Chapter 10
Regulation of Striatal Neuron Activity by Cyclic Nucleotide Signaling and Phosphodiesterase Inhibition: Implications for the Treatment of Parkinson's Disease

Fernando E. Padovan-Neto and Anthony R. West

Abstract Cyclic nucleotide phosphodiesterase (PDE) enzymes catalyze the hydrolysis and inactivation of cyclic nucleotides (cAMP/cGMP) in the brain. Several classes of PDE enzymes with distinct tissue distributions, cyclic nucleotide selectivity, and regulatory factors are highly expressed in brain regions subserving cognitive and motor processes known to be disrupted in neurodegenerative diseases such as Parkinson's disease (PD). Furthermore, small-molecule inhibitors of several different PDE family members alter cyclic nucleotide levels and favorably enhance motor performance and cognition in animal disease models. This chapter will explore the roles and therapeutic potential of non-selective and selective PDE inhibitors on neural processing in fronto-striatal circuits in normal animals and models of DOPA-induced dyskinesias (LIDs) associated with PD. The impact of selective PDE inhibitors and augmentation of cAMP and cGMP signaling on the membrane excitability of striatal medium-sized spiny projection neurons (MSNs) will be discussed. The effects of cyclic nucleotide signaling and PDE inhibitors on synaptic plasticity of striatonigral and striatopallidal MSNs will be also be reviewed. New data on the efficacy of PDE10A inhibitors for reversing behavioral and electrophysiological correlates of L-DOPA-induced dyskinesias in a rat model of PD will also be presented. Together, these data will highlight the potential of novel PDE inhibitors for treatment of movement disorders such as PD which are associated with abnormal corticostriatal transmission.

Keywords Phosphodiesterase • cAMP • cGMP • Dopamine • Striatum • Medium spiny neuron • Parkinson's disease • L-DOPA-induced dyskinesia

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10.1 Cyclic Nucleotide Synthesis

Neurotransmitters in the central nervous system (CNS) such as norepinephrine, dopamine (DA), adenosine, and others exert their actions via heterotrimeric membrane-bound G-protein coupled receptors (GPCRs). Heterotrimeric G proteins are composed of α, β, and γ subunits and in the inactive form, the α subunit is bound to guanosine diphosphate (GDP) resulting in an inactive αβγ-complex (Gilman 1987). Neurotransmitter-induced activation of GPCRs dissociates the αβγ-complex and starts a biochemical reaction that modifies target proteins and initiates a series of intracellular signaling cascades. These signaling cascades are linked to the regulation of second messenger synthesis and degradation. The first second messenger to be discovered was 3′-5′-cyclic monophosphate (cAMP) (Berthet et al. 1957). Today, we know that many other molecules including cyclic guanosine monophosphate (cGMP), nitric oxide (NO), and calcium are second messengers in the CNS with important functions in a variety of biological processes (Seifert et al. 2015). Adenylyl cyclase (AC) is the effector enzyme that triggers the generation of cAMP via adenosine triphosphate (ATP). A total of nine isoforms of membrane-bound AC and one isoform of soluble AC synthesize cAMP. AC can be modulated by signals other than GPCRs like calcium and protein kinases, suggesting that cAMP production is complex and requires the integration of extracellular and intracellular signals (Mons et al. 1998; Seifert et al. 2015). The distinct localization of ACs in neuronal sub-compartments likely results in cAMP production within spatially confined distribution zones which are functionally coupled to various regulatory processes. A variety of GPCRs are coupled to membrane-bound AC and the production of cAMP is facilitated by neurotransmitter-induced activation of stimulatory (G_s, G_{olf}) GPCRs (e.g., norepinephrine (NE) β-adrenergic receptors, DA D1-like receptors, adenosine A2A receptors) and inhibited by neurotransmitter coupling to inhibitory (G_i) GPCRs (e.g., DA D2-like receptors, M4 muscarinic receptors). cAMP modulates many physiological processes via activation of protein kinase A (PKA) and cyclic nucleotide-gated channels (CNGC) (Fig. 10.1).

The next second messenger to be identified was cGMP (Ashman et al. 1963). Synthesis of cGMP occurs via activation of either membrane-bound particulate guanylyl cyclase (pGC) or soluble guanylyl cyclase (sGC) by natriuretic peptides and the neuromodulator NO, respectively (Boehning and Snyder 2003; Bredt 2003; Bredt et al. 1990; Garthwaite 2008). NO is a gaseous free radical with an unpaired electron that does not require energy to disperse through the cells. Due to its short half-life, NO signaling is limited to the modulation of biochemical processes confined within 10–20 cell diameters (i.e. 100–300 μm) (Murad 2011). NO can be produced by three different isoforms of NO synthase (NOS; neuronal NOS (nNOS), inducible NOS (iNOS), endothelial NOS (eNOS)) (Alderton et al. 2001; Garthwaite 2008). Unlike other classical neurotransmitters, NO is not stored in vesicles and upon release can act on both pre- and post-synaptic terminals to modulate synaptic plasticity, including short and long-term changes in the efficacy of excitatory and inhibitory synaptic transmission (see below). In the CNS, the NO-sensitive sGC is

