [41], suggesting that stimulation of the D1 receptor–PKA–DARPP32–PP1 pathway is required for the induction of these two opposing forms of synaptic plasticity. Furthermore, dopamine can enhance NMDA receptor-channel currents in dissociated medium striatal spiny neurons through a D1 receptor- and DARPP32-mediated mechanism [46]. This mechanism might have a pivotal role in the induction of corticostriatal LTP.

Dopamine-mediated control of pathological forms of neuronal plasticity

Although the accepted hypothesis of synaptic plasticity considers that the enduring changes of glutamatergic transmission are ‘physiological’ synaptic correlates of learning and memory processes, many of the molecular pathways involved in the induction and maintenance of LTP and LTD are also observed during synaptic plastic changes induced by pathological stimuli. Dopamine also seems to crucially influence these ‘pathological’ forms of synaptic plasticity.

Postischaemic long-term potentiation

Experimental studies of brain injury *in vitro* have shown that neurons can respond to the acute energy deprivation associated with the ischaemic insult by the generation of pathological forms of synaptic plasticity. In the striatum, transient oxygen and glucose deprivation (*in vitro* ischaemia) can induce an NMDA-dependent postischaemic LTP (i-LTP) at corticostriatal synapses [47,48]. Pharmacological and genetic manipulations of dopamine-mediated signalling have shown that dopamine, through its interaction with D1 receptors, facilitates the expression of i-LTP on the AMPA-mediated component of the EPSPs. Accordingly, blockade of the D1 receptor–cAMP–PKA pathway prevents a long-lasting increase in the EPSP amplitude caused by ischaemia [49]. Because a large release of dopamine occurs during ischaemic events in the striatum [50] and endogenous dopamine can amplify the neuronal damage induced by energy deprivation [51], it is possible to hypothesize that dopamine could also facilitate both acute necrotic and delayed apoptotic neuronal death through its influence on this pathological form of synaptic plasticity.

L-DOPA-induced dyskinesia

Because PD is primarily characterized by the degeneration of dopaminergic neurons projecting into the striatum, several studies have been performed to characterize the modification of the main forms of striatal neuronal plasticity in experimental models of PD [52]. In the 6-OHDA model of PD, LTP is lost. Nevertheless, in animals sustaining unilateral 6-OHDA lesions of the substantia nigra, corticostriatal LTP can be restored by chronic treatment with the dopamine precursor L-DOPA [53]. L-DOPA is still the most effective therapeutic option for patients suffering from PD. Unfortunately, however, involuntary movements, or 'dyskinesias', represent a dramatic complication of long-term treatment with this pharmacological compound in the vast majority of patients with PD [54]. Interestingly, after the induction of LTP at corticostriatal synapses, a low-frequency stimulation (LFS) protocol can reverse the previously potentiated EPSP to pre-LTP levels. This form of plasticity, named 'depotentiation', seems to facilitate information storage in neuronal networks and is selectively lost only in dyskinetic animals chronically treated with L-DOPA, whereas animals that do not develop involuntary movements maintain the physiological reversal of synaptic strength after LFS [53]. Moreover, the lack of depotentiation that probably represents the electrophysiological correlate of the abnormal motor patterns is attributable to changes occurring along the D1 receptor–PKA–DARPP32–PP1 pathway, because D1 receptor agonists and adenylate cyclase activators can prevent LFS-induced depotentiation [53].

3-Nitropropionic acid-induced long-term potentiation

3-Nitropropionic acid (3-NP) is a suicide inhibitor of succinate dehydrogenase (respiratory complex II), a functional member of both the Krebs cycle and the aerobic respiratory chain. Chronic administration of 3-NP in both rodents and nonhuman primates provides useful experimental models of Huntington's disease (HD), replicating most of the clinical and pathological hallmarks of this neurodegenerative disorder [55].

The dicarbanion form of 3-NP can irreversibly inhibit the active site of the enzyme, leading to a depletion of intracellular ATP, membrane depolarization and NMDA toxicity through the relief of a voltage-dependent Mg^{2+} block [56]. At corticostriatal synapses, 3-NP can induce a metabotropic glutamate type 1 receptor–protein kinase C (PKC) pathway-dependent LTP of NMDA-mediated corticostriatal transmission [57]. Moreover, this pathological form of synaptic plasticity seems to require endogenous dopamine. The 3-NP-induced LTP, in fact, is absent after the 6-OHDA-induced nigrostriatal dopaminergic denervation, after pharmacological blockade of D2 receptors and in mice lacking D2 receptors [58]. 3-NP-induced LTP is also blocked by forskolin, an activator of adenylyl cyclase [58]. All these data suggest that the involvement of the D2 receptor–PKA pathway is a crucial requirement for the generation of this form of pathological synaptic plasticity.

