Chapter 11
Role of Phosphodiesterases in Huntington's Disease

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Abstract Huntington's disease (HD) is an autosomal-dominant rare inherited neurodegenerative disease characterized by a wide variety of symptoms encompassing movement, cognition and behaviour. The cause of the disease is a genetic mutation in the *huntingtin* protein. The mutation leads to an unstable CAG expansion, translated into a polyglutamine domain within the disease protein. Indeed, huntingtin has a CAG/polyglutamine expansion in the range of 6–39 units in normal individuals, whereas it reaches 39–180 units in HD patients. Mutant *huntingtin* interacts with and impairs the function of a number of transcription factors. Indeed, the expression and function of cAMP response element-binding protein (CREB) and the brain-derived neurotrophic factor (BDNF) are severely affected in HD. Drugs targeting CREB loss of function and BDNF decrease have been considered as powerful tools to treat HD. Recently, cyclic nucleotide phosphodiesterase (PDE) inhibitors have been shown to reduce striatal and cortical degeneration in transgenic mouse model of HD. The neuroprotective effect is due to the competency of PDE4, 5 and 10 inhibitors to positively modulate CREB and BDNF protein levels, both in striatum and cortex in HD models. In this chapter, we will summarize the data supporting the use of PDE inhibitors as a therapeutic approach to fight HD, deepening the possible mechanisms of action underlying these effects.

Keywords Huntington's Disease • Phosphodiesterase inhibitors • BDNF • striatum

11.1 Introduction

Huntington's disease (HD) is an autosomal dominant rare neurodegenerative disorder, characterized by motor disfunction, cognitive decline and psychiatric disturbances. Motor symptoms are dominated by chorea, an involuntary muscle contraction that results from the impairment of the basal ganglia, which is the main target of HD. HD is caused by the mutation of *IT15* gene, which is located on the

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short arm of chromosome 4 and is characterized by a CAG expansion encoding a polyQ repeat at N-terminus of huntingtin protein (Albin and Tagle 1995). The polyQ tract promotes the formation of toxic oligomers and aggregates. In physiological conditions, people have fewer than 36 glutamine repeats in the polyQ region resulting in the production of the cytoplasmatic huntingtin. A sequence of 36 or more CAG repeats results in the production of mutated huntingtin. Generally, the number of CAG repeats is related to the severity of the disease and accounts for about 60% of the variation of the age of the onset of symptoms. In fact, 36–39 repeats result in a reduced penetrance form of the disease with a later onset and slower progression of symptoms. Conversely, a large repeats count determines a full penetrance of HD disease, which might occur even before the age of 20, when it is then referred to a juvenile HD, and this accounts for about 7% of HD carriers.

Huntingtin interacts with over 100 other proteins, and appears to have multiple biological functions. The behavior of the mutated protein is not completely understood, but it is known to be toxic to certain cell types, particularly in the brain, because of the formation of neuronal intranuclear inclusions (NIIs) of mutated huntingtin (Di Figlia et al. 1997). Early damage in HD is most evident in the striatal part of the basal ganglia. The spiny projection neurons, which constitute about 95% of the striatum, degenerate massively in HD (Auer et al. 1984; Smith et al. 1984; Kalimo et al. 1985). Interestingly, a similar marked loss of the striatal projection neurons occurs in experimental cerebral ischemia (Meade et al. 2000). Signs of neurodegeneration are observed also in the cortex, thalamus, and globus pallidus (in the later stages of the disease). Cortical pathology also occurs, contributing to the overall dramatic brain atrophy in the late stages of the disease (Hong et al. 2012, Unschuld et al. 2012, Gray et al. 2013, Samadi et al. 2013 Moreover, signs of cortical dysfunction are often observed before a neuropathological signs are apparent.

One of the mechanisms underlying the vulnerability of striatum in HD is explained by the fact that these neurons do not synthesize sufficient amounts of BDNF. BDNF is very important for survival of mature neurons in the striatum (Zuccato and Cattaneo 2007). Striatal BDNF depends on the cortex for its synthesis and release, as it is synthesized by cortical neurons and released in the striatum by cortico-striatal anterograde transport (Zuccato et al. 2003). This microtubule-based transport depends on huntingtin and is altered in HD. Low levels of BDNF mRNA have been reported in the rat striatum (Baquet et al. 2004).

CREB is a transcription factor, and its function is impaired by mutated huntingtin (Altar et al. 1997; Steffan et al. 2000; Sugars et al. 2004). This supports the hypothesis that inhibition of cAMP response element-mediated gene transcription contributes to HD. In fact, cAMP levels are decreased in cerebrospinal fluid of HD patients and transcription of CREB-regulated genes is reduced in the R6⁄2 transgenic mouse model of HD (Luthi-Carter et al. 2000; Nucifora et al. 2001; Wyttenbach et al. 2001).

