

## REVIEW ARTICLE

# Inhibition of phosphodiesterases as a strategy to achieve neuroprotection in Huntington's disease

Antonella Cardinale | Francesca R. Fusco 

Laboratory of Neuroanatomy, Santa Lucia Foundation IRCCS, Rome, Italy

## Correspondence

Francesca R. Fusco, Laboratory of Neuroanatomy, Santa Lucia Foundation IRCCS, Rome, Italy.  
Email: f.fusco@hsantalucia.it

## Summary

Huntington's disease (HD) is a fatal neurodegenerative condition, due to a mutation in the IT15 gene encoding for huntingtin. Currently, disease-modifying therapy is not available for HD, and only symptomatic drugs are administered for the management of symptoms. In the last few years, preclinical and clinical studies have indicated that pharmacological strategies aimed at inhibiting cyclic nucleotide phosphodiesterase (PDEs) may develop into a novel therapeutic approach in neurodegenerative disorders. PDEs are a family of enzymes that hydrolyze cyclic nucleotides into monophosphate isoforms. Cyclic nucleotides are second messengers that transduce the signal of hormones and neurotransmitters in many physiological processes, such as protein kinase cascades and synaptic transmission. An alteration in their balance results in the dysregulation of different biological mechanisms (transcriptional dysregulation, immune cell activation, inflammatory mechanisms, and regeneration) that are involved in neurological diseases. In this review, we discuss the action of phosphodiesterase inhibitors and their role as therapeutic agents in HD.

## KEYWORDS

cyclic nucleotides, Huntington's disease, neuroprotection, PDE inhibitors, phosphodiesterase (PDEs)

## 1 | INTRODUCTION

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder and is characterized by motor impairment and cognitive and psychiatric symptoms.<sup>1,2</sup> Currently, only symptomatic drugs are available to cure HD. Tetrabenazine was approved by FDA in 2008 for the treatment of choreic movements in HD. Other symptoms, such as hypokinesia and rigidity and/or depressive and behavioral defects, are usually treated with antiparkinson, antidepressant, and antipsychotic drugs.<sup>3-7</sup>

The neuropathological hallmark of HD is the degeneration of striatum. However, several studies have shown repercussions on other parts of the brain, such as cerebral cortex, globus pallidus, thalamus, substantia nigra, and cerebellum. Moreover, not all the striatal neurons are affected in the same way: While aspiny neurons (cholinergic interneurons marked with somatostatin, neuropeptide  $\gamma$ ) are spared, medium spiny neurons (MSNs) undergo a massive degeneration that

begins at the early stages of the disease. MSNs are divided into two different subtypes: enkephalin-containing neurons project to the external segment of globus pallidus (GPe) (indirect pathway) and substance P neurons projecting to internal segment of globus pallidus (GPi) (direct pathway). Neurons of the indirect pathway are more vulnerable to HD degeneration.<sup>8-12</sup>

Many mechanisms are involved in HD neurodegeneration and include both loss and gain of function mutated huntingtin-polyglutamine aggregates formation of mutant protein, alteration of axonal transport and energy metabolism, oxidative stress, excitotoxicity, impairment of synaptic signals, and transcriptional dysregulation.<sup>13</sup> In particular, it is known that transcriptional dysregulation plays a major role in HD, since mutated huntingtin alters the cAMP response element-binding protein (CREB) and its related transcriptional action.<sup>14-18</sup> Brain-derived neurotrophic factor (BDNF) gene transcription is regulated by CREB,<sup>19</sup> and its expression is stimulated by huntingtin that lost this function

when mutated.<sup>20,21</sup> Several studies have shown a downregulation of BDNF levels in cellular and animal models,<sup>19,21–23</sup> as well as in postmortem brain of HD patients.<sup>21,24</sup>

Thus, strategies aimed at increasing CREB transcription—and, consequently, the expression of BDNF—have neuroprotective effects in HD animals.<sup>25–27</sup> CREB activation is mediated by a cAMP-dependent protein kinase (PKA). The balance of intracellular cAMP/cGMP levels, thus, represents an important aspect in the regulation of neuronal processes.

