Purinergic Signalling in Parkinson’s Disease: A Multi-target System to Combat Neurodegeneration

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Abstract
Parkinson’s disease (PD) is the second most common neurodegenerative disorder, characterized by progressive loss of dopaminergic neurons that results in characteristic motor and non-motor symptoms. L-3,4 dihydroxyphenylalanine (L-DOPA) is the gold standard therapy for the treatment of PD. However, long-term use of L-DOPA leads to side effects such as dyskinesias and motor fluctuation. Since purines have neurotransmitter and co-transmitter properties, the function of the purinergic system has been thoroughly studied in the nervous system. Adenosine and adenosine 5′-triphosphate (ATP) are modulators of dopaminergic neurotransmission, neuroinflammatory processes, oxidative stress, excitotoxicity and cell death via purinergic receptor subtypes. Aberrant purinergic receptor signalling can be either the cause or the result of numerous pathological conditions, including neurodegenerative disorders. Many data confirm the involvement of purinergic signalling pathways in PD. Modulation of purinergic receptor subtypes, the activity of ectonucleotidases and ATP transporters could be beneficial in the treatment of PD. We give a brief summary of the background of purinergic signalling focusing on its roles in PD. Possible targets for pharmacological treatment are highlighted.

Keywords Adenosine · Adenosine receptors · ATP · Parkinson’s disease · Purinergic receptors

Abbreviations
ADOR2A Adenosine A2A receptor
ADP Adenosine 5′-diphosphate
AP4A Diadenosine tetraphosphate
ATP Adenosine 5′-triphosphate
cAMP Cyclic adenosine monophosphate
CB1 Cannabinoid receptor type 1
DA Dopamine
GABA γ-Amino butyric acid
GRIN2A Glutamate ionotropic receptor NMDA type subunit 2A
5-HT1A 5-Hydroxytryptamine-serotonin receptor 1A
LPS Lipopolysaccharide
LRRK2 Leucine-rich repeat kinase 2
6-OHDA 6-hydroxydopamine
mGlu Metabotropic glutamate receptor
MPP+ 1-Methyl-4-phenylpyridinium
MPTP 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MSA Multiple system atrophy
NMDA N-methyl-D-aspartate
PD Parkinson’s disease
ROS Reactive oxygen species
UDP Uridine 5′-diphosphate
UTP Uridine 5′-triphosphate

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Introduction

Parkinson’s Disease: Pathophysiological Background

Parkinson’s disease (PD) is the second most common neurodegenerative disorder, characterized by progressive loss of dopaminergic neurons in the substantia nigra pars compacta that results in dopamine (DA) deficiency in the striatum. The ongoing degeneration of this peculiar pathway causes the characteristic motor symptoms such as resting tremor, rigidity, bradykinesia and postural instability [1, 2]. Besides dopaminergic neural degeneration, the presence of Lewy bodies (protein aggregates) due to misfolding of α-synuclein occurs in various regions of the affected brain [3]. In spite of many studies on the pathogenesis of PD, the precise mechanism underlying these events has not been unraveled yet. However, a genetic predisposition associated with disturbed proteostasis due to impaired ubiquitin–proteasome system, mitochondrial dysfunction, oxidative stress and neuroinflammation seems to play cardinal roles for the α-synuclein aggregation and the progression of pathology in PD [4–7]. Among these factors, the pathological, self-amplifying interaction between mitochondrial dysfunction and oxidative stress has been early recognized, which might be a key factor responsible for the selective vulnerability of dopaminergic neurons in PD, and one potential reason behind the clinical failures of neuroprotective therapies so far [8]. Dysfunction of the mitochondrial complex I results in an enhanced production of reactive oxygen species (ROS), which, in turn will inhibit complex I and other vital metabolic enzymes such as alpha-ketoglutarate dehydrogenase, whilst the latter also serves as a source of ROS generation in mitochondria [9, 10]. Simultaneous or preceding mitochondrial dysfunction exacerbates the effect of oxidative stress on pathological monoamine release from nerve terminals [11, 12]. This process leads to the formation of toxic, oxidative DA metabolites, such as dopamine quinone, which might further amplify the ongoing degeneration process [13]. Therefore, disease-modifying potential could be primarily expected from those novel multi-target therapies, which simultaneously target the above mentioned pivotal pathological pathways and prevent their pathological interaction [14, 15].

The Current Treatment of PD

As for the symptomatic treatment of PD, the clinical breakthrough came with the first clinical trials of DA replacement therapy using the high dosage of the DA precursor l-3,4 dihydroxyphenylalanine (l-DOPA) [16–19]. l-DOPA is able to cross the blood–brain barrier and converts into DA that engages specific DA receptor subtypes (D_1 to D_5) [20]. However, long-term use of l-DOPA leads to a dysbalance of striatal circuits of the motor system and leads to side effects such as l-DOPA induced dyskinesias and motor fluctuation in 50% of patients after 5 years of continuous treatment [21, 22]. The therapeutic management of these complications is difficult and there is a need for developing effective and new pharmacological therapies against motor fluctuation and dyskinesias [23].

