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REVIEW

Purinergic Receptors in Basal Ganglia Diseases: Shared Molecular Mechanisms between Huntington's and Parkinson's Disease

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Abstract Huntington's (HD) and Parkinson's diseases (PD) are neurodegenerative disorders caused by the death of GABAergic and dopaminergic neurons in the basal ganglia leading to hyperkinetic and hypokinetic symptoms, respectively. We review here the participation of purinergic receptors through intracellular Ca^{2+} signaling in these neurodegenerative diseases. The adenosine A_{2A} receptor stimulates striatopallidal GABAergic neurons, resulting in inhibitory actions on GABAergic neurons of the globus pallidus. A_{2A} and dopamine D2 receptors form functional heteromeric complexes inducing allosteric inhibition, and A_{2A} receptor activation results in motor inhibition. Furthermore, the A_{2A} receptor physically and functionally interacts with glutamate receptors, mainly with the mGlu5 receptor subtype. This interaction facilitates glutamate release, resulting in NMDA glutamate receptor activation and an increase of Ca^{2+} influx. P2X7 receptor activation also promotes glutamate release and neuronal damage. Thus, modulation of purinergic receptor activity, such as A_{2A} and P2X7 receptors, and subsequent aberrant Ca^{2+} signaling, might present interesting therapeutic potential for HD and PD.

Keywords Purinergic receptor · Central nervous system · Huntington's disease · Parkinson's disease · 6-hydroxydopamine

Introduction

Huntington's and Parkinson's Disease: Common Anatomical Basis

Huntington's (HD) and Parkinson's disease (PD) are neurodegenerative disorders that cause severe motor impairment. HD is mainly a genetic disease caused by a mutation in the huntingtin gene that was described in the '90s of the past century. However, no efficient therapy for HD has been developed since then. The huntingtin gene has a CAG repeat stretch that codes for a polyglutamine expansion (polyQ) in the N-terminal domain of the protein. Thus, > 36 repetitions of polyQ in this region lead to the development of the disease, resulting in massive brain degeneration marked by brain atrophy and loss of GABAergic neurons in the basal ganglia (Fig. 1) [1, 2], mainly through the accumulation of mutated protein in the cells, overwhelming the proteasome system [3] (Fig. 1)

PD, like HD, is associated with cell death in the basal ganglia, although the most affected cells are the dopaminergic neurons in the substantia nigra pars compacta [4].

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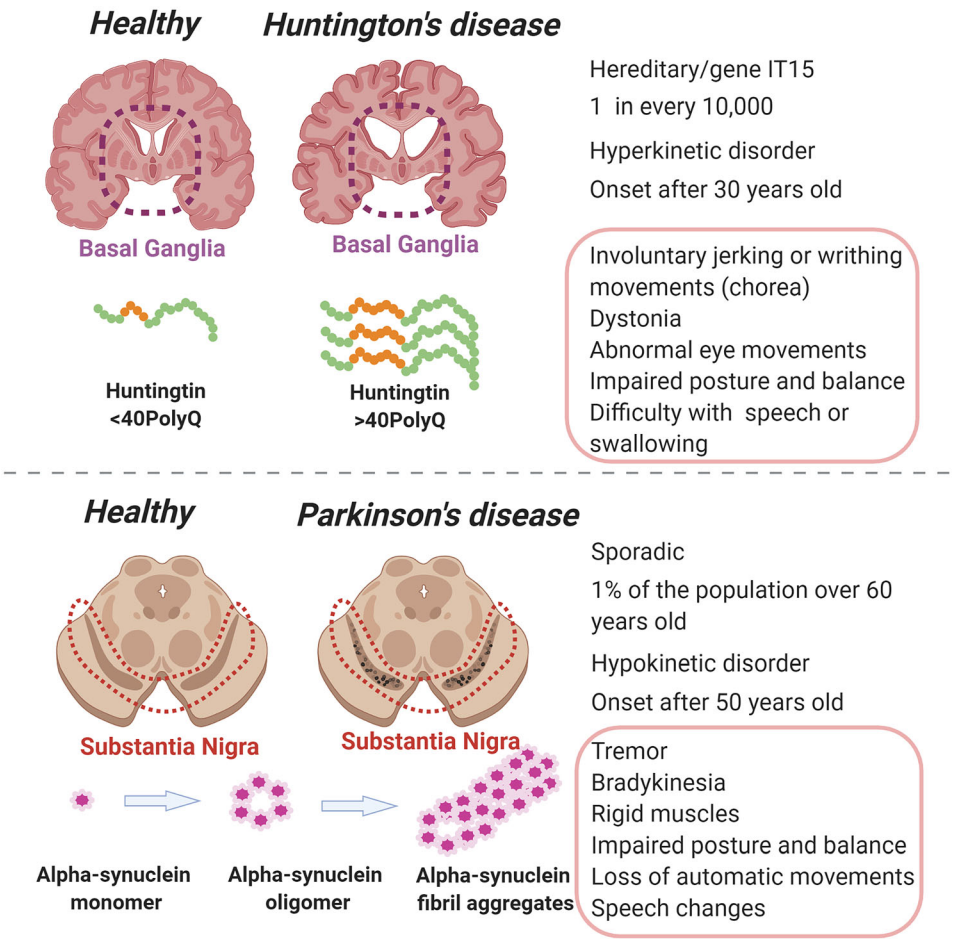

Fig. 1 Huntington's and Parkinson's disease characteristics.

This disease may be caused by the formation of Lewy bodies, which are intraneuronal inclusions of α-synuclein, resulting in decreased levels of dopamine secretion by the nerve terminals [5, 6] (Fig. 1)

In contrast to HD, PD is mostly a sporadic disease, and only ∼ 10%–15% of cases are related to gene inheritance [7]. These genes typically encode proteins involved in autophagy and mitochondrial housekeeping, as well as endo- and exocytosis in synapses [8, 9]. Both diseases have progressive symptoms, with disease onset at ∼ 30 years old in HD patients, and 60 years old in PD patients. However, there is a severe form of HD with a faster progression that occurs in children [10].

Both diseases present protein aggregates, degeneration in basal ganglia structures, and motor disabilities. However, HD is an autosomal dominant hyperkinetic disease, while PD is a mostly sporadic hypokinetic disease. HD and PD show distinct prevalence in the population and affect people in different age groups.