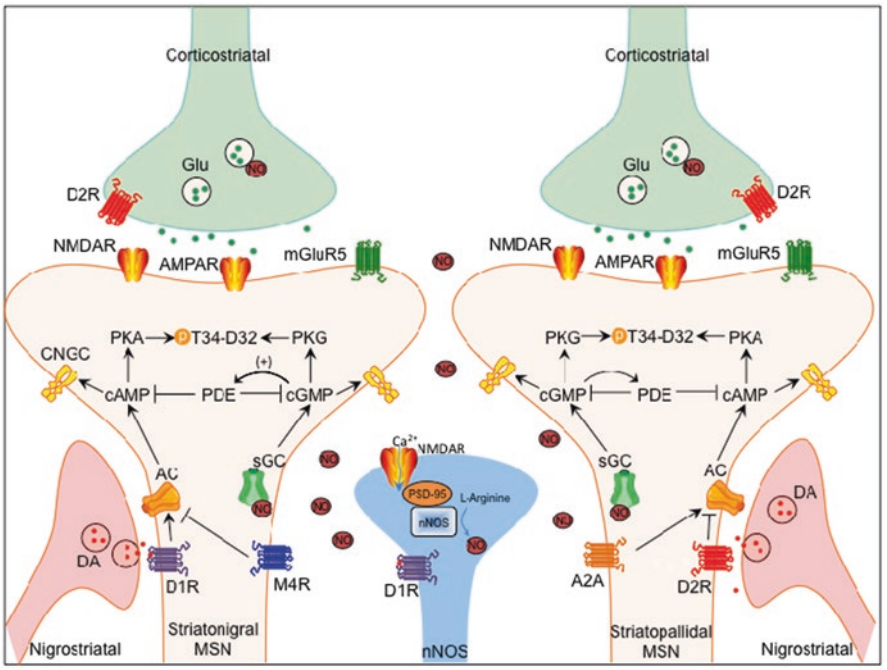

Fig. 10.1 Schematic diagram of the roles of DA-AC-cAMP-PKA and NO-sGC-cGMP-PKG signaling and PDE function in the regulation of MSN membrane excitability. DA released from nigrostriatal terminals binds to D1-like or D2-like DA receptors on the postsynaptic MSN and leads to either stimulation or inhibition of AC, respectively. Increases in cAMP tone will activate PKA, which can phosphorylate DARPP-32 at threonine 34 to have complex effects on downstream signaling pathways, neurotransmitter receptors, and voltage-gated ion channels. cAMP (along with cGMP) can also stimulate CNGCs in the plasma membrane which can lead to cation influx and membrane depolarization. Tonic NO signaling increases glutamatergic transmission across corticostriatal synapses potentially via nitrosylation of presynaptic release proteins or a sGC-cGMP-dependent mechanism. NO transmission can also activate sGC in the postsynaptic MSN and stimulate cGMP production. cGMP can activate CNGC, stimulate PDEs, or activate PKG. Transient activation of NO-sGC-cGMP signalling in the intact striatum increases the responsiveness of MSNs to excitatory glutamatergic drive and facilitates short-term potentiation of corticostriatal synaptic transmission. Together these studies suggest that like DA D1/5 receptor modulation, the net impact of NO-sGC-cGMP-PKG signalling on membrane excitability may depend on the steady-state membrane potential of MSNs and interactions with glutamateric drive and NMDA receptor activation (modified from Threlfell and West 2013)

the major receptor for NO. NO binds to the heme domain on sCG and increases enzyme activity approximately 200–400-fold (Stone and Marletta 1994). sGC catalyzes the conversion of guanosine 5′-triphosphate (GTP) to cGMP. cGMP modulates many biological processes via activation of cGMP-gated ion channels, cGMP-dependent protein kinases (protein kinase G, PKG), cyclic nucleotide-dependent phosphodiesterases (PDEs) and others (Fig. 10.1).

10.2 Impact of Striatal Dopamine Signaling on Striatal Neuronal Excitability

In the striatum, five GPCRs (D1–D5) regulate cAMP production through DA signaling. D1-like receptors (D1 and D5) stimulate $G_{s/olf}$ proteins, allowing the α_s subunit to dissociate from the βγ-complex and stimulate AC to produce cAMP from ATP. D2-like receptors (D2, D3 and D4) stimulate G_i proteins and the α_i subunit inhibits AC and reduces cAMP production. It is now accepted that there is a segregation of dopaminergic receptors and peptide neurotransmitters in striatonigral and striatopallidal GABAergic medium-sized spiny projection neurons (MSNs). Although there is some degree of coexpression (Perreault et al. 2010), the majority of striatonigral MNSs exclusively express D1 dopaminergic receptors, as well as the neuropeptides dynorphin, and substance P, whereas the majority of the striatopallidal MSNs express D2 dopaminergic receptors and enkephalin (Gerfen and Young 1988). Therefore, upon activation of D1- or D2-like receptors, DA can increase or decrease the production of cAMP inducing opposite effects on signaling pathways in striatonigral and striatopallidal MSNs. cAMP can affect numerous downstream signaling pathways via the activation of PKA. Once activated, PKA has numerous cellular targets including voltage-gated ion channels, transcription factors, glutamate receptors and the DA- and cAMP –regulated phosphoprotein MW 32 kDA (DARPP-32) (Greengard et al. 1999; Hemmings et al. 1984). DA facilitates corticostriatal transmission via activation of D1-like receptors and stimulation of postsynaptic AC-cAMP-PKA signaling. Conversely, D2-like receptor activation produces the opposite effect in part by suppressing AC-cAMP-PKA signaling cascades in both pre- and postsynaptic elements.

DARPP-32 is a potent inhibitor of protein phosphatase-1 (PP-1) which is involved in the regulation of AMPA and NMDA receptor function and trafficking, expression of transcription factors such as CREB and ΔFosB, and neural plasticity (Svenningsson et al. 2004). DARPP-32 is expressed in areas receiving massive dopaminergic nerve terminals from the substantia nigra compacta (SNc) and ventral tegmental area (VTA), such as the striatum and nucleus accumbens, respectively (Hemmings and Greengard 1986; Ouimet et al. 1992, 1998). Immunohistochemical studies demonstrated that DARPP-32 is expressed in the perikarya including the dendritic spines, axon terminals, and the nucleus (Ouimet and Greengard 1990). Given that DARPP-32 is one of the primary targets of the cAMP-PKA signaling pathway, the cellular localization of this protein suggests that cAMP can regulate important cellular processes through DARPP-32. Via PKA activation, cAMP can transfer the extracellular pre-synaptic signal to DARPP-32 proteins located in the axon terminals and impact on the signal output of neurons and regulate long-term neural plasticity processes such as long-term depression (LTD) and long-term potentiation (LTP) (Calabresi et al. 2000). In the nucleus, DARPP-32 may also participate in the regulation of gene expression by increasing the phosphorylation of histone H3 (Stipanovich et al. 2008). cAMP-PKA signaling also stimulates cAMP

response element binding protein (CREB) phosphorylation, which regulates the expression of immediate early genes (IEGs) including members of the Fos and Jun family (Svenningsson et al. 2004).

10.3 Role of Striatal NO-cGMP Signaling in the Modulation of Striatal Neuron Excitability

NO is a gaseous neuromodulator implicated in the regulation of numerous physiological and pathophysiological processes in both the peripheral and central nervous system (Garthwaite 2008). NO is produced in the striatum by a subclass of GABAergic interneurons that co-express nNOS, neuropeptide Y and somatostatin (Kawaguchi et al. 1995). The synthesis of NO requires concurrent NMDA and DA D1 receptor activation (West and Tseng 2011). These interneurons are aspiny having 12–25 mm in diameter, fusiform or polygonal somas, and comprise less than 3% (~21,000 cells) of the total neuronal population of the striatum (West et al. 1996). The NO effector enzyme sGC is highly expressed in MSNs of both the direct and indirect pathways (Ariano 1983; Ding et al. 2004) and its activity is reported to be higher in the striatum than in any other region of the brain (Hofmann et al. 1977; Matsuoka et al. 1992). The nNOS-NO-sGC-cGMP-PKG pathway can phosphorylate DARPP-32 on the amino acid threonine 34 (Thr-34) (Tsou et al. 1993; Calabresi et al. 2000) and affect many other molecular signaling pathways. Studies performed in brain slices from rats and mice have shown that the nNOS-NO-sGC-cGMP-PKG signaling pathway mediates a rapid, transient increase in DARPP-32 phosphorylation at Thr-34 residue in striatal MSNs that is dependent on glutamatergic stimulation of NMDA, AMPA and metabotropic glutamate subtype 5 receptors, as well as an increase in intracellular calcium levels (Nishi et al. 2005).