Purinergic Signalling: Concept and Purinergic Receptors

The concept of purinergic signalling, being adenosine 5′-triphosphate (ATP) as an extracellular signalling molecule with neurotransmitter properties was proposed in the early 1970s [24, 25]. A couple of years later, purines were also described as co-transmitters and neuromodulators in the peripheral and central nervous system (CNS), as they are able to modulate other signalling pathways and neurotransmitter systems [26–28]. ATP is co-released with acetylcholine, catecholamines, γ-amino butyric acid (GABA), glutamate and DA in the CNS [29–34]. Extracellular ATP is released from cells under physiological conditions. The levels of extracellular ATP are controlled by ectonucleotidases that catalyze its degradation [35, 36].

There are two families of purinergic receptors, which are distinguished by their main agonists [37]. P1 receptors are G protein-coupled metabotropic receptors activated by adenosine and can be subdivided into four subtypes (A_1, A_2A, A_2B, A_3). P2 receptors are subdivided into two classes: P2X_(1-7) ionotropic receptors, activated by ATP and G protein-coupled metabotropic P2Y_(1-12) receptors, activated by ATP, adenosine diphosphate (ADP), uridine di- and triphosphate (UDP and UTP), or UDP-glucose depending on the receptor subtype [38–40]. ATP is able to bind to the extracellular ligand-binding site of P2X receptors and leading to conformational change that opens a permeable channel to Na^+, K^+ and Ca^{2+}. The activation of these ionotropic receptors is important for Ca^{2+}-induced intracellular signalling pathways [41–43]. Depending on the activated adenosine and P2 receptor subtype, the induced signalling pathway may vary. These activated receptors are able to make alterations in Ca^{2+} levels, which modulate the activity of several secondary messengers involved in physiological processes [44–46]. The final effects of purinergic receptor-mediated signalling depend on the cell type and other physiological (neurogenesis, proliferation, cell death, stem cell differentiation) or pathological cellular conditions (inflammatory, neurological, psychiatric, oncological, cognitive, neuromuscular and neuromotor diseases) [47–66]. Purinergic receptor...
activation may have para- or autocrine nature, which is characteristic for astrocytes in the regulation of neuronal activity [67]. Not only purinergic receptors but membrane nucleotide/nucleoside transporters, channels and ectonucleotidases also play important role in purinergic signalling [36,68–70]. Adenosine is the predominant, presynaptic modulator of neurotransmitter release in the CNS, although ATP has presynaptic modulator effect as well [71–73]. Adenosine is produced by enzymatic breakdown of released ATP, but some CNS cells are able to release adenosine directly [74]. A1 and A2A receptors have higher affinity (activated by physiological extracellular levels of adenosine) and A2B and A3 receptors have lower affinity (activated by higher extracellular levels of adenosine) for the ribonucleoside [75–77]. The adenosine A1 and A2A receptors are highly expressed in the brain and CNS, where they have profound influence on neuronal activity. Adenosine A1 receptor is the dominant adenosine receptor subtype in the CNS. Adenosine A1 receptors can be found in various cortical and subcortical regions of the brain, while A2A receptors are mainly expressed in the striatum [78–81] (Table 1). In contrast, adenosine A2B and A3 receptors are mainly found in peripheral tissues, even though low levels of these receptors are also expressed in some regions of the brain [82–84].

There is a heterogeneous distribution of P2 purinergic receptors in the CNS as well. For instance P2X1 receptors are predominantly expressed in the cerebellum, while P2X3 receptors are expressed in the brainstem [85,86], and they can be found in the basal ganglia with variable expression level [87] (Table 2). Various P1 and P2 receptor subtypes are also expressed by microglia, astrocytes and oligodendrocytes [88–93]. Extracellular nucleotides act as messengers between neuronal and non-neuronal cells, thereby integrating functional activity between neurons, glial and vascular cells in the CNS [94–98]. Adenosine and ATP—as key players in neuron–glia interaction and microglial activation—are modulators of neuroinflammatory processes, oxidative stress, excitotoxicity and cell death [99–102]. Aberrant purinergic receptor signalling can be the cause or result of numerous pathological conditions, including neurodegenerative disorders [103]. Here, we explore the importance of purinergic signalling in PD to suggest potential targets for novel therapies.