In light of this, PDEs and their inhibitors can play an important role in a therapeutic scenario for HD. In fact, PDEs are enzymes that catabolize cAMP and/or cGMP in the cell. Thus, their inhibition could be beneficial in the neuronal degeneration in the central nervous system (CNS).

In this review, we will discuss the inhibition of PDEs and its neuroprotective action in HD by upregulation of the cyclic nucleotide signaling.

## 2 | MOLECULAR MECHANISM OF PDES FUNCTION

Phosphodiesterases (PDEs) are fundamental enzymes that belong to intracellular signal transduction cascade, hydrolyzing cyclic nucleotides cAMP, and/or cGMP. PDEs are divided into 11 families and variants, encoded by 21 genes. Moreover, they are classified as cAMP (PDEs 4,7,8), cGMP (PDEs 5,6,9) or double specific PDEs (PDEs 1,2,3,10,11).<sup>28,29</sup>

Cyclic nucleotides are second messengers in the signal transduction process and synaptic transmission in dopaminergic, noradrenergic and glutamatergic systems in neurons.<sup>30–33</sup> cAMP and cGMP derives, respectively, from ATP and GTP by the reaction of adenylyl (AC) and guanylyl cyclase (GC). In particular, the cellular mechanism involved is the following: the binding of hormones, neurotransmitters, chemokines, autocrine, and paracrine receptor factors to GPCR receptors (G protein-coupled receptors) activates the heterotrimeric G proteins, consisting of the three subunits (alpha, beta and gamma).<sup>34,35</sup> In fact, the trans-membrane adenylylated cyclic (tAC), activated by the stimulatory G protein (Gs) and inhibited by the inhibitory G protein (Gi), produces 3',5'-cyclic adenosine monophosphate (cAMP) from ATP; however, it is also synthesized in the brain by soluble adenylyl cyclase (AC), whose production is stimulated by bicarbonate ( $\text{HCO}_3^-$ ) and calcium in neuronal cells and in glia. At this point, cyclic AMP stimulates the protein kinase A, the exchange factors directly activated by cAMP 1 (EPAC1 and EPAC2), and/or the cyclic nucleotides gated channels (CNGs). In the case of the production of 3',5'-cyclic guanosine monophosphate (cGMP), however, nitrogen monoxide (NO) activates soluble GC (sGC), whereas particulate guanylyl cyclase (pGC) is activated through binding of natriuretic peptides (NPs) to coupled receptors. The cGMP, produced from the GTP, will in turn activate the protein kinase G and CNGs. Formation of both cAMP and cGMP involves activation of CREB by phosphorylation, generating the transcription of several genes.

As previously mentioned, both cAMP and cGMP are neutralized through the hydrolysis performed by phosphodiesterases.<sup>36–42</sup>

## 3 | PDES IN NEURODEGENERATIVE DISORDERS

Many cellular processes are impaired in neurodegenerative disorders, as an imbalance of cyclic nucleotides with consequent alteration of PDEs functions and neuronal survival.<sup>43</sup> Cyclic nucleotides can be considered a central player in many cellular processes, such as long-term potentiation, synaptic plasticity, memory, neurogenesis, neurotransmission, in which they regulate—by PKA (protein kinase A) and ERK (extracellular regulated kinase) signaling pathway—many proteins and their transcription and translation.<sup>44,45</sup> As mentioned above, CREB is an important target of cAMP and cGMP.<sup>46,47</sup> CREB has a pivotal role in neuronal survival and plasticity, and one of its target gene is BDNF, a key growth factor for the striatum. BDNF is a neurotrophin involved in synaptic plasticity, neuronal survival, and differentiation. It is known that BDNF expression is altered in neurodegenerative diseases, and a reduction in its levels occurs in people affected by Alzheimer's disease, Parkinson's disease, and Huntington's disease. Particularly in HD, BDNF shows a dysregulation in cellular transport mechanisms, and in transcription and post-synaptic signaling. Moreover, only in HD, BDNF levels are linked to huntingtin mutation. In fact, wild-type huntingtin has a stimulating effect on BDNF expression. Consequently, a reduction in BDNF protein level occurs in the striatum.<sup>21,22,48,49</sup> PDEs are largely diffused in neuronal cells, and thanks to modulating cAMP/cGMP content, they have attracted the attention of neuroscientists as possible key molecules in the battle against neurodegenerative diseases.<sup>50–53</sup> Furthermore, a bulk of data point out the role of PDEs in dopaminergic pathways. Thus, their inhibition seems to be a useful strategy to fight diseases such as Alzheimer's disease, Parkinson's disease, HD, depressive and cognition disorders.<sup>54</sup>