Early work by our group demonstrated that intrastriatal infusion of the NO generator SNAP increased firing rate and burst duration of striatal neurons (West et al. 2002). On the other hand, systemic administration of NOS inhibitors decreased spontaneous firing activity of striatal MSNs and attenuated striatal NO efflux evoked by train stimulation of the frontal cortex (Ondracek et al. 2008). Intrastriatal infusion of the NO scavenger CPT-I0 decreased the responsiveness of striatal neurons to intracellular current injection (West et al. 2002), and also decreased the amplitude of excitatory postsynaptic potentials (EPSPs) evoked during electrical stimulation of the prefrontal cortex (West and Grace 2004). Consistent with this, we have recently demonstrated that genetic disruption of nNOS decreased the subpopulation of striatal neurons that exhibited spontaneously firing activity by approximately 50%, suggesting that tonic NO-cGMP levels play an important role in facilitating MSN activity in the striatum (Padovan-Neto et al. 2015b). Additionally, cortically-evoked responses were depressed in nNOS knockout mice as compared to wild type controls, showing that NO-cGMP signaling mediates synaptic facilitation during stimulation of corticostriatal afferents (Padovan-Neto et al. 2015b). Similar effects

were observed following manipulation of sGC activity. Thus, systemic administration of the sGC inhibitor ODQ reduced cortically-evoked MSN spike activity (Sammut et al. 2010) and the non-specific NOS/sGC inhibitor methylene blue attenuated striatal NO efflux evoked by train stimulation of the frontal cortex (Sammut et al. 2007). Taken together, these findings demonstrate that in the intact system, striatal NO signaling enhances the membrane excitability of striatal MSNs and facilitates corticostriatal transmission via a cyclic nucleotide-dependent mechanism (Padovan-Neto et al. 2015b; West and Grace 2004).

10.4 Phosphodiesterase Control of Striatal Neuronal Excitability

Numerous studies have shown that under physiological conditions, elevations in cyclic nucleotide levels facilitate MSN excitability (Threlfell and West 2013). Corticostriatal transmission is facilitated by drugs that increase cAMP and cGMP synthesis as well as agents which decrease their degradation (e.g., PDE inhibitors or cyclase activators). Conversely, corticostriatal transmission is depressed by drugs that produce opposite effects (e.g., cyclase inhibitors). Early studies using brain slice preparations demonstrated that bath application of the AC activator forskolin or a PKA activator enhanced the amplitude and duration of EPSPs evoked by electrical stimulation of cortical fibers, suggesting that AC-cAMP-PKA signaling pathway participates in the regulation of glutamatergic excitatory synaptic transmission in the striatum (Colwell and Levine 1995).

In agreement with the above observations, boosting intracellular cyclic nucleotide levels with PDE inhibitors or cGMP analogues (e.g. 8-Br-cGMP) has a facilitatory effect on membrane excitability and responsiveness of MSNs to corticostriatal inputs (West and Grace 2004; Threlfell et al. 2009; Sammut et al. 2010; Padovan-Neto et al. 2015b). The intracellular application of the PDE inhibitor zaprinast (non selective inhibitor of PDEs 5, 6, 9, 10 and 11) induced longer up-state durations compared with controls, an effect that was also observed with intracellular injection of cGMP (West and Grace 2004). In addition to this, zaprinast robustly depolarized the membrane of MSNs and increased the spontaneous spike activity of these cells (that is driven by glutamatergic inputs) (West and Grace 2004). Likewise, inhibition of intracellular cyclic nucleotide metabolism with the PDE10A inhibitor papaverine increased the duration of the depolarized up states and depolarized the average steady-state membrane potential (Threlfell and West 2014). Also, inhibition of PDE10A with papaverine or TP-10 increased responsiveness of MSNs to cortical inputs (Threlfell et al. 2009; Padovan-Neto et al. 2015b). This facilitatory effect of PDE10A inhibition was abolished via local sGC inhibitor infusion and absent in nNOS knockout mice (Padovan-Neto et al. 2015b). Taken together, these results indicate that PDE10A activity may act to dampen asynchronous or weak cortical input so that only strongly coherent corticostriatal transmission is capable of

producing spike activity in MSNs. Thus, attenuation of this filtering capacity of PDE10A with selective inhibitors is expected to increase intracellular cAMP/cGMP tone, and therefore the responsiveness of MSNs to glutamatergic corticostriatal transmission. Given its key role in controlling corticostriatal drive, manipulating the filtering capacity of PDE10A using pharmacological tools represents a promising strategy for treating neurodegenerative disorders like Parkinson's disease (PD), while perhaps, minimizing the side effects of DA-replacement therapies (see below).

10.5 Phosphodiesterase Expression and Control of Striatal Striatonigral and Striatopallidal Projection Pathways

PDEs are subdivided into 11 families and encoded by 21 genes resulting in more than 100 functionally distinct enzymes produced by alternate splicing (Menniti et al. 2006; Conti and Beavo 2007). The dual substrate enzymes PDE1B, PDE2A, and PDE10A are all highly enriched in the striatum. The cAMP specific enzymes PDE3A, PDE3B, PDE4D, PDE7B, and PDE8B are also prominently expressed in striatum. The cGMP specific enzyme PDE9A is moderately expressed in the striatum (Bender and Beavo 2006). PDEs have a significant modulatory role in second-messenger signaling due to their critical metabolic control over cAMP and cGMP. The large number of PDE isoforms expressed in striatum allows for precise temporal and spatial control over the function of individual MSNs, thereby enabling the coordination of electrical and chemical activity in the striatonigral and striatopallidal subpopulations of MSNs. The following sections will review our current state of knowledge on the role of PDE isoforms in the regulation of striatal processing and MSN output.

10.5.1 Dual-Substrate Phosphodiesterases

PDE1B: PDE1B is soluble and is abundantly expressed in the striatum (Polli and Kincaid 1994). PDE1B knockout mice have enhanced exploratory activity (Reed et al. 2002) and also increased DA turnover (Siuciak et al. 2007). The administration of the DA D1 receptor agonist SKF81297 to striatal slices obtained from PDE1B knockout mice increased phosphorylation of DARPP-32 at Thr34 and the GluR1 AMPA receptor at Ser845 (Reed et al. 2002). These findings suggest that PDE1B acts to filter cyclic nucleotide signaling mediated by DA D1 receptor stimulation in striatonigral MSNs. This filtering property of PDE1B is lost in the knockout mice and the abnormal cAMP signal amplification may result in the hyperphosphorylation of downstream target signaling proteins and increased activation of the direct striatonigral (i.e., go) pathway.

PDE2A: The PDE2A family (PDE2A1 – soluble; PDE2A2 and PDE2A3 – membrane bound) is abundantly expressed in the mammalian forebrain with particularly strong immunoreactivity exhibited in the striatum (Russwurm et al. 2009; Stephenson et al. 2009). PDE2A knockout mice cannot be used for behavioral studies because they die at gestational day 17–18 (Stephenson et al. 2009). Recent experiments have demonstrated however, that selective PDE2A inhibitors increased cAMP levels in response to stimulation of AC with forskolin, specifically in striatopallidal MSNs, whereas no effect was observed in striatonigral MSNs (Polito et al. 2013). This dichotomy disappeared when the broad-spectrum PDE inhibitor IBMX was administered, suggesting that at least one other PDE plays a dominant role in cAMP degradation in striatonigral MSNs (Polito et al. 2013). Therefore, although PDE2A is expressed similarly in both striatonigral and striatopallidal MSNs, it is likely that this enzyme controls cAMP metabolism preferentially in striatopallidal MSNs.