Huntingtin modulates the expression of neuron-restrictive silencer factor (NRSF)-controlled neuronal genes, including *BDNF* gene (Zuccato et al. 2003). Therefore, wild-type huntingtin directly stimulates production of BDNF, whereas mutant huntingtin inhibits it. In fact, BDNF is decreased in the brain of HD patients

and in mice transgenic for mutant huntingtin (Ferrer et al. 2000; Duan et al. 2003; Zhang et al. 2003). Overexpression of BDNF showed to be neuroprotective in the R6/1 mouse model of HD (Gharami et al. 2008; Yuxiang et al. 2010). However, mice overexpressing BDNF display higher susceptibility to seizure to kainic acid *in vivo* and hyper-excitability in CA3 region of the hippocampus and entorhinal cortex *in vitro*, because of the effects of BDNF on epileptogenic regions, such as the entorhinal cortex and hippocampus (Papaleo et al. 2011). Moreover, overexpression of BDNF in experimental animals leads to increased anxiety-like behavior and deficits in working memory (Bimonte et al. 2003). Thus, both excess and insufficient BDNF can be detrimental, and such issues have to be addressed before BDNF is used to treat HD patients. BDNF knockout mice have not only an earlier age of onset, but also more severe motor symptoms. Thus, a specific involvement of BDNF was demonstrated in the pathophysiology of the disease in several ways.

11.2 Cyclic Nucleotides Phosphodiesterases

The cyclic nucleotide phosphodiesterases (PDEs) are a group of enzymes that selectively catalyze the hydrolysis of the 3′ cyclic phosphate bonds in the second messenger molecules of adenosine and/or guanosine 3,5′ cyclic monophosphate (cAMP and cGMP). They can regulate the localization, duration, and amplitude of cyclic nucleotide signaling within subcellular domains. cAMP and cGMP are second messengers responsible of the transduction of several extracellular signals, including hormones and neurotransmitters. Cyclic nucleotides are formed from ATP and GTP by the catalytic reactions of adenylyl cyclase (AC) and guanylyl cyclase (GC). These enzymes are activated when agonists bind to their appropriate G-protein coupled receptors (GPCR) and stimulate the heterotrimeric G-protein Gs (Lefkowitz 2004) or following activation of a diffusible second messanger, such as nitric oxide (NO) (Corbin et al. 2000; Das et al. 2005) or via an intracellular signal, such as calcium(Ca^{2+2+})/calmodulin (Goraya and Cooper 2005). The synthesized cAMP diffuses throughout the cell to sites where it can bind to and activate its target enzymes represented by cAMP- and cGMP-dependent protein kinases, such as protein kinase A (PKA) and protein kinase G (PKG). These kinases act phosphorylating substrates such as ion channels, transcription factors and contractile proteins that regulate key cellular functions. cAMP and cGMP signaling responses are compartmentalized, and this compartmentalization allows spatially distinct pools of PKA and PKG to be differentially activated. This idea was confirmed by observations of cAMP signaling in live cells by FRET, that showed that the accumulation of this second messenger occurs in localized cAMP pools (Houslay 1995, 1998). Such microdomains are created by physical interactions between different components of signaling cascades and structural elements of the cell (Houslay and Milligan 1997). Signal termination mechanisms are essential for cellular homeostasis in order to modulate fluctuations of cAMP within these compartments. Such critical process is catalyzed by cAMP/cGMP hydrolyzing enzymes known as cyclic nucleotide PDEs. In fact,

the basis of cyclic nucleotide gradients is concerted by the activity and localization of both cyclases, which generate cAMP or cGMP, and PDEs, which degrade them. In particular, sequestration and anchoring of PDEs to distinct sites is the principal mechanism to create cyclic nucleotide gradients allowing selective actions (Houslay and Milligan 1997; Houslay and Adams 2003). The basis of this compartmentalization is that various PKA isoforms are anchored to different specific intracellular sites by proteins called A-kinase anchoring proteins (AKAPs) (Rubin 1994). It is postulated that AKAPs, with their distinct pattern of intracellular distribution, allow discrete PKA populations to control the gradients of cAMP in the cell and to modify localized target proteins. In this way, AKAPs sequester PKA to distinct subcellular locations, and position specific enzymes to respond to changes in local cAMP concentrations (Sanderson and Dell'Acqua 2011). However, the predominant regulatory event is the hydrolysis of cAMP by phosphodiesterases. High PDE activity reduces cellular cAMP levels and thus decreases the ability of anchored PKA to become active, whereas reduced PDE activity will favor PKA activation (Bauman and Scott 2002). Inhibition of PDE activity in the brain can, thus, lead to increased intracellular cAMP and/or cGMP levels, thereby modulating neuronal function. Twenty-one genes encode for the superfamily of PDEs, which is subdivided into 11 families according to structural and functional properties (Bender and Beavo 2006). Each PDE family has several different isoforms and splice variants (Beavo et al. 1994); they differ in their three-dimensional structure, mode of regulation, intracellular localization, cellular expression, pharmacological properties and sensitivity to inhibitors. PDEs activity are localized in the cytosol and in a number of membrane, nuclear and cytoskeletal structures (Hardingham and Bading 1998; Houslay 2001). Individual isozymes modulate distinct regulatory pathways in the cell, and on the basis of substrate specificity can be divided into three groups: cAMP-selective hydrolases (PDE 4, 7 and 8), cGMP-selective hydrolases (PDE 5, 6, and 9), and dual (cAMP and cGMP) hydrolases (PDE 1, 2, 3, 10, and 11).