## 4 | PHOSPHODIESTERASES IN DOPAMINERGIC PATHWAYS

As mentioned previously, the dopaminergic system is altered in neurodegenerative and neuropsychiatric diseases, and among these also in Huntington's disease. These diseases have in common the cortico-striato-thalamic systems, which work in a synergistic and complex way,<sup>55–59</sup> and in which the alteration of the balance involves the appearance of motor, cognitive, and behavioral dysfunctions typical of these disorders. Dopamine appears to be the modulator of these circuits both in the frontal cortex and in the striatum, regions in which dopamine receptors are strongly distributed.<sup>57,60,61</sup> In fact, as it is well known, some of these diseases, such as PD, use dopaminergic therapy to fight its symptoms, although it subsequently involves various side effects. Dopamine, originating from the pars compacta of the substantia nigra or from

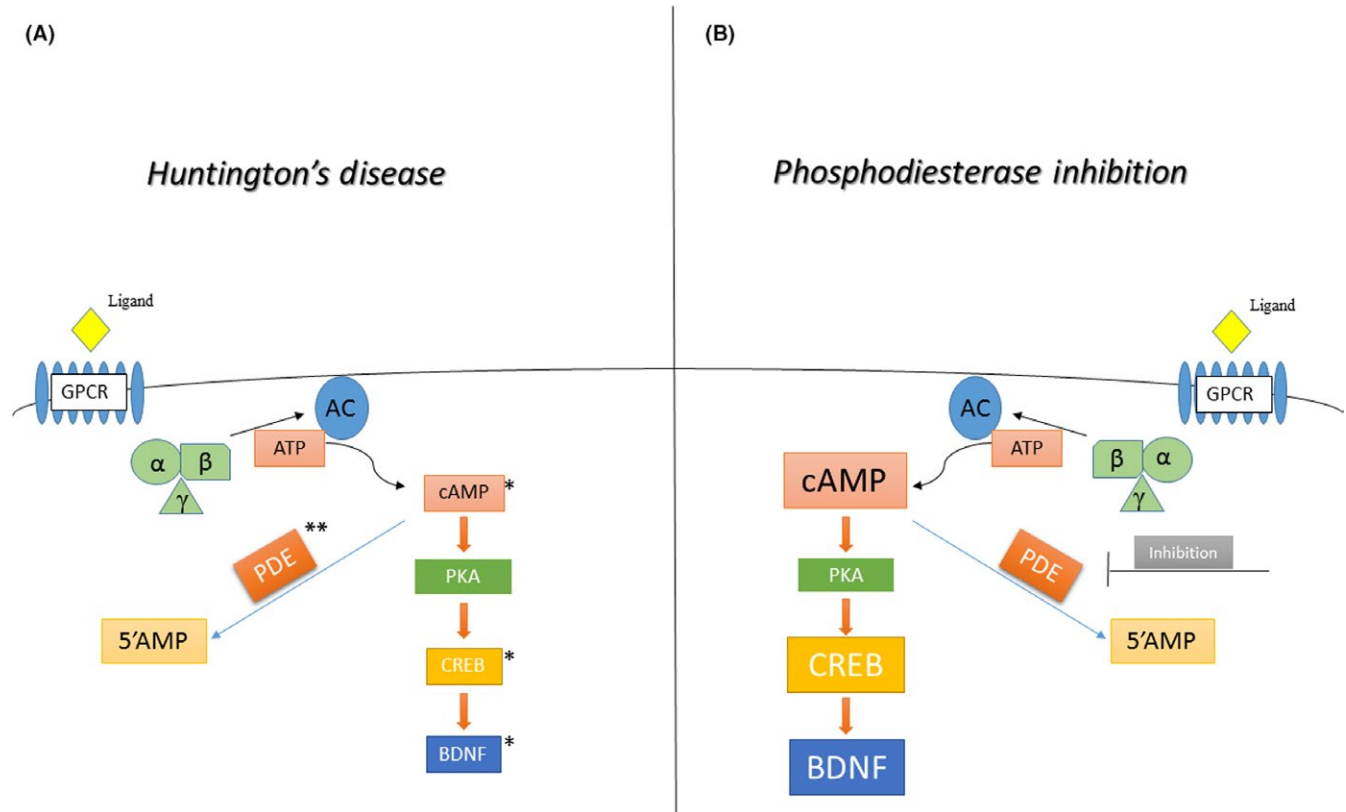
**TABLE 1** The principal phosphodiesterases in HD and their relative inhibitors