Controversies

Characterization of the physiological action of dopamine in the modulation of long-lasting striatal synaptic changes is complicated by the differential distribution of D1 and D2 receptors. In fact, although still controversial, the prevailing opinion is that D1 and D2 receptors are segregated in two subpopulations of projecting GABA-releasing spiny neurons, forming two large efferent streams that are thought to differ in their axonal targets [59] (Figure 1).

According to this hypothesis, D1 receptors are found predominantly in the striatonigral neurons of the 'direct pathway', whereas D2 receptors are mainly expressed by the striatopallidal neurons of the 'indirect pathway' [60].

Because the induction of LTD requires activation of both D1 and D2 receptors, according to this hypothesis, LTD should be inducible in neurons from only one of the two projection systems of the striatum. However, because of the high percentage of neurons exhibiting LTD [19], it is possible to hypothesize that the induction of LTD in neurons expressing D1 receptors could be sustained by the D2 receptor-dependent reduction of M1 receptor tone, whereas in neurons expressing D2 receptors the activation of D1 receptors could be required to facilitate NO release from NOS-positive interneurons (Figure 1).

By contrast, according to analysis of mRNA expression, it seems possible that a subpopulation of medium spiny neurons express both D1 and D2 receptor subtypes [61]. According to the hypothesis of co-expression of the two dopamine receptor subtypes, all the described mechanisms underlying the induction of LTD and LTP could be potentially represented in the same neuron and differentially activated, depending on the physiological activity at both sides of the synapse (Figure 3).

How the patterns of dopamine release lead to differential activation of dopamine receptors, thereby biasing the synapses towards the preferential induction of LTP or LTD, is still a matter of debate.

Interestingly, *in vivo* measurement of the timing of spontaneous fluctuations in the membrane potential of striatal neurons has demonstrated that these cells show subthreshold shifts in membrane potential, fluctuating