11.2.1 PDEs in the Brain

11.2.1.1 Regional Distribution of PDEs

Several PDEs are expressed in neurons, each playing different roles in cAMP and cyclic GMP (cGMP) signaling. *In situ* hybridization and immunohistochemistry demonstrated that the PDE1A isoform is expressed especially in cerebral cortex, striatum and pyramidal cells of the hippocampus (Polli and Kincaid 1994). PDE1B isoform is also expressed in several brain areas such as striatum, nucleus accumbens, dentate gyrus of hippocampus, medial thalamic nuclei, and brainstem (Menniti et al. 2006). Mice lacking PDE1B exhibit increased DARPP-32 phosphorylation at Thr34, thus indicating that PDE1B normally down-regulates cAMP/PKA signaling in striatal neurons (Reed et al. 2002). PDE2A expression is highest in the brain, where the enzyme is typically localized in the cortex, hippocampus and striatum

(Repaske et al. 1993). PDE3A is relatively highly expressed in platelets, as well as in vascular smooth muscle, cardiac myocytes, adipose tissue, liver, and in several cardiovascular tissues (Shakur et al. 2001). PDE4 family is the most widely studied of the PDEs. There are four genes that encode different PDE4 enzymes, of which PDE4A, PDE4B and PDE4D, but not PDE4C, are expressed in the CNS with high concentrations in the cortex, hippocampus, area postrema and striatum (Cherry and Davis 1999).

In the rodent brain, PDE5A mRNA was studied in the Purkinje cells of the cerebellum, in the pyramidal cells of CA1, CA2 and CA3, as well as in the dentate gyrus of the hippocampus (Van Staveren et al. 2003). PDE6 was initially thought to be exclusively distributed to the retina, however, PDE6B mRNA expression was also described in mouse hippocampus (Jarnaess and Tasken 2007). The PDE7 family is composed of two genes coding for high-affinity, rolipram-insensitive, cAMP-specific enzymes PDE7A and PDE7B. While the distribution of these enzymes at the protein level has not been reported, high mRNA concentrations of both PDE7A and PDE7B are expressed in rat brain and in numerous peripheral tissues. Peak concentrations of PDE7 mRNA are found in the olfactory bulb and tubercle, the hippocampus, particularly in the granule cells of the dentate gyrus, and several brainstem nuclei as well as in cerebellum and several thalamic nuclei (Andreeva et al. 2001, Van Staveren et al. 2004).

The expression of mRNA of PDE9A in the rodent brain was described in the Purkinje cells and granule cells of the cerebellum, striatum, olfactory bulb, tubercle as well as CA1 and dentate gyrus of the hippocampus (Fujishige et al. 1999; Sasaki et al. 2002). In the human brain, PDE9 mRNA expression has been reported in the insula and in the visual cortex as well as in the CA1, CA2 and CA3 subfields and dentate gyrus of the hippocampus (Loughney et al. 1999). According to immunohistochemistry and *in situ* hybridization studies, PDE10A is particularly expressed in the brain with the highest levels in both the dorsal and ventral striatum (caudate nucleus, nucleus accumbens, and olfactory tubercle) and, to a lesser extent, in the cerebellum, thalamus, hippocampus, and spinal cord (Seeger et al. 2003, Hebb et al. 2004, Reyes-Irisarri et al. 2005, Reyes-Irisarri et al. 2007). The presence of mRNA transcript PDE10A in the caudate region of the basal ganglia suggests a role in modulating striato nigral and striato pallidal pathways (Coskran et al. 2006).