Phosphodiesterase	Substrate	Isoforms	Distribution	Modulation	Inhibitors
PDE1	cAMP/cGMP	PDE1A PDE1B PDE1C	Cortex, Hippocampus, Striatum	Ca <sup>2+</sup> /Calmodulin	Vinpocetine
PDE4	cAMP	PDE4A PDE4B PDE4D	Cortex, Hippocampus, Striatum	Phosphorylation	Rolipram
PDE5	cGMP	PDE5A	Spinal cord, Cerebellum	cAMP/Phosphorylation	Sildenafil, Vardenafil, Tadalafil,
PDE10	cAMP/cGMP	PDE10A	Striatum	cAMP/Phosphorylation	TP 10 TAK-063 PF-0254920

PDE, Phosphodiesterase.

the VTA, is bound to the D1 receptors on the MSNs neurons of the direct pathway activating the stimulatory (Golf, Gs) and stimulating the production of cAMP, or to the D2 receptors of the indirect pathway that bind to the inhibitory G protein (Gi) that inhibits the production of cAMP.<sup>57,62-66</sup> This information therefore establishes the central role played by dopamine in the regulation of psychomotor mechanisms. As mentioned above, the action of dopamine occurs through the signal transduction mechanism operated by the cAMP/PKA system and is also controlled by phosphodiesterases.<sup>67</sup> In the striatum, the regulation of cAMP and cGMP turnover plays a fundamental role because of their inhibitory and excitatory effects of the nigro-striated-pallid circuits, mentioned before, in neurons. In the striatum are expressed many phosphodiesterase isoforms, which have various localizations and functions influencing synaptic plasticity and excitability of the membrane.<sup>68</sup> Furthermore, the activation of the signal transduction mechanism of cAMP and cGMP, as mentioned, involves the activation of a series of downstream proteins, such as PKA and PKG, respectively, which in turn activates other modulators of neuronal excitability as ion channels and phosphatases. For example, in the striatum, their activation involves the phosphorylation of DARPP-32, which plays a central role in the regulation of dopamine and its action on the GABAergic and glutamatergic pathway. The phosphorylation of DARPP-32 involves the activation of its inhibitory phosphatase activity of PP1, which is inactivated and makes PKA unable to stimulate other substrates such as CREB.<sup>30,69-71</sup> All this information highlights the importance of the PKA/PKG pathway in the execution of complex motor mechanisms through the regulation of striatal synaptic transmission.<sup>72,73</sup> In fact, MSNs, striatal projection neurons, have high levels of ACs and GCs, whose activation is regulated by various neurotransmitters (eg, dopamine, 5HT, neuropeptide Y, adenosine, glutamate) that act through GPCRs and NO synthesis stimulation, respectively. The different isoforms of PDEs are highly expressed in the striatum.<sup>30,74,75</sup> The inhibition of phosphodiesterases involves a regulation of the cAMP/PKA signal transduction mechanism, resulting in the stimulation of dopamine synthesis at the dopaminergic terminal level, the inhibition of