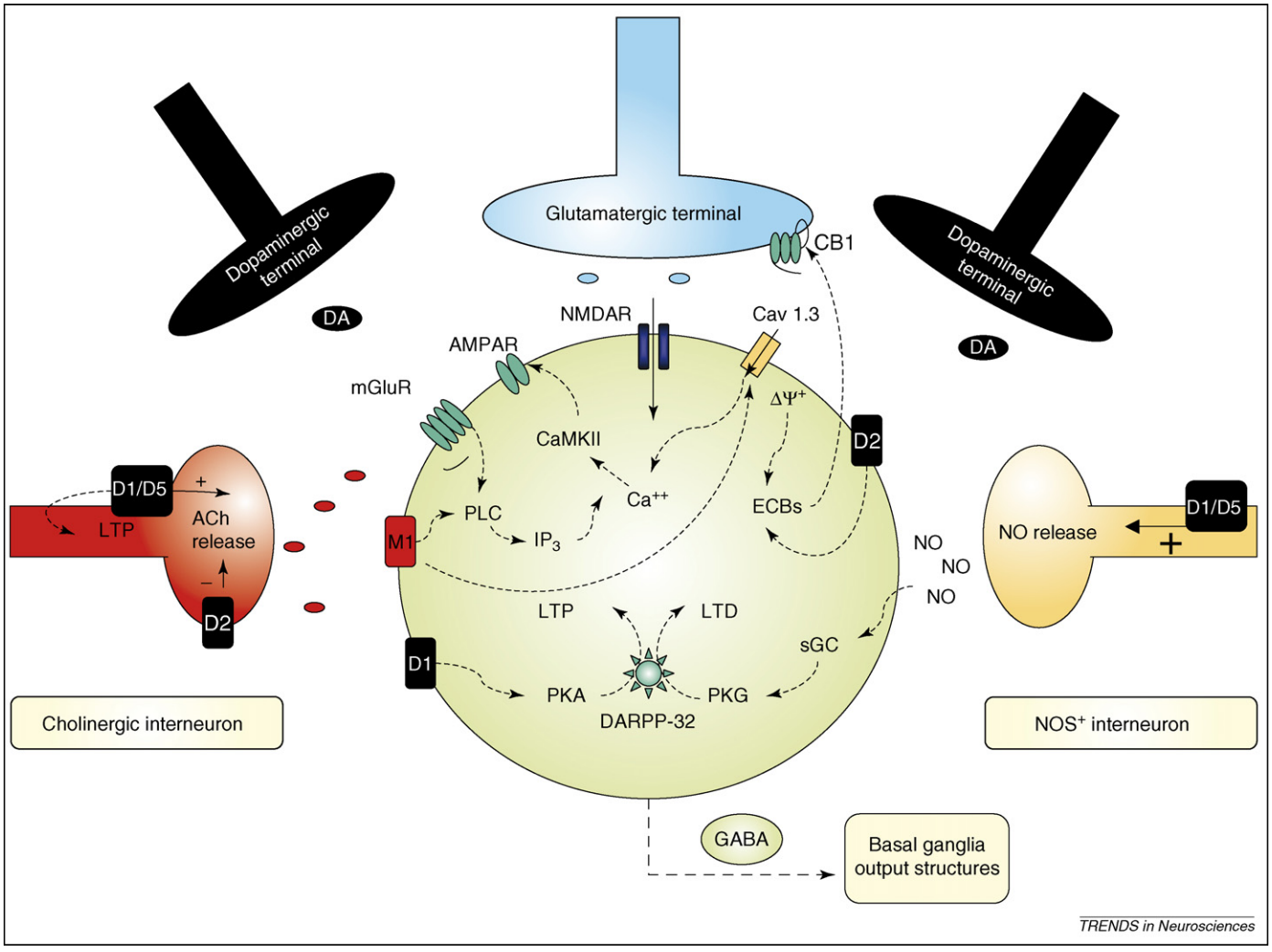

Figure 3. Effects of dopamine receptors interacting in projecting striatal neurons that co-express D1 and D2 receptors. In the subset of striatal neurons that co-express D1 and D2 receptors, the mechanisms underlying long-term modification of the efficacy of synaptic transmission probably co-exist. Activation of both receptor subtypes influences the phosphorylation state of DARPP32 through the modulation of the intracellular levels of cAMP. The activation of dopamine receptors on cholinergic interneurons leads to different effects, depending on the receptor subtype activated. The activation of D1 receptors enhances acetylcholine (Ach) release and triggers the induction of LTP through a phospholipase C (PLC)-mediated mechanism. By contrast, the activation of D2 receptors favours the induction of LTD by the disinhibition of Cav1.3 Ca^{2+} channels. Membrane depolarization ($\Delta\Psi^{+}$) and D2 receptor activation on projecting neurons facilitates the release of ECBs and the induction of an ECB-mediated LTD. Finally, the activation of D1-like receptors on NOS-positive interneurons facilitates the induction phase of LTD through the activation of the cGMP pathway. Abbreviations: CaMKII, Ca^{2+}–calmodulin-dependent kinase II; CB1, cannabinoid receptor 1; IP_3, inositol 1,4,5 trisphosphate; PKG, protein kinase G; sGC, soluble guanylyl cyclase.

between a hyperpolarized 'down' state and a depolarized 'up' state [62–64]. Both preferred membrane potentials are subthreshold and action potentials usually seem to be triggered by noisy fluctuations in the 'up' state [63]. It has been hypothesized that these shifts in membrane potential could reflect firing of the cortical cell that provides an excitatory input, and thus represents the result of convergent patterned inputs arising from various cortical areas.

Therefore, repetitive transmission at a corticostriatal synapse (such as that mimicked by the HFS protocol) that occurs in the 'up' state and during strong activation of dopamine receptors will probably favour the induction of LTP, according to the higher probability of NMDA receptors opening at 'up'-state values of the membrane potential. By contrast, the same tetanic stimulus that occurs during the 'down' state and accompanied only by weak stimulation of dopamine receptors will probably lead to LTD (Figure 4). In fact, the induction of LTD probably requires a weaker dopaminergic input because of the higher affinity of D2 receptors for dopamine compared with D1 receptors [65]. Although the model of 'up' and 'down' states explains the corticostriatal activity recorded *in vivo* from anaesthetized animals, wakefulness seems to be associated with a completely different striatal pattern of temporally disorganized, depolarizing synaptic events of variable amplitude [66].