As noted above, HD and PD are basal ganglia diseases. The basal ganglia are comprised of the striatum (caudate and putamen), globus pallidus (external and internal; GPe and GPi), substantia nigra (SN), and subthalamic nucleus (STN) (Fig. 1B) [11, 12]. Glutamatergic neurons project from the thalamus to the motor cortex (divided into primary and secondary motor cortices), from the motor cortex to the putamen, and from the STN to the GP and SN (Fig. 2). GABAergic neurons project from the putamen to the GP and SN, which projects to the thalamus. Dopaminergic neurons project from the SN to the striatum, constituting the nigrostriatal pathway. Generally, thalamocortical projections must be released from inhibition for the initiation of movement [11, 12].

In the direct pathway (Fig. 2C), striatal GABAergic neurons expressing mainly D1 receptors, receive excitatory inputs from glutamatergic neurons of the motor cortex and project to the GPi and SN. GABAergic neurons from GPi inhibit GABAergic neurons that project to the *thalamus*. Thus, the disinhibition of glutamatergic neurons from the thalamus projecting to the motor cortex enables voluntary movements [11–13].

In the indirect pathway (Fig. 2C), excitatory stimuli from cortical glutamatergic neurons activate striatal GABAergic neurons expressing dopamine D2 receptors. These neurons inhibit GABAergic neurons of the GPe that project to the STN, disinhibiting this pathway. The STN

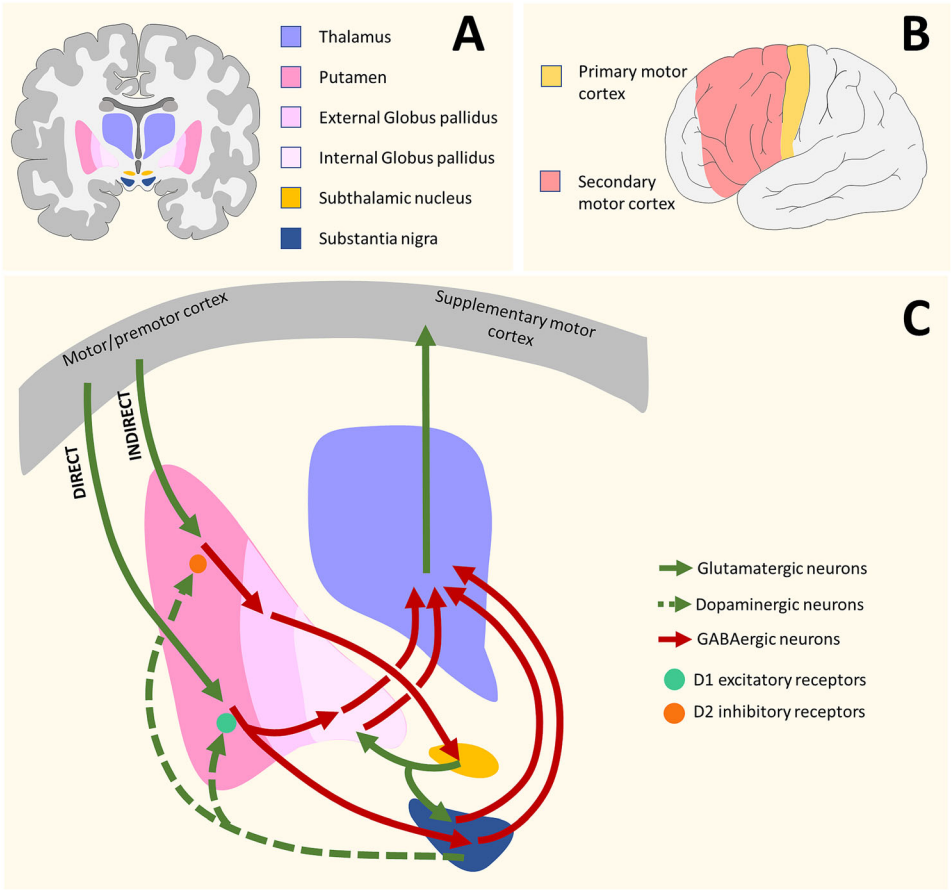

Fig. 2 Basal ganglia. **A** Locations of primary and secondary motor cortex. **B** Basal ganglia structures involved in the pathophysiology of HD and PD. **C** Neuronal network involved in the pathophysiology of HD and PD. Cortical glutamatergic excitatory neurons connect to inhibitory GABAergic neurons in the putamen, that innervate the SN and the GP. The direct pathway is regulated in the putamen by dopaminergic afferents exerting excitatory effects through D1 receptors, and the indirect pathway with inhibitory effects through D2 receptors. These receptors are modulated by A_1 and A_{2A} receptors, respectively.

has glutamatergic projections to the SN and GPi, which result in the activation of GABAergic neurons projecting to the thalamus. As expected, inhibition of thalamic neurons results in resting glutamatergic neuron projecting to the motor cortex, preventing unwanted muscle contractions would that compete with voluntary movements [11, 12].

Differential expression of excitatory D1 and inhibitory D2 receptors in both pathways leads to different effects of dopaminergic stimulation: dopamine release in the striatum activates neurons expressing D1 receptors, whereas dopamine inhibits neurons expressing D2 receptors in the indirect pathway [11, 12].

Diseases such as PD present hypokinetic symptoms. Decreased motor function by abnormally high output of the basal ganglia leads to augmented inhibition of thalamocortical projection neurons. In PD, the decrease of dopaminergic signaling in the direct pathway induces disease-characterizing symptoms: muscle rigidity, tremor at rest, and slowness to initiate and execute movements [14]. In turn, hyperkinetic disorders, such as HD, are caused by reduced basal ganglia output from the indirect pathway, leading to unwanted movements [14]. Motor symptoms such as the uncontrolled rapid and jerky movements in HD are due to the death of the GABAergic neurons that project to the GPe in the indirect pathway, resulting in disruption of the indirect pathway and thus characterizing hyperkinetic disorders [14].