PDE2A is also regulated by cGMP signals in striatal MSNs (Polito et al. 2013; Lin et al. 2010). In the absence of cGMP, PDE2A activity is low, whereas the binding of cGMP to PDE2A increases its activity and drives cAMP hydrolysis (Martinez et al. 2002). In agreement with this, the NO donor SNAP attenuated forskolin-induced cAMP upregulation and this effect was abolished following PDE2A inhibition (Polito et al. 2013), confirming the role of PDE2A in the inhibitory crosstalk between cGMP and cAMP signaling. Also, the increase in intracellular levels of cAMP induced by DA D1-like receptors on striatonigral MSNs is negatively modulated by cGMP-dependent activation of PDE2A (Polito et al. 2013; Lin et al. 2010). These observations indicate that one of the functions of NO-cGMP signaling is to act as a negative feedback pathway which inhibits further cAMP synthesis following the activation of D1-like receptors on striatonigral MSNs, and potentially, on nNOS interneurons.

PDE10A: PDE10A immunoreactivity is abundant in MSNs (Xie et al. 2006) and recent studies suggest that this enzyme is also expressed in striatal interneurons (Leuti et al. 2013). Depending on its phosphorylation at threonine 16 (Thr 16), PDE10A can be tethered to the membrane or expressed in the cytosol (Charych et al. 2010; Kotera et al. 2004). Phosphorylated PDE10A is localized to the cytosol, whereas the non-phosphorylated form of PDE10A is attached to the membrane (Charych et al. 2010). The membrane attachment of PDE10A is controlled by palmitoylation, a posttranslational modification that facilitates tethering of proteins to the membrane and controls subcellular localization. When cAMP levels are high, PDE10A is phosphorylated by PKA at Thr 16 and accumulates in the cytosol to regulate cAMP levels (Charych et al. 2010). When intracellular cAMP levels are low, PDE10A becomes palmitoylated and attaches to membranes (including intracellular transport vesicles) where it can be transported and impact on corticostriatal signal transmission (Charych et al. 2010). The isoforms PDE10A1 and PDE10A2 are expressed in humans and the PDE10A2 and PDE10A3 isoforms are expressed in rodents (Kotera et al. 2004). PDE10A1 and PDE10A3 are enriched in the cytosol whereas the PDE10A2 isoform is enriched in membrane fractions. PDE10A was found to be the major cAMP PDE in lysates of mouse striatum, being responsible

for about 60% of cAMP degrading activity (Russwurm et al. 2015). In synaptosomal membranes, the PDE10A enzyme is part of a large multiprotein complex that contains the scaffold protein AKAP150 (A-kinase anchoring protein 150), PKA, PSD-95 (postsynaptic density protein 95), and NMDA receptors (Russwurm et al. 2015). Due to its ability to associate with membranes in striatal MSNs, it is likely that PDE10A has an important role in the integration and processing of motor information within the basal ganglia (Coskran et al. 2006; Seeger et al. 2003; Xie et al. 2006). Indeed, genetic deletion of the PDE10A enzyme induces hypolocomotion in mice, supporting the idea that PDE10A is critical for the regulation of striatal output and purposeful movement (Siuciak et al. 2006b).

While papaverine has been commonly used to explore the role of PDE10A in the regulation of striatal function, the synthesis of more potent and selective PDE10A inhibitors like TP-10 and MP-10 (developed by scientists at Pfizer) has moved the field forward considerably over the past decade (Schmidt et al. 2008). Early studies demonstrated elevations of cAMP and cGMP in striatal dialysates following papaverive and TP-10 administration (Siuciak et al. 2006a; Schmidt et al. 2008). Inhibition of striatal PDE10A activity also robustly increased the phosphorylation of DARPP-32 at Thr34, GluR1 at Ser845 and CREB (Schmidt et al. 2008; Nishi et al. 2008; Grauer et al. 2009).

The potent effects of PDE10A on basal ganglia output have been attracting considerable interest as selective enzyme inhibitors might prove efficacious for the treatment of numerous diseases associated with striatal dysfunction. Like D1 agonists and D2 antagonists, PDE10A inhibition induces expression of substance P and enkephalin mRNA in striatonigral and striatopallidal MSNs, respectively (Strick et al. 2010). Importantly, these outcomes have been corroborated at the behavioral level (Megens et al. 2014). The effects of PDE10A inhibitors appear to depend on the activation state of striatonigral and striatopallidal MSNs. Therefore, when the activity of direct pathway MSNs is reduced by D1 antagonism resulting in behavioral expression of catalepsy, PDE10A inhibitors potentiate catalepsy by increasing the inhibitory actions of the indirect pathway (acting as a D2-like antagonist) (Megens et al. 2014). In contrast, PDE10A inhibitors (acting as a D1-like agonist) can reverse catalepsy induced by the D2 antagonist haloperidol (Megens et al. 2014), although the opposite effect was observed with lower doses of haloperidol (Siuciak et al. 2006a).

By increasing intracellular levels of cyclic nucleotides, PDE10A inhibitors activate both striatonigral and striatopallidal MSNs, exerting the same function as D1 agonists and D2 antagonists. Several studies have suggested that PDE10A inhibitors activate the striatopallidal MSNs to a greater extent than the striatonigral MSNs (Nishi et al. 2008; Threlfell et al. 2009; Polito et al. 2015; Wilson et al. 2015). In one of the first studies to examine the impact of PDE10A inhibition on striatal MSNs, Nishi et al. (2008) demonstrated that papaverine-induced PDE10A inhibition potentiated D1 receptor signaling and increased DARPP-32 phosphorylation at Thr34 two-fold in striatonigral MSNs. PDE10A inhibition also activated cAMP/PKA signaling in striatopallidal MSNs potentiating adenosine A2A signaling and inhibiting D2 dopaminergic receptor signaling (Nishi et al. 2008). Furthermore, PDE10A

inhibition increased DARPP-32 phosphorylation at Thr34 sixfold in striatopallidal MSNs, suggesting a preferential action of PDE10A inhibitors on the indirect pathway (Nishi et al. 2008). In agreement with these outcomes, electrophysiological data provided by our group demonstrated that the PDE10A inhibitor TP-10 increased cortically-evoked activity in putative striatopallidal MSNs and did not affect cortically-evoked activity in antidromically-identified striatonigral MSNs (Threlfell et al. 2009).