11.2.2 Cellular and Subcellular PDEs Distribution

Originally, PDE10A immunoreactivity was described only in medium spiny neurons (Xie et al. 2006). In contrast, studies reported that PDE10A was not expressed in striatal interneurons. However, recent studies demonstrated that the striatal interneurons (parvalbuminergic, calretininergic and somatostatinergic) share a common pattern of PDE10A immunoreactivity (Leuti et al. 2013). Indeed, all these interneurons have a nuclear localization of PDE10A, with little or no perikaryal immunoreactivity. Immunoreactivity for PDE10A was observed in moderate

amounts in the nuclei of all striatal interneurons except for cholinergic ones. The observation of PDE10A exclusively in the neuronal nuclei of interneurons was intriguing, as it sheds light on the idea that cyclic nucleotide signaling is highly compartmentalized within cells, and that PDEs exert distinct physiological functions within the cell (Sample and Yang 2012; Van Staveren et al. 2002, 2003).

Each PDE might have differential localization within single neuronal types. This different cellular compartmentalization could be important to control distinct physiological processes and signaling pathways; an example is the differential distribution of PDE2A and PDE10A in hippocampal pyramidal neurons. Indeed, the nuclear localization of PDE10A in interneurons is possibly explained by the observation that cyclic nucleotides and protein kinase A have been described in the nuclei of brain cells (Van Staveren et al. 2003). By contrast, PDE2A is excluded from the soma but densely distributed throughout the neuronal processes (Hepp et al. 2007).

11.2.3 Functions of PDEs in Relation to their Distribution

PDE1B and PDE10A, as well as PDE2A, can metabolize both cAMP and cGMP, while PDE10A is membrane-bound in the vast majority of neurons, and PDE1B is contained only in a soluble intracellular compartment. Moreover, membrane-bound PDE2A is specifically enriched in lipid rafts associated with high concentrations of adenylyl cyclase V/VI and PKA. Because of their distinct subcellular distribution in the medium spiny neurons, they play a different role in regulating the excitability of medium spiny neurons (Siuciak et al. 2008; DiPilato et al. 2004). Moreover, PDEs, because of their ability to modulate cAMP/PKA signaling, can control the dopaminergic signaling in the striatum, where dopamine plays a key role in the regulation of motor and cognitive functions. Moreover, cAMP/protein kinase A (PKA) signaling cascade is essential for dopamine transmission (Zhu et al. 2004; Siuciak et al., 2006a; Siuciak et al. 2006b). Dopamine can have distinct effects in striatonigral or striatopallidal neurons. In fact, by acting on D1 receptors, dopamine stimulates cAMP/PKA signaling via active G protein-mediated activation of adenylyl cyclase, whereas by acting on D2 receptors, it inhibits cAMP/PKA signaling via inactive G protein-mediated inactivation of adenylyl cyclase (Seino and Shibasaki 2005). PDE10A and PDE4 are differently expressed in neuronal subtypes in the striatum, and such discrete cellular localization confers distinct roles in dopaminergic neurotransmission. Striatal PDE10A is localized proximally to the plasma membrane of postsynaptic sites in medium spiny neurons dendritic spines (Stoof and Kebabian 1981; Kotera et al. 2004). This particular localization allows PDE10A to regulate post-synaptic cyclic nucleotide signaling, which is involved in the integration of glutamatergic and dopaminergic neurotransmission. PDE10A is also highly expressed in medium spiny neurons axons/terminals in the SNr and external globus pallidus.

In particular, PDE10A regulates cAMP/PKA signaling (Sano et al. 2008) as well as gene expression (Nishi et al. 2008) in both direct and indirect pathway neurons. In neurons of the direct pathway, PDE10A inhibition by papaverine upregulates

cAMP/PKA signaling, thus leading to the potentiation of dopamine D1 receptor signaling by phosphorylation of cAMP-dependent substrates, including CREB and extracellular receptor kinase (ERK). PDE10A inhibition by papaverine is also able to upregulate cAMP/PKA signaling, in neurons of the indirect pathway, by potentiating adenosine A2A receptor signaling and inhibiting dopamine D2 receptor signaling simultaneously (Strick et al. 2010). Thus, PDE10A inhibition effectively counteracts dopamine D2 receptor signaling in striatopallidal neurons and potentiates D1 receptor signaling in striatonigral neurons, mainly via cAMP-mediated effects (Threlfell et al. 2009; Padovan-Neto et al. 2015). Because the inhibition of conditioned avoidance response has been used as a measure of antipsychotic activity of many drugs (Grauer et al. 2009), PDE10A inhibitors have been suggested as therapeutic agents for schizophrenia. Indeed, the PDE10A inhibitor papaverine counteracts dopamine D2 receptor signaling and potentiates dopamine D1 receptor signaling, so that the pharmacological profile of papaverine resembles that of atypical antipsychotics (Siuciak et al. 2006a). This observation supports the concept that PDE10A inhibition is beneficial for symptoms and cognitive deficits of psychosis.