dopamine signal in the D2 receptors in striato-pallidal neurons, and stimulation of dopamine D1 receptors in striatonigral neurons.<sup>67</sup> In fact, numerous studies have shown that, under physiological conditions, compounds that activate the production of cAMP and cGMP in the MSNs (such as the aforementioned PDEs inhibitors or cyclase activators) positively regulate cortico-striatal transmission. In the opposite case, when drugs, such as cyclase inhibitors, decrease the levels of these species in neuronal cells, there is a reduction in synaptic activity.<sup>76-79</sup> All these considerations lead to the hypothesis of the central role played by AC-cAMP-PKA mechanism in MSNs, enhancing the activation of AMPA and NMDA receptors during cortico-striatal transmission. As mentioned previously, the excitatory effect of NMDA receptors is due to dopamine binding to D1 receptors, with activation of the AC-cAMP-PKA signal transduction system. On the contrary, binding to D2 receptors inhibits the cascades of the AC-cAMP-PKA signal.<sup>80-85</sup> As mentioned above, these mechanisms, widely described so far, are altered in neurodegenerative and neuropsychiatric diseases, and therefore also in Huntington's disease. In HD, the pathological mechanism of the disease is the neuronal death of striatal MSNs neurons, and in particular of the striatal cells of the indirect pathway. The death of these neurons appears at least in part due to the overexpression of mutant huntingtin, although the underlying mechanism is not yet clear.<sup>86</sup> Various studies, conducted in vitro and in vivo (using the different HD animal models available) but also in patients with HD, have highlighted the reduced level of expression of cAMP, CREB, and nNOS mRNA.<sup>47,87-89</sup> These data underline the alteration of the cAMP/cGMP mechanism and of the PDE signals. These reports confirm what was said previously: the activity of phosphodiesterase inhibitors which increase the levels of cyclic nucleotides in striatal neurons seems to regulate the striatal cortical transmission in a positive way.<sup>68</sup> Moreover, it is known that dopamine undergoes changes in the levels of expression and release in the course of the HD. Dopamine has a biphasic modulation in the striatum during the course of HD disease. In particular, it seems that in the initial stages of the disease there is an increase in dopamine neurotransmission which involves hyperkinesia in the



**FIGURE 1** Figure shows the signaling cascade of cAMP (cGMP not shown in figure) in Huntington's disease, where there is a reduction in cAMP levels and cAMP response element-binding protein (CREB) activity of transcription gene. Inhibition of phosphodiesterases seems to improve motor and cognitive deficits and restore cAMP and CREB normal expression. \*Reduced levels of cAMP, CREB, and brain-derived neurotrophic factor (BDNF) levels. \*\*Phosphodiesterase (PDEs) levels changes according to the different isoforms analyzed (please see main text)

movement. On the contrary, in the late stages of the pathology, there is a reduction in dopamine neurotransmission with the consequent appearance of hypokinesia. Various studies have also observed the loss of dopaminergic innervation and a reduction in TH+ neurons in the striatum of postmortem brains of HD patients.<sup>90</sup> These observations were confirmed in PET studies conducted both on patients with overt disease and on patients with the modified gene but who still had not shown the typical symptoms of the disease.<sup>91,92</sup> These data have been confirmed in animal models.<sup>93-95</sup> Furthermore, a reduction in dopamine D1 and D2 receptor levels was also evidenced.<sup>96</sup>

## 5 | PDES IN HUNTINGTON'S DISEASE

In the following section, we examine the different PDEs that play a role in HD pathology, with regard to their tissue distribution, and to the inhibitors that have been tested so far in clinical and preclinical trials in HD (Table 1).