Using c-Fos immunoreactivity as a marker of neuronal activation, recent studies have shown that the response to PDE10A inhibition was higher in the dorsolateral than the dorsomedial striatum (Wilson et al. 2015). This pattern of expression is similar to what is observed with the D2 antagonist haloperidol, whereas the expression of c-Fos in response to the DA D1 receptor agonist SKF82958 occurred preferentially in the dorsomedial areas (Wilson et al. 2015). In contrast, a recent *in situ* hybridization study demonstrated that IEGs were equally expressed in striatonigral and striatopallidal MSNs following PDE10A inhibition (Gentzel et al. 2015). However, while the methodologies used in these studies provide a quantitative measure of the number of neurons that were activated by PDE10A inhibition, they do not determine the level of activation of each individual MSN subtype. To address this issue, a recent study used cytoplasmic and nuclear biosensors in striatal slices to detect PKA-dependent protein phosphorylation and demonstrated that, although forskolin induced similar increments of cAMP in both striatonigral and striatopallidal MSNs, PKA-dependent phosphorylation was higher in the cytoplasm and nucleus of striatopallidal MSNs (Polito et al. 2015). Once activated, PKA can translocate to the nucleus and phosphorylate nuclear proteins. By monitoring the histone H3 phosphorylation (PH3) *in vivo*, Polito et al. (2015) demonstrated that 93% of striatopallidal MSNs in the dorsomedial striatum were immunorreactive for PH3 one hour after administration of the PDE10A inhibitor TP-10, whereas in the dorsolateral striatum both striatonigral and striatopallidal MSNs were positive for PH3 (Polito et al. 2015).

10.5.2 cAMP-Specific Phosphodiesterases

PDE 4: The PDE4 family (PDE4A-PDE4D) is made up of cAMP-specific PDEs widely distributed in the CNS (Perez-Torres et al. 2000). PDE4B exhibits immunoreactivity in the dorsal striatum, but to a lesser degree than the nucleus accumbens (Cherry and Davis 1999). Also, the expression of PDE4B is higher in striatopallidal MSNs as compared to striatonigral MSNs (Nishi et al. 2008). PDE4 also regulates DA synthesis and release at striatal dopaminergic terminals, and regulates cAMP-PKA signaling in MSNs (Nishi et al. 2008; West and Galloway 1996). Inhibition of PDE4 with rolipram increased DARPP-32 phosphorylation at Thr-34 in striatopallidal MSNs after administration of an agonist of adenosine A2A receptors, but had no effect on DARPP-32 phosphorylation at Thr-34 in striatonigral MSNs when a DA D1 receptor agonist was administered (Nishi et al. 2008). Therefore, inhibition

of PDE4 with rolipram potentiated cAMP-PKA signaling preferentially in striatopallidal MSNs, suggesting a selective function for this enzyme in the regulation of cAMP signaling in the indirect pathway.

PDE7: PDE7A and PDE7B are members of the PDE7 family and are expressed in the striatum. PDE7B mRNA is highly expressed in over 70% of GABAergic cells within the dorsal striatum and nucleus acumbens (Reyes-Irisarri et al. 2005). PDE7A mRNA is moderately expressed in the dorsal striatum but not in the nucleus accumbens (Miro et al. 2001). PDE7B mRNA colocalizes with AC5 in striatonigral and striatopallidal MSNs (de Gortari and Mengod 2010). PDE7B mRNA levels are enhanced after D1 but not D2 agonist administration (Sasaki et al. 2004), suggesting that PDE7B might participate on the regulation of intracellular cAMP tone following DA D1 receptor stimulation in striatonigral MSNs.

10.5.3 cGMP-Specific Phosphodiesterase

PDE9A: PDE9A is a key modulator of cGMP levels and therefore regulates neuronal cGMP signaling downstream of multiple signaling pathways (Fisher et al. 1998; Kleiman et al. 2012). The splice variant PDE9A5 localizes exclusively to the cytoplasm, whereas PDE9A1 is confined to the nucleus (Wang et al. 2003). PDE9 mRNA is localized throughout the CNS and has an abundant expression in the caudate-putamen (Van Staveren et al. 2003; Reyes-Irisarri et al. 2007). While PDE9A inhibitors have not been thoroughly explored in terms of striatal function, studies by the Pfizer group have shown that reverse microdialysis of a selective PDE9A inhibitor increases extracellular cGMP levels substantially (Verhoest et al. 2009). Our unpublished data indicate that similar to PDE10A inhibition and cGMP analogues, PDE9A inhibition acts to potentiate corticostriatal transmission (data not shown).

10.6 Cyclic Nucleotide Control of Striatal Synaptic Plasticity

Long-term synaptic plasticity occurs in the striatum and is important for the regulation of motor planning and learning and memory processes (Kreitzer and Malenka 2008). Both LTP and LTD can occur at corticostriatal inputs to striatopallidal and striatonigral MSNs. Long-term plasticity in the striatum is bidirectional and LTP can be reversed to baseline levels to reduce synaptic strength and increase the efficiency of information storage by a mechanism termed depotentiation (Calabresi et al. 2007). In striatal networks, depotentiation is thought to be involved in "forgetting" mechanisms in cases where motor information no longer needs to be stored (Huang and Hsu 2001). Interestingly in PD, the lack of depotentiation at corticostriatal synapses might result in abnormal storage of unnecessary motor-related information that will be translated into aberrant motor responses (Picconi et al. 2003, 2008).

High frequency stimulation (HFS) or spike-timing dependent plasticity (STDP) protocols can induce LTD in striatopallidal MSNs. This form of plasticity requires activation of metabotropic glutamate receptors (mGluRs) (Gubellini et al. 2001; Sung et al. 2001), DA D2 receptors (Calabresi et al. 1992c, 1997a) and CB1 receptors (Choi and Lovinger 1997; Gerdeman et al. 2002; Kreitzer and Malenka 2005; Ronesi et al. 2004). The effects of glutamate activation on postsynaptic mGluRs combined with calcium entry through L-type calcium channels stimulate MSNs to release endocannabinoids (eCB). DA activation of D2 receptors contributes to the release of eCB from MSNs, which activates CB1 receptors on the presynaptic glutamate terminals via retrograde signaling leading to reduction of glutamate release and induction of LTD. Therefore, eCB-induced LTD of corticostriatal synapses onto MSNs is initiated postsynaptically, but expressed presynaptically through reduction in neurotransmitter release. In contrast, LTD induced by NO occurs post-synaptically and appears to block eCB-induced LTD of corticostriatal synapses (Rafalovich et al. 2015). How LTD of corticostriatal transmission occurs in striatonigral MSNs is still not completely understood, but a recent study demonstrated a role of acetylcholine actions on G_i-coupled M4 muscarinic receptors (Shen et al. 2015) which are expressed in high levels at striatonigral MSNs (Bernard et al. 1992; Hersch et al. 1994). This study suggested that M4 muscarinic receptors promote LTD at corticostriatal synapses onto striatonigral MSNs (Shen et al. 2015) by decreasing intracellular cAMP levels via G_i protein-induced inhibition of AC (Augustin et al. 2014; Kheirbek et al. 2009).