Calcium Signaling as a Common Pathway in PD and HD

Besides alterations in basal ganglia neurotransmission, changes in intracellular calcium concentration ($[Ca^{2+}]_i$) and signaling provide another similarity between HD and PD. Ca^{2+} is a universal intracellular messenger, and its concentration is maintained by fine mechanisms in order to maintain homeostasis [15].

Robust mechanisms fine-tune inward and outward Ca^{2+} currents. At rest, cells maintain $[Ca^{2+}]_i$ levels at $\sim$ 100 nmol/L. Increased $[Ca^{2+}]_i$ occurs through: (a) influx from the extracellular milieu *via* ion channels (voltage-dependent, ligand-gated, store-operated, and other channels) and exchangers (e.g. Na^+/Ca^{2+} exchanger); (b) efflux from the endoplasmic reticulum (ER) upon activation of inositol trisphosphate (IP_3) or ryanodine receptors; and (c) release from mitochondria (mitochondrial permeability transition pore). The cellular machinery that counterbalances $[Ca^{2+}]_i$

elevation buffers this cation by binding to proteins, pumping it into intracellular organelles like the ER and mitochondria [16–19], or extruding it from the cell through the plasma membrane.

Proteins containing an EF-hand Ca^{2+} binding domain, like the stromal interacting molecules, function as sensors of the ER [Ca^{2+}] store. These proteins oligomerize and translocate to the cytosol during depletion of ER stores, leading to the opening of Orai family channels localized in the plasma membrane that replenish intracellular Ca^{2+} stores [20–25].

$[Ca^{2+}]_i$ elevation triggers the activation of downstream signaling pathways comprised of kinases, phosphatases, transcription factors, and proteins related to synaptic vesicle fusion in neurons [17, 26–29]. Alterations in Ca^{2+} homeostasis that need stress overcompensation usually lead to cell death by excitotoxicity and apoptosis. An imbalance of Ca^{2+} signaling initiating cell death by excitotoxicity and apoptosis is very common in neurodegenerative diseases like HD and PD, causing massive neuronal loss.

In HD, the main cause of the dysregulation of $[Ca^{2+}]_i$ homeostasis is the accelerated delivery of N-methyl-D-aspartate receptors (NMDARs) to the plasma membrane in GABAergic neurons [30–36]. Increased NMDAR expression augments Ca^{2+} influx, resulting in toxic levels of $[Ca^{2+}]_i$ and cell death [28, 34, 35, 37].

The mutant form of huntingtin can also interact with other proteins related to Ca^{2+} homeostasis, such as voltage-gated Ca^{2+} channels and IP_3 receptors [28, 38, 39]. In HD, the IP_3 receptor has a higher affinity for its natural ligand IP_3 and also increases the leakage of Ca^{2+} through ryanodine receptors and depletion of ER stores [38, 39]. As noted above, intracellular Ca^{2+} depletion activates stromal interacting molecules and consequently higher inflow of Ca^{2+} from extracellular milieu occurs [40, 41].

In PD, a new connection between Ca^{2+} signaling and α-synuclein has been recently described. Lautenschläger and coworkers reported that, besides the interaction of the N-terminus of α-synuclein with unilamellar vesicles, its C-terminus also binds to Ca^{2+}, increasing its lipid-binding capacity. Moreover, the interaction with Ca^{2+} also controls the localization of α-synuclein at the pre-synaptic terminal and in synaptic vesicle clustering upon increased $[Ca^{2+}]_i$ [42]. Those findings strengthen the modern consideration of PD as an ion channel disease [43].

All PD cases with hereditary characteristics are associated with mitochondrial dysfunction due to imbalanced $[Ca^{2+}]_i$ signaling [44–46]. Dopaminergic neurons in the SN have spontaneous Ca^{2+} pacemaker activity triggered by L-type voltage-gated Ca^{2+} channels (Cav1.3), making mitochondria vulnerable to oxidative stress [47–52]. Furthermore, mutations in Orai channels result in decreased dopamine production due to reduced tyrosine hydroxylase expression [28, 53].

In addition to the voltage-gated Ca^{2+} channels NMDAR and Orai, other receptors like purinergic receptors also modulate $[Ca^{2+}]_i$ signaling and have been reported to participate in PD and HD, as follows.

Purinergic Receptors

Purinergic signaling is mediated by extracellular nucleotides and nucleosides that have been implicated in a range of physiological processes. In the central nervous system (CNS), these receptors participate in neurotransmission, neuromodulation, and neuroinflammation. Studies show that the proliferation, differentiation, and apoptosis of neural cells are also mediated by purinergic receptors, indicating an important role in neurogenesis and repair [54–56].

When tissue damage occurs as a consequence of injury or pathophysiological processes, a high concentration of adenosine 5'-triphosphate (ATP) is released by dying cells into the extracellular space and is degraded by ectonucleotidases. The ectonucleotide pyrophosphatase/phosphodiesterase family together with ectonucleoside triphosphate diphosphohydrolases and 5´ectonucleotidase catalyze the hydrolysis of ATP into adenosine [57, 58].

ATP and its metabolites activate purinergic receptors on the cell membrane, divided into P1 and P2 receptors. P1 receptors, also known as adenosine receptors, are G protein-coupled and are activated by endogenous adenosine. P2 receptors are endogenously activated by the extracellular nucleotide molecules ATP, UTP, UDP, ADP and their derivatives. Based on their structural characteristics, P2 receptors can be subdivided into two categories: ligand-gated cation channels (P2X receptors) and G protein-coupled receptors (P2Y receptors) [59].

Currently, seven subtypes of the trimeric structure of the P2X receptor have been cloned, namely P2X1–7 receptors, which are mainly distributed in excitable cells such as neurons, smooth muscle cells, and glandular cells. The P2X receptor is a non-selective ATP-gated cation channel. After activation, the cell permeability to cations increases and leads to enhanced transient $[Ca^{2+}]_i$ levels. Ca^{2+} influx depolarizes the cell membrane, causing a series of physiological or pathological changes such as the rapid transmission of synaptic signals in the central and peripheral nervous systems, smooth muscle contraction, platelet aggregation, macrophage activation, cell proliferation, and apoptosis. Abnormal Ca^{2+} influx is mainly mediated by the P2X7 receptor. Long-term or excessive activation of this receptor can open abnormal large membrane pores, leading

to massive Ca^{2+} influx and eventually to cell death [60]. Divalent cations like Ca^{2+} and Mg^{2+} are capable of allosteric blockade of the P2X7 receptor, as proposed by Virginio and colleagues in 1997 [61].