Hebbian forms of plasticity operate by positive feedback rules that drive neurons towards maximal and minimal frequency ranges of action potential firing, which render neurons unable to encode subsequent plastic changes. By contrast, homeostatic forms of plasticity might provide the global negative feedback necessary to maintain synaptic strength and plasticity within a functionally dynamic range [67]. Interestingly, it was recently shown that LTP and LTD can be induced selectively by different stimulation patterns and are evoked with similar efficiency in non-Hebbian and

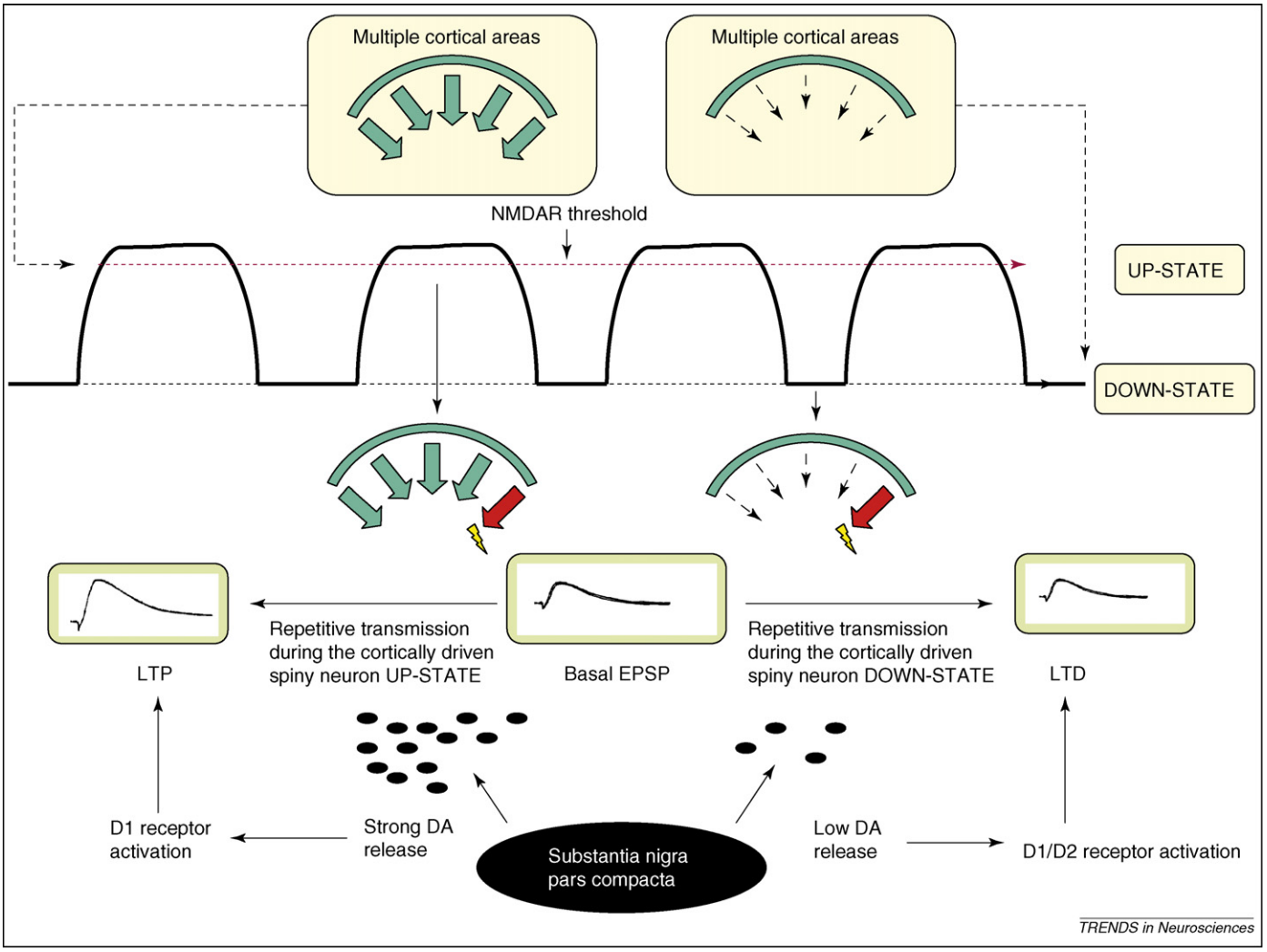

Figure 4. Spontaneous oscillation in the membrane potential of projecting striatal spiny neurons influences the direction of synaptic plastic changes. The membrane potential of projecting spiny neurons is crucially influenced by the neural inputs arising from several cortical areas and converging into the striatum. The membrane potential values of spiny neurons oscillate between a depolarized 'up' state and a hyperpolarized 'down' state, depending on the degree of cortical stimulation. If repetitive neuronal transmission occurs during the 'up' state (overcoming the threshold for activation of NMDA receptors) and is associated with a strong release of dopamine (DA) from the SNpc, the synapse is biased towards the induction of LTP. By contrast, repetitive transmission that occurs in the 'down' state, in association with weak dopamine-mediated stimulation, will lead to LTD. Note that a membrane depolarization that leads to the opening of L-type Ca^{2+} channels is also required for the induction of LTD and is achieved by repetitive activation of a specific group of corticostriatal synapses.

Hebbian modes. This latter observation suggests that bidirectional plasticity could occur at the same striatal synapse, providing an efficient homeostatic mechanism by resetting the corticostriatal synapses and thereby avoiding synaptic saturation [68].

Moreover, striatal activity is crucial in understanding the contingencies between goal-directed responses and rewarding or punishing outcomes [69]. Dopaminergic neurons show phasic activation followed by depression in response to novel or intense stimuli, especially during environmental events with rewarding value [70]. It is possible to hypothesize that such a phasic dopaminergic input, occurring co-incidently with the repetitive activation of corticostriatal fibres and the 'up' state of the postsynaptic neuron, will favour the induction of LTP. By contrast, because the induction of LTD probably requires a weaker dopaminergic input, this form of plasticity might occur in conditions associated with reduced dopaminergic cell firing, such as in the absence of a predicted reward [7,70].

Accordingly, *in vivo* electrophysiological recordings obtained from projecting striatal neurons have shown that stimulation of the substantia nigra reliably induces potentiation of corticostriatal postsynaptic potentials, depending on the activation of dopamine receptors [71]. The last study strongly supports the role of dopamine-mediated control of LTP and LTD in the acquisition of reward-related learned behaviours.