NO has an important role in plasticity and regulates the vesicular GABA transporter (VGAT) and GABA transmission at axon collaterals in striatal MSNs by a mechanism that requires cGMP-induced CREB phosphorylation (Sagi et al. 2014). The NO-cGMP signaling pathway also contributes to LTD induction. For example, increasing levels of cGMP with the PDE inhibitor zaprinast mimics the effect of HFS of corticostriatal fibers and also induces LTD in the striatum (Calabresi et al. 2000). LTD in MSNs can also be pharmacologically induced following stimulation of PKG and is blocked by administration of the sCG inhibitor ODQ and nNOS inhibitors, demonstrating that NO-cGMP signaling is necessary for this type of plasticity (Calabresi et al. 1999). As opposed to LTD induced by eCB signaling, NO-induced LTD occurs post-synaptically and it is not dependent on DA D2 or CB1 receptors, and is not affected by changes in intracellular levels of Ca^{2+} (Rafalovich et al. 2015).

LTP also occurs at corticostriatal synapses (Charpier and Deniau 1997) and requires glutamate activation of NMDA receptors and concurrent increase on intracellular calcium levels (Kerr and Plenz 2002). STDP-induced LTP at striatopallidal MSNs is mediated by adenosine A2A receptor activation and disrupted by it antagonism (Shen et al. 2008). In striatonigral MSNs, activation of DA D1 receptors is necessary for LTP induction (Kerr and Wickens 2001; Centonze et al. 1999).

According to the outcomes observed in the previous studies, the level of intracellular cAMP seems to be a determinant factor for striatal bidirectional plasticity. Under physiological conditions, DA has dual opposite effects on striatonigral and striatopallidal MSNs by acting on D1 (facilitatory) and D2 (inhibitory) DA receptors,

respectively. Due to the fact that D1 receptors are linked to $G_{s/olf}$ protein and D2 receptors are linked to G_i protein, MSNs can respond in opposite ways to dopaminergic stimulation mediated by stimulation or inhibition of AC. In fact, AC control of cAMP levels is essential for long-term plasticity and AC subtype 5 knockout mice exhibit impaired LTD that is not recovered by coactivation of D2 and mGlu receptors (Kheirbek et al. 2009). Also, inhibition of PKA blocks LTD and LTP induced by corticostriatal HFS (Centonze et al. 2003). Recent experiments demonstrated an important role of intracellular cAMP levels in LTD induction in striatopallidal MSNs (Augustin et al. 2014). The authors combined either HFS or LFS of glutamatergic inputs to the striatum with postsynaptic depolarization to mimic the upstate of MSNs, and therefore, activate L-type calcium channels and NMDA receptor function (Carter and Sabatini 2004). These studies demonstrated that HFS of corticostriatal fibers and low levels of cAMP are able to produce LTD at striatopallidal MSNs (Augustin et al. 2014). In contrast, LTP was observed in conditions where LFS was combined with high intracellular cAMP levels (Augustin et al. 2014). These observations are consistent with current models of the pathophysiology of PD: DA depletion would lead to hyperactivity of the indirect pathway and the lack of DA actions onto D2 receptors would increase cAMP levels and block LTD induction. LTD is also blocked by DA receptor antagonists (Calabresi et al. 1992b) and by the genetic ablation of D2 receptors (Calabresi et al. 1997b). In contrast, agonism of D2 receptors with quinpirole (Augustin et al. 2014) or exogenous DA replacement with L-DOPA (Picconi et al. 2003) decrease intracellular cAMP levels and restore LTD in the striatopallidal pathway in a manner with also rescues motor performance (Beeler et al. 2012).

In summary, the nature of GPCR (and the downstream effect on AC and cAMP levels) is a critical determinant factor for the direction of striatal synaptic plasticity. In striatopallidal MSNs stimulation of G_i-coupled DA D2 receptors is required for the induction of LTD, whereas G_{olf}-coupled adenosine A2A receptors facilitates LTP (Shen et al. 2008). In striatonigral MSNs, LTP is induced by stimulation of $G_{s/olf}$-coupled DA D1 receptors, whereas LTD is dependent on acetylcholine actions on G_i-coupled M4 muscarinic receptors (Shen et al. 2015).

10.7 Targeting Cyclic Nucleotide Phosphodiesterases for the Treatment of L-DOPA-Induced Dyskinesia in PD

The severity and pattern of DA depletion that occurs in PD can be experimentally replicated in animals by toxins (Lane and Dunnett 2008). The most common PD models are produced by injections of 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP), or by intracerebral injection of 6-hydroxydopamine (6-OHDA). Administration of L-DOPA to patients or animal models of PD effectively restores purposeful movement, however, with repeated administration, L-DOPA can cause

abnormal involuntary movements called L-DOPA-induced dyskinesias (i.e, LIDs). Studies in parkinsonian rodents have shown that L-DOPA causes dyskinesia only when a severe (>80–90%) lesion of the nigrostriatal system is achieved (Meredith et al. 2008). Substantial research efforts have been conducted to understand the molecular mechanisms that underlie the development and expression of LIDs (Huot et al. 2013). Since DA is required for both forms of long-term plasticity, rodent models exhibiting substantia DA depletion that occurs in PD do not express LTP and LTD at corticostriatal synapses (Calabresi et al. 1992a; Centonze et al. 1999; Picconi et al. 2003; Wang et al. 2006). Chronic L-DOPA administration is able to restore LTP in MSNs of 6-OHDA-lesioned rats, but once dyskinesias are established, depotentiation of LTP is lost (Picconi et al. 2003, 2008). The lack of depotentiation at corticostriatal synapses during LIDs might result in abnormal storage of maladaptive motor-related information that will be translated in aberrant motor responses.

Corticostriatal LTP is also reduced in the parkinsonian striatum (Picconi et al. 2003). DA denervation in rodent models of PD impairs corticostriatal LTP and chronic (but not acute) L-DOPA treatment is able to restore LTP in both dyskinetic and non-dyskinetic rodents (Picconi et al. 2003, 2008). Bidirectional plasticity is observed at corticostriatal synapses in non-dyskinetic animals where a physiological reversal of synaptic strength occurs after LFS (Picconi et al. 2003). Depotentiation is lost in the dyskinetic striatum (Picconi et al. 2003), but the precise subtype of striatal MSN involved in this mechanism remains to be determined. Pioneering studies by Calabresi and colleagues showed no difference in terms of physiological and pharmacological responses between striatopallidal and striatonigral MSNs using double immunohistochemical labeling with biocytin and adenosine A2A or substance P, respectively (Picconi et al. 2011). In contrast, more recent work using brain slices from D1 or D2 bacterial artificial chromosome (BAC) transgenic mice demonstrated that depotentiation in dyskinetic animals is related to changes at the level of the DA D1 receptor signaling pathway (Shen et al. 2015).

Rodent models of LIDs show abnormally low levels of cAMP/cGMP in striatum during peak occurrence of LIDs (Giorgi et al. 2008; Sancesario et al. 2014), suggesting that PDE activity might be increased (or synthesis decreased), resulting in augmented metabolism of cyclic nucleotides. Systemic (Giorgi et al. 2008) or intrastriatal (Picconi et al. 2011) administration of PDE inhibitors (zaprinast or the sildenafil analogue UK-343664) was found to reduce the incidence of LIDs in parkinsonian rats by preventing both the L-DOPA-induced decrease of cyclic nucleotide tone, and the rescuing of striatal LTD. These results suggest that PDE inhibitors could be useful therapeutic agents in the treatment of LIDs due to their ability to restore abnormal glutamatergic transmission.