On the other hand, PDE4B regulates cAMP/PKA signaling at striatal dopaminergic terminals, and inhibition of PDE4 by rolipram upregulates TH phosphorylation and dopamine synthesis, leading to an increase in dopaminergic tone (Menniti et al. 2007).

The level of expression level of PDE4B is higher in striatopallidal neurons than in striatonigral neurons where PDE4 inhibition selectively potentiates cAMP/PKA signaling. Rolipram treatment increases phosphorylation of Thr34 DARPP-32 in response to an adenosine A2A receptor agonist, but has no effect on phosphorylation mediated by a dopamine D1 receptor agonist (Menniti et al. 2007).

11.3 Role of PDE in the PKA/CREB/BDNF Pathway

PDEs degrade cyclic nucleotides, which makes them responsible for neuronal cAMP/cGMP content regulation. PDE4 has been reported to play a major role in this mechanism, and PDE4 specific-inhibitors, such as rolipram, exhibit antidepressant effects (Krebs and Beavo 1979) by increasing the levels of activated CREB (Itoh et al. 2004). CREB is a transcription factor required for the survival of adult CNS neurons, and it is known to mediate nuclear calcium-regulated gene transcription following a variety of extracellular and intracellular signals, such as neuronal cell membrane depolarization (Hosoi et al. 2003). It has been largely established that CREB plays a key role in proliferation, growth, survival and differentiation of all types cells.

CREB is phosphorylated and activated by cAMP-dependent protein kinase, PKA. CREB phosphorylation on its Ser^{133} site, which togheter with CREB-binding protein (CBP), bind he Ca^{2+} and cyclic AMP response elements (Ca^{2+} CREs) on the promoter region of many target DNAs, leading their transcription (Hardingham and Bading 1998). Many genes are regulated by phosphorylated CREB-binding protein (pCREB) among the striatal neurons, under both physiological and pathological

conditions, such as neuropeptides (Konradi et al. 1994) and immediate early genes (Vallejo 1994; Andersson et al. 2001). The pCREB-regulated inducible gene expression is thought to contribute to transcription-dependent adaptive changes in neural plasticity related to memory, especially to long-term mental illnesses derived from dysfunctional striatal neuronal activities (Kobierski et al. 1999). Consequently, it facilitates the transcription of a large number of genes playing an important role in memory, especially in long-term memory formation following new protein synthesis (Nestler and Aghajanian 1997). One of the CREB target genes is BDNF, suggesting a protective role of pCREB in several neurodegenerative diseases (Guzowski and McGaugh 1997).

In HD, the activity of CREB is impaired by mutated huntingtin (Steffan et al. 2000; Luthi-Carter et al. 2000). In fact, it has been postulated that inhibition of CRE-mediated gene transcription contributes to HD pathology. The inhibition of PDE activity in the brain can lead to increased intracellular cAMP/cGMP levels, thereby modulating the neuronal function. Interestingly is that PDE10A inhibition induced by the specific inhibitor TP-10 (Pfizer) results in robust increase in cAMP and in CREB phosphorylation in the striatum. Indeed, augmenting cAMP signaling through PDE4 inhibition is associated with the consolidation and retention of long-term memory. Moreover, there has also been a longstanding interest in the use of PDE4 inhibitor Rolipram for the treatment of depression (Schmidt et al. 2008). Recent studies also indicate that PDE4 inhibitors could provide a new approach to the treatment of psychosis (Siuciak et al. 2007; Halene and Siegel 2008; Wieschollek and Manahan-Vaughan 2012). Furthermore, it was shown that pCREB is differently modulated in the different neuronal populations of the striatum according to their unique vulnerability to HD in the rat Quinolinic Acid excitotoxic model, in which the striatal spiny neurons die in a way that resembles HD. In particular, levels of pCREB decrease progressively in projection neurons, parvalbumin (PARV) and calretinin (CALR) interneurons, whereas they remain stable in cholinergic and somatostatin interneurons (Giampà et al. 2007). Thus, it has been speculated that the ability of cholinergic interneurons to maintain their levels of CREB after excitotoxic lesions is one of the factors determining their protection in Huntington's disease (Fusco et al. 2003).

Furthermore, a decreased transcription of CREB-regulated genes was observed in HD transgenic animals. Decreased cAMP in cerebrospinal fluid of HD patients was observed, and CBP was found in the nucleus of 100% of wild- type cells and only in 18% of HD mutant cells (Gines et al. 2003).