There are eight subtypes of P2Y receptors (P2Y1, 2, 4, 6, 11, 12, 13, 14), which are widely distributed in the CNS as well as in other tissues. P2Y1, P2Y2, P2Y4, P2Y6 and P2Y11 receptors are coupled to Gq proteins, activate phospholipase C-β, produce IP_3 and diacylglycerol, and mobilize Ca^{2+} from intracellular stores [62]. Subsequent protein kinase C (PKC) activation may stimulate the mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase signaling pathways involved in the proliferation, differentiation and regeneration processes [63]. On the other hand, the P2Y12, P2Y13 and P2Y14 receptors are coupled to Gi proteins and, upon activation, inhibit cAMP production [62].

The P1 receptor family activated by adenosine is composed of A_1, A_{2A}, A_{2B} and A_3 subtypes. A_1 and A_3 receptors are coupled to G_i/G_o proteins, inhibiting adenylate cyclase and reducing cAMP levels, while A_2 receptors coupled to Gs protein activate adenylate cyclase and increase intracellular cAMP levels. In the CNS, ATP and adenosine receptors are associated with many neurodegenerative diseases, including PD and HD. In the following topics we focus on purinergic receptors that have been intensely investigated in PD and HD. The receptors that we do not consider (A_{2B}, A_3, P2X2–6, P2Y1, P2Y2, P2Y4, P2Y6, and P2Y11–14) may also be involved in pathophysiology, but they are still poorly investigated in these contexts. Recently, the P2Y2 receptor has been shown to play key roles in the development of HD by controlling intracellular Ca^{2+} oscillations and consequently the activation of transcription factors related to GABAergic neuronal fate [64].

Shared Purinergic Receptors in HD and PD

The strict relationship between HD and PD pathophysiology extends to the involvement of purinergic receptors. Their participation in neurodegenerative diseases, including PD, is well established [55]. However, there are few studies in the literature regarding the involvement of purinergic receptors in HD. So far, two receptors have been found to be involved in both diseases: A_{2A} and P2X7 receptors. Their function in healthy and diseased brains is summarized in Table I.

A_{2A} Receptors

The A_{2A} receptor is a member of the G protein-coupled receptor family that activates adenylyl cyclase to induce the synthesis of cAMP and activation of phospholipase C, consequently increasing $[Ca^{2+}]_i$. This receptor is strongly expressed in the caudate nucleus, putamen, nucleus accumbens, olfactory tubercles, and GPe [65]. The cortex [66], hippocampus [66, 67], cerebellum [68] and olfactory bulb [69] also express this receptor, but to a lesser extent. The A_{2A} receptor is present in neurons, astrocytes, oligodendrocytes and microglia and may modulate dopaminergic and glutamatergic neurotransmission [70], neuroinflammation, and neurodegeneration [71, 72]. The striatopallidal pathway has already been demonstrated to play a relevant role in the pathophysiology of PD and HD. In this sense, the A_{2A} receptor has attracted attention, since it is largely expressed in the striatum and GPe, specifically in GABAergic and glutamatergic striatopallidal medium spiny neurons [73–75].

The interaction between striatal A_{2A} and D2 receptor subunits is well established. The A_{2A}–D2 dimer is a functional heteroreceptor that induces allosteric inhibition. When the A_{2A} receptor is activated by adenosine, the affinity of the D2 receptor for dopamine is reduced [76] and elicits a decrease in the G-protein coupling of the D2 receptor [77]. Under basal conditions, A_{2A} receptor signaling is slightly activated. Consequently, the D2 receptor affinity is not impaired by A_{2A} receptor activation, and cAMP–protein kinase A (PKA) signaling does not contribute to GABAergic neuronal activity [78]. When the A_{2A} receptor is over-activated, adenylate cyclase stimulation occurs and induces opposite effects, commonly elicited by the D2 receptor. These stimuli lead to an increase in cAMP levels and consequent activation of PKA. The cAMP–PKA pathway activates MAPK signaling and the constitutive transcription factor CREB [78]. Further, this pathway phosphorylates AMPA receptors and DARPP-32 at Thr34 [79], decreasing its phosphorylation at Thr75 [80], and executing important signal cascade for the control of GABAergic neuronal excitability [81]. Considering the vast majority of evidence in the literature, A_{2A} receptor activation has been strongly suggested to stimulate GABAergic neurons [74, 75, 81–88]. However, few reports have suggested that A_{2A} receptor activation may inhibit GABAergic neuronal activity [89, 90]. A_{2A}–D2 receptor heterodimers are present in GABAergic striatopallidal neurons and subsequent signaling may result in motor inhibition [83]. An *in vivo* study investigating this interaction found that mice with D2 receptor knockout exhibited motor impairment and that istradefylline, a selective A_{2A} receptor antagonist, reverted this condition [91].

Remarkably, A_{2A} receptors also interact with glutamate receptors, mainly NMDA and mGlu5 receptors. A_{2A} receptors may prompt long-term potentiation by NMDA-excitatory postsynaptic currents, depending on NMDA and mGlu5 receptors due to postsynaptic Ca^{2+} flow [65, 92, 93]. In addition, the formation of heteromeric

complexes between A_{2A} and glutamatergic mGlu5 receptors [94, 95] may facilitate glutamate release [95]. Moreover, ample evidence indicates functional interactions between A_{2A}, mGlu5, and D2 receptors that could contribute to the striatopallidal pathway [83, 96–99]. A study demonstrated that A_{2A} and mGlu5 receptors have synergistic effects since their simultaneous blockade elicits a pronounced increase in locomotor activity [98]. Motor stimulation enhanced by mGlu5 antagonism depends on D2 and forebrain A_{2A} receptors [98].

In this sense, interactions among A_{2A}, mGlu5, and D2 receptors seem to be important for the pathophysiology of PD. A literature review showed that antagonists of the mGlu5 receptor attenuate L-DOPA-induced dyskinesias in different animal models of PD [100].