Concluding remarks and future perspectives

Activation of dopamine receptors seems to represent a crucial factor in the formation of the two alternative forms of neuroplasticity at corticostriatal synapses. LTP and LTD are strongly influenced by dopamine produced by the substantia nigra and lost after pharmacological manipulation or genetic disruption at different levels of the dopamine-mediated signalling pathway. Interestingly, dopamine is also involved in the control of the induction of LTD exerted by other neurotrasmitters: dopamine, functioning at its D2 receptor, leads to the release of ECBs and

an ECB-dependent LTD [32]; stimulation of D2 receptors, which inhibits acetylcholine release from cholinergic interneurons and then removes the acetylcholine-dependent activation of M1 receptors located on medium spiny neurons, facilitates the induction of LTD [28]; and stimulation of D1 and D5 receptors located on NOS-positive striatal interneurons leads to NO production and facilitates LTD through the cGMP pathway [35].

Dopamine seems to influence several forms of synaptic plastic changes associated with human pathological conditions, such as addiction or L-DOPA-induced dyskinesia. Cocaine treatment can induce a dopamine-dependent loss of depotentiation at corticostriatal synapses [72] that probably underlies the persistence of addictive behaviour despite the efforts to abstain in drug abusers. Accordingly, striatal synaptic plasticity seems to have a crucial role in addiction and habit formation [73]. Moreover, the development of dyskinesia in L-DOPA-treated PD patients probably depends on the loss of selective forms of synaptic plasticity at corticostriatal synapses. In addition, synaptic depotentiation is selectively lost in dyskinetic animals chronically treated with L-DOPA [53], and LTP-like plasticity is deficient in PD patients and restored by L-DOPA in nondyskinetic, but not in dyskinetic, patients [74]. Therefore, the abnormal motor patterns observed in this disabling human disease probably reflect the induction of abnormal neural circuitries within the basal ganglia network.

Studying the mechanisms underlying the modulation of projecting striatal neurons and interneurons by dopamine will provide new insights in the comprehension of dopamine-dependent forms of pathological synaptic plasticity and their potential roles during human pathological conditions.

Acknowledgements

This work has been supported by the Fondo per gli Investimenti della Ricerca di Base 2003 (FIRB2003), Ricerca Scientifica di Rilevante Interesse Nazionale 2005 (PRIN2005), Progetti Finalizzati e Strategici Ministero della Salute 2004, Progetto Dopamina Istituto Superiore della Sanità and Fondazione Cassa di Risparmio Perugia (P.C.).

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