The pharmacological manipulation of PDE signaling pathways is complex and its relationship with LIDs is not completely understood. The PDE inhibitor used in the previous studies (zaprinast) exhibits relatively poor potency and selectivity across cGMP preferring PDE sub-families and isoforms, and as such, is likely to produce undesirable side effects. In support of this, a study using the *Pitx3*$^{-/-}$ aphakia mouse, a genetic model of PD, demonstrated zaprinast is able to reduce established LIDs, but also reduced motor performance on the rotarod (Solis et al. 2015).

The relationship between striatal NO-cGMP signaling in LIDs is still controversial (Lorenc-Koci et al. 2013; Takuma et al. 2012; Solis et al. 2015; Padovan-Neto et al. 2009, 2015a; Sancesario et al. 2014; Picconi et al. 2011). nNOS inhibitor co-treatment has been shown to prevent the development of LIDs and maintain L-DOPA antiparkinsonian efficacy throughout the chronic treatment period (Padovan-Neto et al. 2009, 2015a; Takuma et al. 2012). Although this result is in contrast with the effects obtained with zaprinast on LIDs (Picconi et al. 2011), it was recently demonstrated (Solis et al. 2015) that decreasing NO/cGMP levels with the selective nNOS inhibitor 7-nitroindazole (7-NI), or boosting NO/cGMP signaling pathway with the NO donor molsidomine or the PDE inhibitor zaprinast, significantly diminished the incidence of AIMs in the *Pitx3*$^{-/-}$ aphakia mouse model of PD. The effects of 7-NI on LIDs do not interfere with the beneficial therapeutic effect of L-DOPA (Padovan-Neto et al. 2009, 2015a; Solis et al. 2015), whereas the antidyskinetic effects of molsidomine and zaprinast occurred at the expense of the antiparkinsonian L-DOPA properties (Solis et al. 2015). Although seemingly paradoxical, these results might occur as a result of a differential rebalancing of the direct (go) and indirect (no-go) pathways: nNOS inhibitors might reduce the over-activation of striatonigral MSNs, whereas the PDE inhibitors might act to disinhibit striatopallidal MSNs which are likely suppressed by L-DOPA-mediated agonism at DA D2 receptors. By re-balancing striatal output within the direct and indirect pathways, both nNOS and PDE inhibitors might be useful pharmacological targets for treating LIDs.

A common view is that LIDs is a consequence of over-activation of DA D1 receptors and over-inhibition of DA D2 receptors on striatonigral and striatopallidal MSNs, respectively (Feyder et al. 2011). The abnormal stimulation of D1 receptors induces post-synaptic expression of molecular markers of LIDs such as the transcription factor FosB/ΔFosB (Andersson et al. 1999; Cenci et al. 1999; Berton et al. 2009; Pavón et al. 2006; Tekumalla et al. 2001), DARPP-32 phosphorylation at Thr 34 (Bateup et al. 2010; Santini et al. 2007, 2010; Picconi et al. 2003; Lebel et al. 2010), PKA-dependent phosphorylation of GluR1 at Ser845 (Santini et al. 2007, 2010) and abnormal levels of phosphorylation of the extracellular signal-regulated kinase 1/2 (ERK 1/2) cascade (Santini et al. 2007, 2010; Gerfen et al. 2002; Pavón et al. 2006; Westin et al. 2007). In agreement with the above studies, antagonism of D1 receptors (Westin et al. 2007; Santini et al. 2009) and genetic deletion of D1 DA receptors (Darmopil et al. 2009) block LIDs in rodent models of PD. In terms of synaptic plasticity, striatonigral MSNs undergo strong LTP as a result of enhanced and abnormal D1 DA receptor stimulation (Picconi et al. 2003; Seifert et al. 2015), and consequently, high intracellular levels of cAMP (Augustin et al. 2014). In support of this, reducing intracellular cAMP tone on striatonigral MSNs by targeting M4 muscarinic receptors with a positive allosteric modulator not only restored depotentiation, but also attenuated LIDs (Shen et al. 2015), confirming the important role of abnormal D1-mediated plasticity in LIDs.

On the other hand, D2 receptor-expressing MSNs are also importantly involved in LID mechanisms. For example, STDP protocols that would normally induce LTP in striatopallidal MSNs, induce LTD in dyskinetic animals (Shen et al. 2015),

contributing to excess inhibition in the indirect pathway. Therefore, knowing that LIDs are characterized by over-stimulation of D1- and over-inhibition of D2-expressing MSNs, PDE10A inhibitors should promote antidyskinetic effects by increasing intracellular cAMP and cGMP levels and restoring LTP in striatopallidal MSNs, releasing this pathway from over-inhibition during LIDs. As discussed before, PDE10A is highly expressed in MSNs and compartmentalized proximal to the plasma membrane of dendritic spines, in position to regulate post-synaptic cyclic nucleotide signaling involved in the integration of glutamatergic and dopaminergic neurotransmission (Xie et al. 2006). Given that other classes of PDE inhibitors exhibit antidyskinetic properties, we recently targeted PDE10A as a possible candidate for the treatment of LIDs. Preliminary studies conducted in our lab demonstrated that chronic (3 weeks) treatment of the PDE10A inhibitor TP-10 together with L-DOPA dose-dependently attenuated LIDs in the 6-OHDA-lesioned rat model of PD, without interfering with rotational or normal behaviors (Figs. 10.2 and 10.3). These observations provide evidence for the first time that robust PDE10A inhibition reduces the incidence and severity of LIDs and indicate that these effects are not due to decreased behavioral activation.

Recent *in vivo* human studies analyzed the availability of PDE10A in PD patients using positron emission tomography molecular imaging with a highly selective PDE10A radioligand (Niccolini et al. 2015). Interestingly, the authors found a loss of PDE10A signaling in the striatum and globus pallidus of PD patients under L-DOPA treatment which was correlated with longer disease duration and more severe motor symptoms (bradykinesia and rigidity), suggesting that compensatory mechanisms might occur to modulate PDE levels in the human basal ganglia. Given the above, future studies will have to clarify how the expression and activity of various PDE subtypes expressed in striatal MSNs changes with disease progression, and how this may impact on pharmacological treatment strategies targeting PDEs for the treatment of LIDs.

PDEs are highly regulated enzymes and participate in many molecular mechanisms responsible for controlling striatal signaling output. Although many groups have provided important behavioral and pharmacological data, little information is available regarding the mechanisms of actions of these enzymes. For example, we now know that PDE10A has a greater impact on striatopallidal MSNs even though the expression of this enzyme is similar in both striatonigral and striatopallidal MSNs. Once we understand the molecular mechanisms that contribute to this effect, better pharmacological approaches will be available to treat neuropsychiatric and movement disorders.