Further, it has been proposed that treatment with A_{2A} and mGlu5 receptor antagonists has antiparkinsonian effects and might enhance the antiparkinsonian activity of dopamine-based drugs [100, 101]. Similarly, synergistic effects between A_{2A} and mGlu5 receptor antagonists stimulate locomotor actions, presenting an antiparkinsonian-like effect in the dopamine depletion model induced by reserpine, indicating that this functional interaction provides a mechanism for motor dysfunction in PD [98]. However, this mechanism needs to be deeply studied, since it has also been demonstrated a selective agonist of the mGlu5 receptor inhibits rotational behavior, an effect that is exacerbated by A_{2A} receptor agonism and attenuated by antagonism of this receptor in the 6-hydroxydopamine (6-OHDA, a toxic dopamine analog) rat model of PD [100].

As noted above, A_{2A} receptors modulate several mechanisms implicated in PD. In many studies, istradefylline treatment of PD patients had beneficial results when administered together with levodopa, a dopamine precursor. In fact, istradefylline is currently used as an adjunct in combination with levodopa in Japan [102]. However, the association between A_{2A} receptors and PD is currently under investigation in order to elucidate the pathology of this neurodegenerative disease. Several findings have shown that adenosine signaling is altered in PD pathology. In the 6-OHDA animal model, a decrease in adenosine levels and an increase in A_{2A} receptor expression has been found in the striatum [103]. These alterations were also found in the GPe and caudate–putamen of PD patients with dyskinesia, a levodopa side-effect [104, 105]. Similar to the clinical findings, 6-OHDA lesioned rats with dyskinesia exhibited increased expression of the A_{2A} receptor in the striatum after levodopa treatment [106]. Remarkably, in the 6-OHDA rat model, basal release of GABA is augmented in the GP, and treatment with istradefylline reverses this increase [107]. These results are in agreement with the morpho-functional association between the activated striatopallidal pathway and A_{2A} receptors in PD [107]. Dopamine depletion prompts degeneration of the spines and glutamatergic synapses of striatopallidal medium spiny neurons through increased Ca^{2+} influx through L-type Ca^{2+} channels [108]. The A_{2A} receptor antagonist 1-(7-imino-3-propyl-2,3-dihydrothiazolo[4,5-d]pyrimidin-6(7H)-yl) urea (IDPU) counteracts the behavioral and oxidative stress impairments induced by 6-OHDA [109]. In addition, IDPU increases intracellular dopamine and decreases the glutamate and $[Ca^{2+}]_i$ levels in 6-OHDA-lesioned rats [109]. It is hypothesized that residual A_{2A} receptors in PD modulate GABAergic activity in the striatum [65].

In non-human primates submitted to the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model of PD, A_{2A} receptor expression is increased in the caudate and putamen [110]. Interestingly, when the animals were concomitantly treated with levodopa and a selective antagonist of the NR1A/2B subunits of NMDAR, A_{2A} receptor expression was restored to control levels [110]. All this evidence indicates that the A_{2A} receptor is extensively expressed in the striatopallidal pathway and is likely involved in the of development PD as well as in the appearance of dyskinesia.

It has been proposed that the neuronal dysfunction and toxicity mediated by exposure to α-synuclein oligomers might be due to the induction of enhanced NMDAR activity leading to increased Ca^{2+} influx in PD [111]. A_{2A} receptor antagonism apparently decreases α-synuclein aggregation in the H4 cell line without affecting oligomerization [112]. In addition, *in vivo* analysis evidenced that A_{2A} receptor blockade abolishes neuronal cell death, as well as the increasing expression of the NR2B subunit of NMDARs, and the impairment of long-term potentiation induced by α-synuclein [112]. Interestingly, the mouse model of α-synuclein *per se* revealed augmentation of A_{2A} receptor expression accompanied by increased α-synuclein inclusions, astrocytic reactivity, cell death, and memory impairment. Genetic deletion of A_{2A} receptors may protect against all of these disease-related effects [113]. It has been hypothesized that α-synuclein monomers bind to the A_{2A} receptor and increases its activity [71].

In HD pathology, neuronal degeneration occurs in the striatum, in which the postsynaptic GABAergic striatopallidal neurons, the most vulnerable cell population, are localized [114]. Thus, the A_{2A} receptor may play an important role in HD. In this sense, the rs5751876 polymorphism of the *ADORA2A* gene has been suggested to be a genetic modifier of the onset age of HD [115]. Unlike the findings in PD, HD patients lose A_{2A} receptor expression [116]. During the initial phase of HD, the GPe presents an aberrant reduction of A_{2A} receptor expression, while the decrease of A_{2A} receptor expression in the caudate and putamen is accompanied by disease

progression [116]. The same results were found in older transgenic HD model mice [117–121]. In line with these data, A_{2A} receptor agonism delays the progressive motor impairment, reverses the reduction of brain weight, enlargement of ventricles, and stimulation of AMPK in transgenic HD mice [122].

However, simultaneous hyperactivation of D1 and A_{2A} receptors may exacerbate cognitive impairment in the R6/1 transgenic mouse [123]. Besides, A_{2A} receptor knockout in transgenic HD mice leads to a worsening of motor deficits and reduced life expectancy and enkephalin expression [120], suggesting impairment of GABAergic neuronal signaling. Further, some studies have shown that blockade of the A_{2A} receptor has beneficial effects that should be considered. In R6/2 transgenic mice, the A_{2A} receptor antagonist SCH58261 abrogates NMDA-induced toxicity, although the motor impairment is not reversed [124]. In addition, istradefylline improves working memory [125].

From these data, the roles of the A_{2A} receptor in GABAergic and glutamatergic striatopallidal neurons are evident, besides its interaction with D2, mGlu5 and NMDA receptors. In PD pathogenesis, it has been suggested that the A_{2A} receptor has a strong and robust association with motor impairment in striatopallidal signaling. Further functions of the A_{2A} receptor in HD remain to be clarified, despite all the evidence pointing to an opposite mechanism of that is seen in PD.