CREB-regulated gene expression has been associated with neuronal survival and neuronal plasticity. Changes in PDE expression and subsequent cyclic nucleotide signaling can modulate neuroprotection via CREB (Jancic et al. 2009). Moreover, BDNF activates the MAPK signaling pathway, which is also an important gene product of CREB-mediated transcription, and is up-regulated by cyclic nucleotide level elevation. The expression of PDEs in several neurodegenerative disorders where neuronal survival and plasticity are impaired merits attention. In fact, changes in PDE expression, cyclic nucleotides and their downstream target genes have been reported in various neurodegenerative disorders, including Alzheimer's disease,

Parkinson's disease, HD (Sancesario et al. 2004). In Alzheimer's disease (AD), the most prominent symptom is the progressive decline in cognitive functions, mainly memory. A chronic, progressive loss of neurons leading to atrophy in mainly temporal and parietal lobes underlies AD cognitive symptoms. The neuropathological hallmarks of AD, namely amyloid β (Aβ) plaques and neurofibrillary tangles, are critical in the disease process. Interestingly, cAMP and cGMP are both affected in AD, and cAMP is thought to play a role in the etiology of neurofibrillary tangles via tau phosphorylation (Shi et al. 2011). Aβ plaques may display a detrimental effect on LTP, via the inhibition of both the cAMP/PKA/CREB and cGMP/PKG/CREB pathway, in addition AC, GC and pCREB levels are reduced in the temporal lobe of AD patients (Vitolo et al. 2002; Puzzo et al. 2005; Hanger et al. 2009). In AD, an increase in the expression of PDE4A, PDE4B, and PDE7A are observed in early stages of AD, while, in the most advanced clinical stages, an increase in PDE8B expression is observed in the brain regions associated with memory, such as the enthorhinal cortex (Walsh et al. 2002). An involvement of PDEs in Parkinson's disease (PD) was demonstrated by the observation that decreased BDNF expression determines loss of dopaminergic neurons in the substantia nigra. Moreover, an impairment in cyclic nucleotide signaling mechanisms has been reported in human PD and in experimental models (Nishino et al. 1993). Phosphodiesterase 7 (PDE7), a cAMP hydrolyzing enzyme, is highly expressed in striatal and nigral neurons. Significant upregulation in neuroinflammatory events have been implicated in dopaminergic neuronal loss in PD. Microglial activation has been demonstrated in SNpc and striatum of postmortem PD brains, as well as in experimental models of PD (Cicchetti et al. 2002; McGeer et al. 2003; Orr et al. 2005). The degeneration of dopaminergic terminals from the substantia nigra pars compacta, along with the decrease in dopamine levels in the striatum, accounts for the motor and cognitive deficits in Parkinson's disease (Calabresi et al. 1996, 2006; Wichmann and DeLong 2003). Levodopa (L-dopa) is a substitutive pharmacological compound directed towards restoring physiological concentration of dopamine in the striatum, and it represents the most effective therapeutic approach for Parkinson's disease (Picconi et al. 2003; Olanow et al. 2006). However, chronic exposure to L-dopa induces movement behavior fluctuations and dyskinesia in most patients with Parkinson's disease. The effects of dopamine loss on cGMP levels are controversial. Indeed, it has been recently observed that striatal cGMP signaling decreases at the peak of L-dopa-induced dyskinesia in Parkinson's disease rat model (Giorgi et al. 2008). On the other hand, an increase in both activity and protein level of GC in striatum after MPTP injection was observed. Moreover, in an experimental rat model of PD, PDE10A mRNA levels were diminished in striatal neurons 10 weeks after 6-hydroxydopamine (6-OHDA) midbrain lesions (Sagi et al. 2014; Giorgi et al. 2011; Tseng et al. 2011; Chalimoniuk and Langfort 2007; Chalimoniuk et al. 2004; Chalimoniuk and Stepien 2004). Lesions of the nigro-striatal dopaminergic projections with 6-OHDA, rather surprisingly, induce an increase in cAMP levels, as demonstrated by increased basal adenylate cyclase activity in dopamine-denervated rat striatum (Hossain and Weiner 1993; Tenn and Niles 1997). Conversely, cGMP levels decrease in response to dopamine loss. Such down-regulation of cGMP is

associated with decreased nitric oxide synthase expression and activity, probably leading to a decrease in the nitric oxide-guanylate cyclase pathway. Furthermore, loss of dopamine increases (PDE1B)1B levels, suggesting that the modulation of second messenger system in dopamine-denervated rat striata may be affected by changes in synthesis as well as catabolism (Tenn and Niles 1997).