Several PDE isoforms are expressed in the striatum but little is known about how these enzymes interact to produce the appropriate motor output. For example, PDE1B is also expressed within MSNs in the striatum. It seems that this isoform has a preferential modulatory effect on the striatonigral MSNs in contrast to the PDE10A, which has been shown to act preferentially on striatopallidal MSNs. Since striatonigral and striatopallidal MSNs have opposing action on motor control, these two PDEs might act together to control striatal motor output. In this case, targeting multiple PDEs isoforms could be an interesting approach to treat hypokinetic

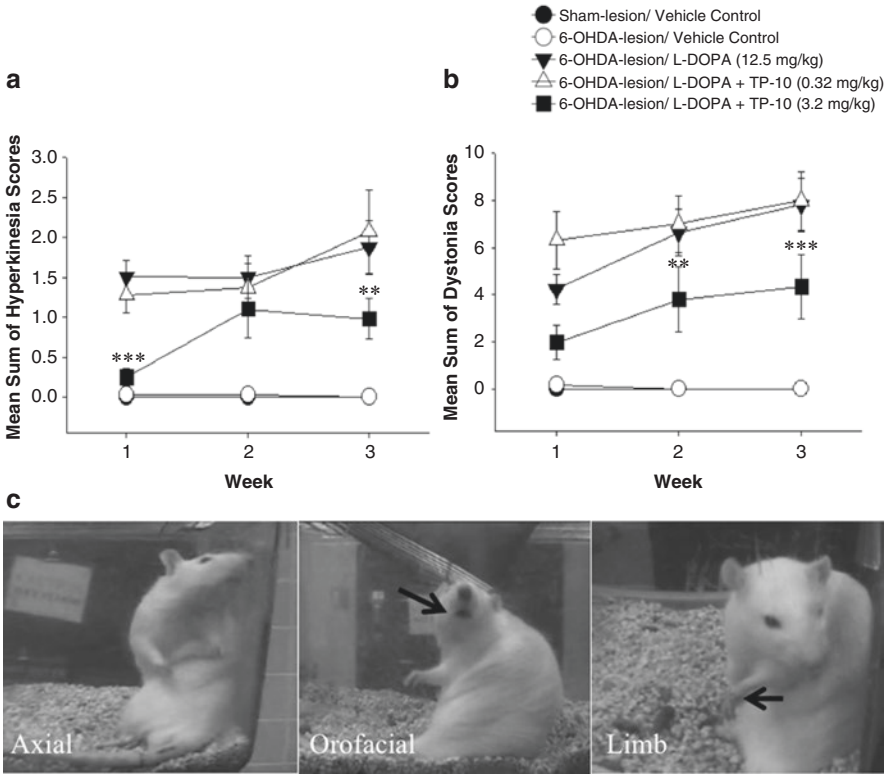

Fig. 10.2 Effects of the PDE10A inhibitor TP-10 co-administration with L-DOPA on dyskinetic behaviors. (**a**) A significant attenuation of hyperkinetic behaviors was observed in weeks 1 and 3 in L-DOPA plus TP-10 (3.2 mg/kg) treated animals as compared to L-DOPA controls (**p < 0.01 ***p < 0.001). There was no significant difference between groups receiving only L-DOPA therapy and L-DOPA plus TP-10 (0.32 mg/kg). (**b**) A significant attenuation of dystonic behaviors was observed in weeks 2 and 3 in L-DOPA plus TP-10 (3.2 mg/kg) treated animals as compared to L-DOPA controls (**p < 0.01 ***p < 0.001). There was no significant difference between groups receiving only L-DOPA therapy and L-DOPA plus TP-10 (0.32 mg/kg). TP-10 didn't affect rotational behavior and normal behavior such as grooming and exploring (data not shown). Data are derived from n = 8–21 rats per group. (**c**) Still images of dyskinetic behaviors (Maries et al. 2006). (*Left*) Severe axial dystonia. (*Middle*) Mild to moderate orofacial dyskinesia (*black arrow*) and neck dystonia. (*Right*) Left forepaw dyskinesia (*black arrow*)

movement disorders like PD. The combination of PDE1B and PDE10A inhibitors could be used alone or together with low doses of L-DOPA to improve motor function since PDE1B inhibition may preferentially enhance striatonigral MSN activity, whereas PDE10A inhibition may preferentially facilitate striatopallidal MSN activity.

Preclinical tests to access the antidyskinetic effects of the PDE10A inhibitors in non-human parkinsonian primates will be of great value for predicting outcomes in future clinical trials. PDE10A inhibitors are currently being tested for Huntington's

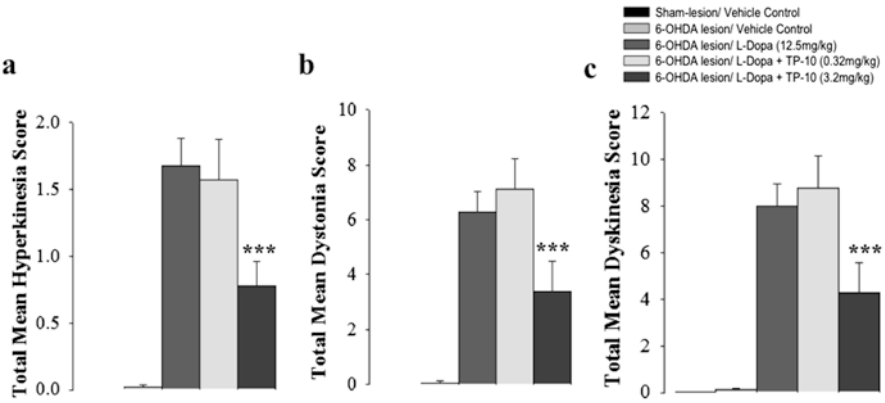

Fig. 10.3 Summary of the effects of PDE10A inhibitor co-administration with L-DOPA on total combined dyskinetic behaviors. (**a**) A significant decrease in hyperkinetic movements was observed in rats receiving L-DOPA plus TP-10 (3.2 mg/kg) as compared to L-DOPA controls (***$p < 0.001$). No significant difference was observed between rats receiving only L-DOPA and those receiving L-DOPA plus the low dose of TP-10 (0.32 mg/kg). (**b**) A significant decrease in dystonia was observed in rats receiving L-DOPA plus TP-10 (3.2 mg/kg) as compared to L-DOPA controls (***$p < 0.001$). No significant difference was observed between rats receiving only L-DOPA and those receiving L-DOPA plus the low dose of TP-10 (0.32 mg/kg). (**c**) The total dyskinesia score was significantly reduced following co-administration of TP-10 (3.2 mg/kg). Data are derived from N = 8–21 rats per group

disease (HD; clinicaltrials.gov: NCT01806896, NCT02197130, and NCT02342548). These outcomes will be of great interest for LID as well since this hyperkinetic disorder shares some similarities with HD. In both LID and early stages of HD the indirect pathway is hypoactive, whereas the direct pathway is hyperactive. DA produced from L-DOPA is responsible for over-inhibition of striatopallidal MSNs in LID and the selective degeneration of striatopallidal MSNs contributes to the appearance of hyperkinetic movements in early stages of HD. If these clinical trials establish the efficacy of PDE10A inhibitors for treating motor symptoms in HD, a new pharmacological tool will be available to treat this and other hyperkinetic disorders.

Conflict of Interest The authors declare that they have no conflicts of interest.

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