P2X7 Receptors

P2X7 receptors are ATP-gated cation channels (for a detailed review see [126]), formerly assumed to be expressed both in neurons and glial cells, but recent results have questioned the presence of these receptors in neurons [127, 128]. This receptor was detected in cultured glial and neuronal cells by *in situ* hybridization, immunodetection, and electron microscopy [129–134], but the used antibodies may lack specificity [135–138]. Corroborating P2X7 receptor expression in neurons, features attributed to stimulation of these receptors in cultured neurons or synaptosomes have been demonstrated by electrophysiological recordings, $[Ca^{2+}]_i$ measurements, and activation of intracellular signaling cascades [130, 139–143]. However, studies have suggested that glial cells could be responsible for some of these P2X7 receptor-mediated effects [144, 145]. Therefore, further studies are still required to confirm P2X7 receptor expression and function in neurons.

Regardless of the P2X7 receptor localization, its activation may lead to glutamate release, stimulation of neuroimmune responses, enhanced production of reactive oxygen species (ROS), protein misfolding, and diminished levels of brain-derived neurotrophic factor, resulting in neuroplasticity impairment and/or neuronal damage [131, 146, 147]. These key mechanisms may contribute to the pathophysiology of HD and PD.

Studies with mouse models of HD (Tet/HD94 and R6/1) have shown that treatment with Brilliant Blue G (BBG), a P2X7 receptor antagonist, ameliorates the motor coordination deficits and body weight loss, and inhibits neuronal loss [148]. Moreover, P2X7 receptor expression and P2X7 receptor-induced Ca^{2+} permeability are increased in these models [148]. *In vitro*, cultured neurons expressing mutant huntingtin show increased susceptibility to apoptosis triggered by P2X7 receptor stimulation [148].

The effects of P2X7 receptor blockade have also been investigated in the 6-OHDA rat model of PD. Injection of A-438079 (30 mg/kg, i.p.), a P2X7 receptor antagonist, before lesion establishment prevents the depletion of dopamine in the striatum with no reduction in dopaminergic neuronal cell death [149]. Moreover, chronic treatment with BBG (45 mg/kg, i.p.; every 48 h for 2 weeks) before unilateral 6-OHDA injection prevents the loss of tyrosine-hydroxylase-positive neurons and attenuates the amphetamine-induced rotational behavior and memory deficits [150]. Corroborating these data, a study by our group showed that one-week treatment with BBG (50 mg/kg, i.p.), every day after lesion establishment, reverses the dopaminergic neuronal loss in the SN and rotational behavior [151]. In a more recent study, we reported that the same treatment protocol with a higher dose of BBG (75 mg/kg) also re-establishes dopaminergic ramifications of the nigrostriatal pathway and decreases the rotation behavior in rats injured with 6-OHDA [152]. Moreover, BBG decreases Iba-1 labeling in the SN compared to the injured hemisphere of animals without treatment, which indicates a reduction of microglial activation [152].

In view of these data, *in vitro* studies indicated that P2X7 receptor antagonists have neuroprotective effects in PD. BV2 microglial cells pretreated with BBG (1 μmol/L) show decreased ROS production induced by α-synuclein [153]. Moreover, pretreatment of neuroblastoma SH-SY5Y cells with the P2X receptor antagonist pyridoxalphosphate-6-azophenyl-2′,4′-disulfonic acid (100 μmol/L) or AZ 11645373 (10 μmol/L) prevent the abnormal Ca^{2+} influx induced by α-synuclein [154].

The 1513A > C (rs3751143) polymorphism that facilitates P2X7 receptor-induced pore formation and increases cell death in humans [155] has been indicated as a risk factor for sporadic PD in a Han Chinese population [156]. Taken together, these studies suggest the P2X7 receptor as a therapeutic target for the treatment of both HD and PD.

Distinctive Purinergic Receptors in HD and PD

Since purinergic receptor involvement in neurodegenerative diseases is being studied worldwide, that some receptors important for either HD or PD, may be important as well for the other disease are the focus of this review. Thus, A_1, P2X1 and P2Y6 receptors are presented in this section. Table 1 summarizes functions of these receptors in healthy and diseased brains.

A_1 Receptors

The A_1 receptor, present in striatal and SN cells, has been suggested to play a significant role in neuroprotection in

Table 1 Purinergic signaling in HD and PD.

	Expressed by (cell type)	Function in the CNS	Function in disease
A_{2A}	Neurons, astrocytes, microglia, and oligodendrocytes [70, 72, 167].	Modulation of dopamine and glutamate neurotransmission, neuroinflammation, and synaptic plasticity [65, 71, 168].	**HD:** A_{2A} receptor expression is downregulated in HD pathogenesis and A_{2A} receptor activation might have beneficial effects HD rodent models [116–118, 120–122], but contradictory results suggest that A_{2A} receptor antagonism improves the motor disease [124, 125]. **PD:** Generally, antagonists of A_{2A} receptors promote motor and cognitive recovery [169]. A selective A_{2A} receptor antagonist is currently used as an adjunct with levodopa [101]. Recent data show that the A_{2A} receptor counteract the aggregation, neuronal degeneration and toxicity induced by α-synuclein [112, 113].
P2X7	Thought to be expressed in neurons and glia, but their presence in neurons has recently been questioned [127, 128].	Glutamate release, stimulation of neuroimmune response, enhanced production of ROS, protein misfolding, and diminished BDNF levels, resulting in neuroplasticity impairment and/or neuronal damage [131, 146, 147].	**HD:** P2X7 receptor antagonism ameliorates motor coordination deficits and body weight loss, and inhibits neuronal loss in animal models of HD (Tet/HD94 and R6/1) [148] **PD:** P2X7 receptor blockade before 6-OHDA lesions in rats prevents depletion of dopamine in striatum [149], hinders the loss of tyrosine-hydroxylase immunoreactivity, attenuates rotational behavior and diminishes memory deficits [150]. P2X7 receptor antagonism re-establishes the dopaminergic nigrostriatal pathway, decreases rotation behavior and reduces microglial activation in 6-OHDA lesioned rats [151, 152]. Pretreatment of BV2 microglia [153] and neuroblastoma SH-SY5Y [154] cells with P2X7 receptor antagonists decreases ROS production and prevents abnormal calcium influx induced by α-synuclein, respectively.
A1	Neurons [170], microglia [171], astrocytes [171], oligodendrocytes [172].	Inhibits excitatory neurotransmitter release [170] and microglial activation [171], decreases astrocyte proliferation [171], stimulates oligodendrocyte migration [172].	A1 receptor activation protects against degeneration and decreases excitatory neurotransmission [158, 160].
P2X1	Sympathetic and sensory neurons, astrocytes, and oligodendrocytes [173].	Noradrenaline and acetylcholine co-transmitters [173].	**PD:** P2X1 receptor activation induces lysosomal dysfunction and increases α-synuclein aggregation [161].
P2Y6	mESC-derived GABAergic neurons [174] and activated microglia [175].	Induces microglial cytokine release and phagocytic activity [164] and microglial phagoptosis [166].	**PD:** P2Y6 receptor activation contributes to neurodegeneration possibly through microglial activation [152].