11.4 PDEs in Huntington's Disease

Intracellular cAMP and cGMP concentrations depend on the rate of their synthesis from ATP and GTP by AC and GC, respectively, the rate of efflux from the cell, and the rate of degradation. PDEs hydrolyze cAMP and cGMP limiting both the duration and amplitude of the cyclic nucleotide signal (Conti and Jin 1999; Francis et al. 2000; Van Staveren et al. 2001). PDE1B levels were reduced in 12-week old R6/2 mice model of HD. Interestingly, PDE4 distribution is mainly observed in the cortex, which was not altered in a major way in HD.

The most interesting PDE in HD is PDE10A, because of its particular distribution in the striatum, which represents the main target of the disease. PDE10A is highly expressed in regions of the brain that are innervated by dopaminergic neurons such as the striatum, nucleus accumbens and olfactory tubercle (Soderling et al. 1999). Moreover, it is highly expressed in GABAergic spiny projection neurons with localization to the membrane of dendrites and dendritic spines. A decrease in the protein levels of the striatum-enriched PDE10A has been found to precede the actual impairment of motor functions in R6/1 and R6/2 HD mice. It is also been described that PDE10A expression levels are reduced in the postmortem brain of HD patients (Hu et al. 2004). Because cyclic nucleotides are important for intracellular signaling, these changes may contribute to changes in cell function that cause motor, cognitive or psychiatric disturbances observed in HD patients.

However, it has been shown that PDE inhibition has a beneficial role in HD animal models, leading to an apparent conflict between the decreased PDEs levels associated with HD and the beneficial effect of PDE inhibitors in a R6/2 mouse model of HD (Giampà et al. 2010). To address this issue, PDE10A protein expression levels in the R6/2 mice was recently investigated, with particular attention to the different neuronal subpopulation of the striatum. The results showed a dramatic increase in PDE10A in medium spiny neurons of R6/2 transgenic HD mice compared to their wild type littermates (Leuti et al. 2013). Conversely, in the striatal cholinergic interneurons, PDE10A levels were lower, and were not significantly modified by disease progression. In the other subsets of striatal interneurons (parvalbuminergic, somatostatinergic, and calretininergic interneurons), PDE10A immunoreactivity was higher in the R6/2 compared to the wild-type mice. However, densitometric studies of the whole striatum showed that PDE10A immunoreactivity was lower in the R6/2 compared to the wild-type mice. Moreover, it was shown that PDE10A increases in the perikarya of projection neurons, but is reduced in the whole striatum of the R6/2 mice. This suggests that, in HD, mutant huntingtin protein disrupts PDE10A synthesis and trafficking, resulting

in PDE10A accumulation in the perikarya of spiny projection neurons, which are vulnerable to the disease, thereby decreasing cAMP and cGMP locally. (Leuti et al. 2013). Therefore, even if levels of PDE10A are lower in the striatum *in toto*, the enzyme might be too abundant in the somata of medium spiny neurons where it downregulates cyclic nucleotides signaling, which is detrimental for cell life. In that study, we observed that cholinergic interneurons, resistant to HD degeneration, have a moderate amount of PDE10A in the early stages, both in the R6/2 and in the wild types (Fusco et al. 1999). A previous study, showed that striatal cholinergic interneurons contain higher amounts of BDNF, compared to the more vulnerable medium spiny neurons and that cholinergic interneurons are more enriched with phosphorylated CREB (Fusco et al. 2003). Therefore, it is possible that the low levels of PDE10A found in cholinergic interneurons are related to their selective resistance to HD neurodegeneration.

PDE10A immunoreactivity was observed in moderate amounts in the nuclei of all striatal interneurons except for cholinergic ones, and its levels were higher in the R6/2 than in the wild type mice (Leuti et al. 2013). As mentioned above, nuclear localization in interneurons, although unexpected, can be explained by the observation that cyclic nucleotides and PKA have been described in the nuclei of brain cells (Van Staveren et al. 2002).

11.4.1 PDEs Inhibition Effects in Huntington Disease

Phosphorylated CREB is differently expressed in several neuronal subpopulations of the striatum, both in control animals and in the quinolinic acid model model of HD. Different levels of activated CREB were described to be associated with the individual vulnerability to excitotoxic lesions (Giampà et al. 2006). In particular, it was suggested that higher levels of CREB could account for the selective resistance of selected neuronal populations (Lee et al. 2004).

In light of this, drugs targeting CREB loss of function could be considered as a powerful therapeutic for the treatment of neurodegenerative disorders such as HD. The PDE4 inhibitor, rolipram, increases CREB phosphorylation. In fact, our early studies showed that rolipram was able to exert a neuroprotective effect and to increase significantly the levels of activated CREB in the striatal spiny neurons, in the QA excitotoxic model of HD (De March et al. 2006). The beneficial effect observed following rolipram treatment were also amenable to the maintenance of BDNF protein expression levels. BDNF is, in fact, synthetized in the cortex and anterogradely transported to the striatum. Thus, the increased CREB phosphorylation exerted by rolipram in the QA model was likely responsible for the neuroprotection through an increase in cAMP levels.