As mentioned above, PDEs and their relative inhibitors could be considered a new therapeutic strategy in HD. In fact, various studies showed beneficial, neuroprotective effects of PDEs inhibitors in animal models of HD improving motor and cognitive

problems but also increasing the expression of species such as pCREB and BDNF, altered, as mentioned, in Huntington's disease<sup>97-100</sup> (Figure 1).

### 5.1 | PDE 1

Phosphodiesterase 1 (PDE1) hydrolyzes both cAMP and cGMP. It has three isoforms (PDE1A, PDE1B, PDE1C), two of which (PDE1A and PDE1B) are expressed in striatum, as well as in cortex and hippocampus as PDE1C. Particularly, PDE1B is ubiquitously distributed in spiny projection neurons and colocalizes with D1 receptors,<sup>101</sup> suggesting a possible involvement of this isoform in striatal neurodegeneration and dopaminergic signaling.<sup>102,103</sup> PDE1 is not localized only in cytoplasm, but, for example, PDE1A is expressed in nucleus, which has a regulation activity of gene transcription.<sup>104</sup> For its high expression in striatum and frontal cortex and its colocalization with D1 receptor, PDE1B could be considered a good target for phosphodiesterase inhibitors in disorders characterized by cognitive complications (schizophrenia) and motor dysfunction. Therefore, PDE1 inhibition was studied in Parkinson's disease. In fact, vinpocetine is a PDE1 inhibitor characterized by the capacity to reduce neuronal inflammation and the expression of TNF- $\alpha$  and IL-1 $\beta$ .<sup>105</sup> In many studies, this compound has shown neuroprotective properties: regulate

oxidative stress and enhance cognition in behavioral test and memory both in animal models and patients.<sup>106-108</sup>

Interestingly, PDE1A2 isoform was found to be preferentially distributed in cholinergic interneurons,<sup>103</sup> suggesting a role in the survival of striatal interneurons in HD.

With the aim of shedding light on the role of PDEs in HD, vinpocetine treatment was shown to ameliorate impaired cognition and motor coordination in a 3-nitropropionic acid-induced HD rat model, by reducing oxidative species, inflammation, and mitochondrial dysfunction.<sup>109</sup>

Recently, a new molecule capable of inhibiting PDE1 has been discovered. It has been tested in PHASE 1 of a clinical trial and has shown positive effects not only in Alzheimer's disease and schizophrenia, but also in movement disorders.<sup>110</sup>

Thus, inhibition of PDE1 could be seen as a potential drug target in HD treatment, although more precise studies are necessary in both clinical and preclinical research in HD.

## 5.2 | PDE 4

The best described PDEs are the PDE4 family, composed by four different enzymes (PDE4A, PDE4B, PDE4C, and PDE4D). With the exception of PDE4C, the other isoforms are ubiquitous in the central nervous systems, and their distribution is particularly high in the striatum, cortex, and hippocampus.<sup>111</sup>

PDE4 has distinct functions in the dopaminergic system because of its different distribution to the various striatal neuronal subtypes. Moreover, indirect pathway presents a higher expression of PDE4B than direct pathway. Thus inhibition of PDE4 regulates and ameliorates cAMP/PKA signaling in the indirect pathway neurons, and at the same time, upregulating TH activation and dopamine formation.<sup>112</sup>

In fact, regulating cAMP balance PDE4 is essential in the PKA/CREB/BDNF pathway, as demonstrated by the CREB-upregulating effects of PDE inhibition in depressive behavior.<sup>113,114</sup>