BDNF, brain-derived neurotrophic factor; HD, Huntington's Disease; mESC, mouse embryonic stem cells; PD, Parkinson's Disease; ROS, reactive oxygen species.

HD. Its main function in the CNS is to inhibit excitatory transmission, and to decrease the affinity of ligands for the D1 receptor [157]. In the rat model of HD induced by 3-nitropropionic acid, treatment with the A_1 receptor agonist adenosine amine congener protects against degeneration and improves motor functions. These effects are accompanied by a decrease in the excitatory postsynaptic potential, suggesting that the neuroprotective effects of A_1 receptor activation involve the modulation of aberrant $[Ca^{2+}]_i$ flow [158]. However, different from the above-cited results, Zuchora and colleagues did not detect any neuroprotection when using the A_1 receptor agonist R-PIA in the same animal model [159].

Taking into account the close relation between HD and PD, A_1 receptor activity modulation could be a potential basis for PD treatment as well. In fact, a study conducted by Alfinito and colleagues showed effects of the A_1 receptor antagonist 8-cyclopentyl-1,3-dipropylxanthine in rats injured with malonate, an inhibitor of mitochondrial function [160]. Injection of 8-cyclopentyl-1,3-dipropylxanthine into the SN exacerbated dopaminergic neuronal death, whereas striatal injection increased the GABAergic neuron loss induced by malonate [160]. Thus, in summary, A_1 receptor activation protects neuronal cells against death in both PD and HD models.

P2X1 Receptors

One hallmark of the PD patient's brain is the α-synuclein aggregation. Spread of α-synuclein clusters occurs in the neurodegenerative environment, and the ATP metabolites resulting from cellular death have been studied as key factors in this process. Since ATP stimulates α-synuclein oligomerization, P2X receptor antagonists were used to evaluate which P2X receptor subtype is implicated in this effect. NF449, a selective P2X1 receptor antagonist, reduces ATP-evoked α-synuclein aggregation *in vitro* [161]. P2X1 receptor activation induces lysosomal dysfunction, decreasing α-synuclein turnover and increasing its concentration [161]. Thus, ATP results in increased α-synuclein aggregation, which augments ATP production. Taking into account that lysosomal dysfunction leads to huntingtin protein accumulation in HD [162], P2X1 receptor antagonism is an interesting subject of study in this disease as well.

P2Y6 Receptors

Recently, P2Y6 receptors were also implicated in PD [152]. In the CNS, P2Y6 receptors are mainly present in neurons and microglial cells [163, 164]. Peripherally, increased expression has been found in peripheral blood mononuclear cells from PD patients [165]. Taking into account that PD induces neuroinflammation and microglia activation *in vivo*, rat primary microglia culture was challenged with lipopolysaccharide. These cells presented increased P2Y6 receptor expression, supporting the neuroinflammatory hypothesis regarding the role of the P2Y6 receptor in PD [165]. Moreover, microglial P2Y6 receptor activation by UDP released during the neurodegenerative process induces cytokine release and phagocytic activity [164].

Oliveira-Giacomelli and colleagues (2019) demonstrated that P2Y6 receptor antagonism prevents the death of dopaminergic neurons in SH-SY5Y cell cultures challenged with 6-OHDA, and in an animal model of PD induced by the same neurotoxin. This effect was accompanied by inhibition of microglial activation in the SN [152]. The authors suggested that this *in vivo* effect could be due to inhibition of the phagoptosis process, in which reactive microglial cells phagocytose viable neurons. This hypothesis is supported by a study showing that P2Y6 receptor antagonism prevents the microglial phagoptosis induced by inflammation in a mixed culture [166]. However, since the same neuroprotective effect was found *in vitro* in the absence of microglial cells, neuronal P2Y6 receptors could be, at least partially, responsible for the beneficial effects. In fact, P2Y6 receptor antagonism or deletion also prevents the SH-SY5Y cell death induced by 1-methyl-4-phenylpyridinium, possibly by reducing ROS production [163, 165].

Taking into account that reactive microglial cells participate in the neuronal loss in the HD brain, microglial P2Y6 receptor activation in HD development and progression seems to be a promising research subject for HD therapy.

Conclusion

Purinergic A_{2A} and P2X7 receptors participate in PD and HD by interfering through diverse mechanisms with intracellular Ca^{2+} signaling in the medium spiny neurons of the striatum. The A_{2A}–D2 receptor dimer is a functional heteroreceptor, whose activation under physiological conditions is blocked by D2 receptor activation, resulting in movement stimulation. Under conditions of PD, the lack of dopamine maintains the heteroreceptor in the active state, triggering intracellular signaling pathways that cause movement inhibition. Thus, the same pathway, due to PKA activation, promotes neurodegeneration by facilitating glutamate release through interaction with the mGlu5 receptor, creating a disturbance of $[Ca^{2+}]_i$ and resulting in aggregation of α-synuclein and mitochondrial oxidative stress in PD. The functions of A_{2A} receptors in HD are controversial, although the most explored hypothesis states