In a later study, it was shown that rolipram is able to increase survival and ameliorate clinical signs in the R6/2 mouse model of HD (De March et al. 2008). In that study, PDE4 inhibition through rolipram was shown to exert a neuroprotective role by increasing both phosphorylated CREB and BDNF in the striatum. Rolipram prevented CREB binding protein sequestration into striatal neuronal intranuclear

inclusions, thus sparing parvalbuminergic interneurons of R6/2 mice, and rescuing motor coordination and motor activity deficits (Giampà et al. 2009). Moreover, an increase in ERK phosphorylation was reported in the medium spiny neurons of R6/2 mice after rolipram tratment. ERK phosphorilation have considerable importance if we consider that extracellular signal-regulated protein kinases activation pattern is altered in HD (Fusco et al. 2012).

Another possible target for neuroprotection in HD is PDE5, selective for cGMP. PDE5 is found in several brain regions including the cortex, hippocampus, and basal ganglia (Marte et al. 2008; Puerta et al. 2009). In a recent study, Puerta and coworkers have shown that PDE5 inhibitors sildenafil and vardenafil were able to ameliorate neurological symptoms, reduce striatal projection neurons loss and increase pCREB levels in the 3-nitroproprionic intoxication model of HD in rats (Puerta et al. 2010). Noteworthy, it was shown that mRNA and protein BDNF levels were significantly elevated in sildenafil treated rat cortex, which accounted significantly for their neuroprotective effects (Wang et al. 2014).

These results provided strong theoretical support for targeting cyclic nucleotides and CREB signaling through PDE inhibition. A PDE10 inhibitor (TP10, Pfizer) was administered to the QA rat surgical model of HD (Giampà et al. 2009). Chronic administration of TP10 was effective in reducing the QA lesion area by 52%, sparing medium spiny neurons, and in increasing CREB levels in the surviving striatal neurons. Interestingly, TP10 treatment also had beneficial effects on cortical neurons. In fact, decreased retrograde cortical neuron loss and increased levels of phosphorylated CREB and BDNF were observed, although the effect of TP10 on cortical levels of BDNF was moderate and only limited to the early time point. Because PDE10A is mostly expressed in striatal medium spiny neurons, it is possible that these effects on the survival of cortical neurons may be indirect. Thus, sparing of striatal neurons by TP10 might have translated into a higher level of activity in the cortical neurons, which in turn would account for the increase in phosphorylated CREB and BDNF (Giampà et al. 2009). Following these results, PDE10A inhibition was further investigated by administering to the R6/2 mouse model of HD (Giampà et al. 2010). Predictably, TP10 was able to rescue striatal neuropathology in terms of neuronal loss, NIIs formation, microglial reaction. Also, TP-10 treatment was associated with a significant increase in phosphorylated CREB and BDNF in cortex and striatum. The increase of cAMP signaling that was recorded in medium spiny neurons and resulted from PDE10A inhibition could be explained by a number of downstream mechanisms. First, PDE10A inhibition in wild-type mouse brain causes a robust increase of CREB phosphorylation downstream of cAMP, which is accompanied by a significant increase in BDNF levels in striatum of R6/2 mice following TP-10 administration. CREB-mediated transcription and BDNF levels both may contribute to the significant amelioration of striatal pathology resulting from treatment of the R6/2 mice with PDE10A inhibitor TP-10. Moreover, PDE10A inhibition also had a beneficial effect on cortical pathology in the R6/2 mice. TP-10 treatment counteracted the decrease in cortical neuron counts by 40%. Amelioration of striatal pathology by PDE10A inhibition might maintain corticostriatal synaptic connections, which may reduce cortical neuron pathology by preventing retrograde

degeneration. However, it is also conceivable that there is a direct effect of TP-10 treatment on cortical CREB phosphorylation and BDNF synthesis resulting from inhibition of the nuclear/perinuclear PDE10A present in the cortex (Fusco and Giampà 2015).

Chronic inhibition of PDE10A stimulates the up-regulation of mRNAs encoding genes such as PDE1C, prodynorphin, synaptotagmin10, and diacylglycerol O-acyltransferase. Moreover, it produces down-regulation of mRNAs encoding choline acetyltransferase and Kv1.6, which suggests that long-term suppression of PDE10A is associated with altered striatal excitability (Fusco and Giampà 2015). These results support the hypothesis that PDE inhibitors could be considered as a valid therapeutic approach for HD. However, more studies regarding the effects of PDEs and their inhibitors on patients health are required to promote clinical trials for neurodegenerative diseases.

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

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