As mentioned earlier, CREB represents an important transcription factor, as it is needed for adult neuronal survival and for mediating nuclear calcium-regulated gene transcription. CREB is activated by cAMP-dependent protein kinase (PKA) by the phosphorylation of its Ser<sup>133</sup>. Consequently, the activated form pCREB binds to CRE elements (cyclic AMP response elements) on the promoter region of DNA and promotes the transcription of various genes involved in memory and neuronal plasticity, such as BDNF.<sup>115-117</sup> Our group previously confirmed the abnormalities in CREB transcription in the quinolinic-induced rat model of HD, describing a differential modulation of pCREB in the striatal neuronal population.<sup>46</sup> Particularly, a decreased expression in the neurons most vulnerable to HD (medium spiny neurons, parvalbumin and carletinin positive interneuron) was observed. On the other hand, cholinergic interneurons conserve adequate pCREB expression, and probably this event confers their neuroprotection.<sup>46</sup>

Interestingly, however, PDE4 in HD was described to be decreased in R6/2 mice, suggesting a compensatory mechanism due to a concurrent decrease in CREB activation, as seen above.<sup>118</sup>

The first generation of PDE4 inhibitor is rolipram. Previous studies of our group showed that this PDE4 inhibitor is able to increase the levels of pCREB (the activated form of CREB) in the medium spiny neurons, with neuroprotective effects both in HD rat model induced by quinolinic acid, and in R6/2 transgenic HD mice. These effects were demonstrated by the reduction of intranuclear formation of mutant huntingtin inclusions, sparing of striatal neurons, decrease in microglial activation, the delay of onset, and decrease in severity of neurological impairment and movement defects.<sup>119-121</sup>

In spite of the promising results obtained in animal models, these inhibitors have not proved to be successful in human clinical trials: rolipram have various side effects, such as nausea and emesis,<sup>122</sup> and in multiple sclerosis MRI showed an increase in brain inflammatory processes measured by brain lesions.<sup>123</sup>

Thus, recently, the new purpose of the research will be to study new inhibitors that do not have the aforementioned side effects.<sup>124,125</sup> The last clinical study in HD is represented by the PDE4 inhibitor GSK356278 (GlaxoSmithKline) that has shown good tolerability in patients although the improvement in motor and cognitive symptoms is not clear.<sup>66</sup>

## 5.3 | PDE 5

PDE 5 is specific to cGMP and is abundant in striatum, cortex, and hippocampus.<sup>126</sup>

Inhibition of these phosphodiesterases showed positive effects in rats as far as it concerns memory amelioration,<sup>127,128</sup> synaptic plasticity,<sup>129</sup> and depressive symptoms.<sup>130</sup>

Sildenafil, known primarily for its use in the erectile dysfunction and pulmonary arterial hypertension due to its vasodilator effects, also showed to exert a neuroprotective effect in various animal models of disease.<sup>126,131</sup> Indeed, Puerta et al<sup>132</sup> demonstrated that sildenafil and vardenafil ameliorate neurological impairment, decrease death of medium spiny neurons, and upregulate pCREB and BDNF expression in a rat model of HD induced by 3 nitropropionic acid. This confirms the importance of cGMP pathway in HD pathology, suggesting PDE5 inhibitors as a possible therapeutic strategy in HD.

## 5.4 | PDE 10

Phosphodiesterase 10 is an enzyme with a double specificity for cAMP and cGMP, characterized by its high level of expression in striatum, nucleus accumbens, and olfactory tubercle. PDE10A is also distributed in hippocampus, thalamus, cerebellum, and spinal cord.<sup>133-136</sup> PDE10 expression in the caudate portion of the basal ganglia suggests a role of this enzyme in striatonigral and striatopallidal pathways.<sup>137</sup> Xie et al<sup>137</sup> described PDE10A localization only in medium spiny neurons, whereas it was not expressed in interneurons. Because of such peculiar expression in medium spiny neurons (MSNs), PDE10A involvement was studied in dopamine signaling. Many studies showed that inhibition of PDE10A involves the activation of D1-direct and D2-indirect pathway.<sup>138-141</sup> In 2008, Nishi et al<sup>142</sup> showed the effects of papaverine, a PDE10A inhibitor, in

D1-DARPP-32-FLAG/D2 DARPP-32-Myc mice and demonstrated that PDE10A controls cAMP/PKA pathway as a dopamine D2 antagonist, activating the indirect pathway.