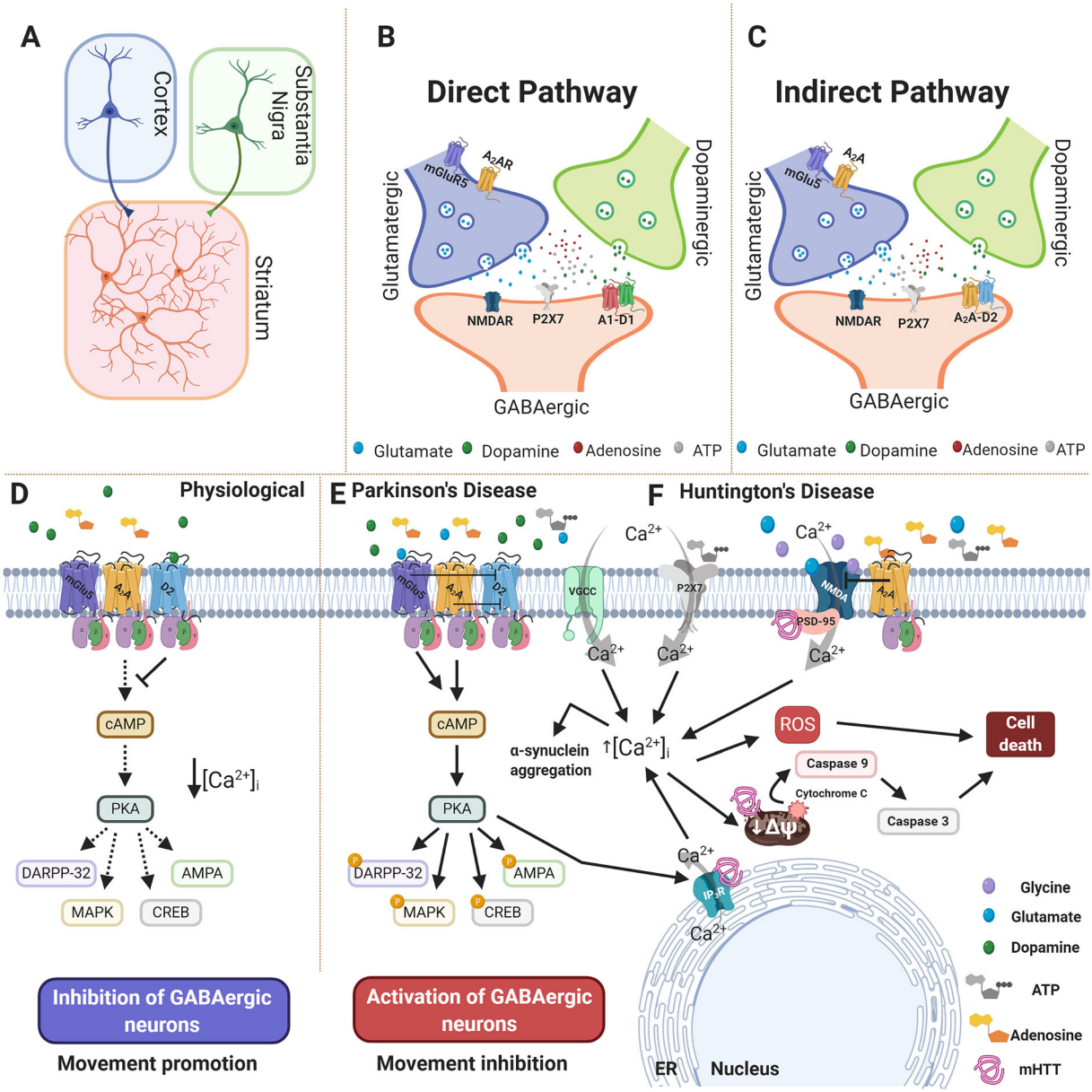

Fig. 3 Purinergic receptors and Ca^{2+} signaling as common mechanisms in PD and HD. **A** Schematic presentation of the corticostriatal and nigrostriatal pathways. The striatum is mainly composed of GABAergic medium spiny neurons that project to direct or indirect movement pathways. **B, C** Glutamate, dopamine, adenosine and ATP control the direct and indirect signaling pathways, depending on the formation of adenosinergic–dopaminergic receptor dimers. The direct pathway stimulates GABAergic medium spiny neurons expressing D1 excitatory receptors, that inhibit motor function when dimerized with the A1 receptor. **C, D** The indirect pathway stimulates GABAergic medium spiny neurons expressing D2 inhibitory receptors. When D2 receptors form complexes with A_{2A} and mGlu5 receptors, these neurons are inhibited with consequent movement promotion. **E** In PD, the dopamine levels in synapses are diminished, favoring A_{2A} receptor activity, which leads to PKA activation and the inhibition of movements, while increasing $[Ca^{2+}]_i$ and the aggregation of α-synuclein. **F** In HD, P2X7 receptors mediate increased Ca^{2+} inflow, moving the cell towards apoptosis pathways through depolarization of mitochondrial membrane potential, the release of cytochrome c and the activation of caspases. Moreover, NMDA receptors interact with mHtt, presenting abnormal Ca^{2+} influx and leading to the same cell death pathways, including the formation of ROS. Abbreviations: NMDA, N-methyl-D-aspartate; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; PKA, protein kinase A; DARPP-32, dopamine- and cAMP-regulated neuronal phosphoprotein; MAPK, mitogen-activated protein kinase/extracellular signal-regulated kinase; CREB, cAMP response element-binding protein; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; ΔΨ, change in membrane potential; ROS, reactive oxygen species; IP3R, inositol trisphosphate receptor; ER, endoplasmic reticulum; mHtt, mutant huntingtin protein.

that A_{2A} receptor inhibition may enhance excitotoxicity due to excessive NDMA receptor activation in some cases, or induce it in knock-out models of this glutamate receptor subtype. While P2X7 receptor activation by itself in microglial cells may lead to glutamate release and subsequent neuroplasticity impairment and/or neuronal damage, antagonism of this receptor by BBG is neuroprotective/neuroregenerative and reverses dopaminergic neuronal loss in the SN in experimental PD. Inhibition of the P2X7 receptor ameliorates the motor coordination deficits and body weight loss and inhibits the neuronal loss and apoptosis triggered by Ca^{2+} influx in HD (Fig. 3).

Altogether, the above data indicate that the negative effects of $[Ca^{2+}]_i$ signaling in PD and HD may be controlled or counterbalanced by the pharmacological modulation of purinergic receptor activity, such as by A_{2A} and P2X7 receptors and possibly other purinergic receptors. Without any doubt, more studies are need to deepen the understanding of the mechanisms of these receptors, mainly in HD, in which their actions are yet controversial.

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