However, our group also found PDE10A protein expressed in interneurons, with a nuclear distribution, suggesting a specific role of the PDEs determined by their distribution.<sup>143-145</sup> Studies described a decrease in PDE10A mRNA expression in striatum of R6/2 mice and in brain samples of HD affected people<sup>118</sup>; also, low cAMP expression was recorded in the striatum of HD patients and in STHdh Q111 cell HD model.<sup>88,146</sup> It is possible that the latter mechanism determines the decrease in PDE10A expression as a compensatory mechanism.<sup>147</sup> Interestingly, in contrast with the findings by Hebb et al 2004,<sup>118</sup> our group found a dramatic increase of PDE10A in MSN of R6/2 mice compared to WT mice. This pattern is repeated in all types of interneurons (parvalbuminergic, somatostatinergic, calretininergic), except in cholinergic ones where PDE10A showed low expression levels during the disease progression.<sup>143</sup> On the basis of these considerations, our group has previously tested the PDE10A inhibitor TP10 (Pfizer) in rats and R62 mice, obtaining a reduction in striatal neuronal loss and an increase in life span. This was associated with the upregulation of pCREB and BDNF protein expression.<sup>148,149</sup> Those results were later confirmed by the study by Beaumont et al.<sup>150</sup> obtained by using PDE10 inhibitors in the Q175 mice that show activation of CREB pathway and of MAP kinase signaling cascades.

Recently, a novel PDE10A inhibitor 1-[2-fluoro-4-(1H-pyrazol-1yl)phenyl]-5-methoxy-3-(1-phenyl-1H-pyrazol-5-yl)pyridazin-4(1H)-one (TAK-063) has been tested in R6/2 mouse HD model. This new compound produces an activation of both indirect and direct pathway MSNs. In this study, TAK-063 showed beneficial effects in mice with amelioration of behavioral and neurological impairment, reduction in neurons loss in striatum, and upregulation of BDNF expression.<sup>151</sup>

The effects of PDE10A inhibition are still under investigation. A Phase II clinical trial has just been concluded: PF-0254920 drug was used to taste safety and tolerability in HD patients. Unfortunately, with the data available so far, the drug does not ameliorate movement and/or behavioral problems.<sup>152</sup>

## 6 | CONCLUSIONS

This review highlighted the important role that phosphodiesterases plays in many cellular processes under physiological and/or pathological conditions. Therefore, we have described in more detail the phosphodiesterases expressed in the striatum and related brain regions, the main target of the Huntington pathology, and more involved in the regulation of the dopaminergic system, universally recognized as altered in the aforesaid pathology. All the studies presented here suggest the use of PDE inhibitors in HD, in order to potentiate cAMP signaling in the striatum.

As mentioned elsewhere, in recent years the therapeutic role of phosphodiesterase regulation has emerged through their inhibition.

Without a doubt, the most known drug among antiphosphodiesterase drugs is viagra, which inhibits phosphodiesterase 5 and improves erectile dysfunction. Few other drugs capable of inhibition phosphodiesterase are used in clinical settings: for example, in the dysregulation of various diseases such as pulmonary hypertension, acute refractory cardiac failure, intermittent claudication, and chronic obstructive pulmonary disease. Moreover, the importance of PDEs inhibition is demonstrated by the NIH clinical trials Web site.<sup>153</sup> In fact, some of FDA-approved PDE drugs in Phase Trials are being tested in AD, HD, and/or other neurodegenerative disease patients.

Therefore, in the last few years, clinical neuroscientists have shifted their attention to the development of new candidates for PDE inhibition, developing isoform selective inhibitors.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## ORCID

Francesca R. Fusco  <http://orcid.org/0000-0003-2226-523X>

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