### Purinergic Signalling Involvement in PD

**Purinergic Gene Polymorphisms in PD**

Two ADORA2A (A2A receptor) polymorphisms (rs71651683, a 5′ variant or rs5996696, a promoter region variant) were inversely associated with genetic PD risk, moreover, there was evidence of interaction with coffee consumption [104]. CYP1A2a is an enzyme, which is responsible for caffeine metabolism, two polymorphisms (rs762551 or rs5996696) of the enzyme in homozygous coffee drinkers reduced PD risk [104]. Humans with R1628P variant (LRRK2 risk variant) who did not take caffeine had a 15 times increased risk of PD [105]. GRIN2A encodes an N-methyl-D-aspartate-2A (NMDA) glutamate receptor subunit involved in central excitatory neurotransmission, which is associated with A2A receptor activation. Carriers of GRIN2A rs4998386-T allele had a lower risk of PD, than carriers of rs4998386-CC.
Adenosine Receptor-Mediated Signalling in PD

A2A receptors are enriched in dopaminergic brain areas (the highest expression of these receptors are in the striatum), thus pointing to a significant role of purines in motor control [109]. A2A and DA D2 receptors are mainly expressed in the neurons of the indirect pathway of striatal circuits projecting to the globus pallidus, in contrast to A1 and DA D1 receptors, which are mainly found on the neurons of the direct pathway of motor control projecting to the internal globus pallidus and substantia nigra pars reticulata. The main adenosine signalling mechanism is via the cyclic adenosine monophosphate (cAMP)-dependent pathway. Activated A2A receptors stimulate the enzymatic function of adenylyl cyclase that increases cAMP levels and depresses the signalling mediated by D2 receptors. Activation of protein Gi-coupled DA D2 receptors leads to reduction in the cAMP level. There is a reciprocal situation in the direct pathway of motor control with protein Gs-coupled D1 and protein Gi/o-coupled A1 receptors. Generally, adenosine acts as a negative modulator of D1- and D2-mediated actions in the direct and indirect pathways [110–112].

The antagonistic functional interaction between adenosine A2A and DA D2 receptors may depend on the formation of receptor heterodimers (A2A-D2 heteroreceptor complexes) in the striatum thereby balancing the inhibitory and excitatory impulses in the striatal circuits [112]. Not only dopaminergic mechanisms, but non-dopaminergic modes of action of A2A receptors may involve interactions with various non-dopaminergic receptors, possibly by forming heterodimeric and/or multimeric receptor complexes [23]. Thus, adenosine A3A receptors may adjust the actions of striatal adenosine A1 receptors (A1-A2A heteroreceptor complexes), metabotropic glutamate receptors (mGlu) 5 (A2A-mGlu5 heteroreceptor complexes), cannabinoid receptor type 1 (CB1) receptors (A2A-CB1 heteroreceptor complexes) and serotonin 1A (5-HT1A) receptors [113–115]. Moreover, studies also suggested the presence of multimeric A2A2-D2 mGlu5 and A2A-CB1-D2 receptor complexes in the striatum [116, 117]. These functional interactions between receptors may modulate the activity of striatal efferent neurons and influence motor behavior [23]. In general, adenosine tone appears as a key for the fine tune control of DA dependent actions in the basal ganglia and affects non-dopaminergic mechanisms also [20].

Adenosine receptor antagonists (especially non-selective A2A receptor antagonists, such as methylxanthines, caffeine, or selective A2A antagonists) have been shown to enhance therapeutic effect of l-DOPA in a wide range of animal models of PD [118–121]. A2A homoreceptor complexes are in balance with DA D2 homoreceptor complexes in intact striatum [122–126]. Dysbalance of striatal circuits leads to motor inhibition and disruption of this balance in PD leads to increased signalling via A2A receptors and decreased signalling via DA D2 receptors. These changes explain the beneficial effect of A2A receptor antagonists on increasing motor functions without worsening l-DOPA-induced dyskinesias [20, 127].

A2A Receptor antagonists have been used in clinical trials in patients with PD (Table 3). Istradefylline is a xanthine-based compound with increased selectivity for A2A receptors against A1 receptors, which is used concomitantly with l-DOPA [128]. The drug was not approved in the USA because there was no significant reduction in off time compared to l-DOPA treatment [129]. In contrast, istradefylline was approved in Japan in 2013 with the trade name Nouriant® to enhance the antiparkinsonian effect of l-DOPA with less long-term side effects [130, 131]. Preladenant is a second-generation A2A receptor antagonist, which failed in phase III clinical trials in the treatment of PD because the compound was not superior to placebo in reducing off state [132, 133]. Vipadenant is a triazolopyrimidine-based drug, which has increased selectivity for A2A receptors versus A1 and A3 receptors [134]. Its development as an antiparkinsonian medication was stopped; however, A2A receptor antagonists have considerable potential in novel immune-oncology and cardiology therapies [113, 135–137]. Another adenosine A2A receptor antagonist, tozadenant was safe, well tolerated and effective in reducing off time in PD patients in phase II trial but phase III clinical trial was discontinued because of serious adverse events (agranulocytosis) [23, 133, 138]. There have been many drug trials for selective A2A receptor antagonists. Most of them were shown to be safe, well tolerated and beneficial; however, the majority did not reach the regulatory threshold for efficacy to be approved as PD drugs [139, 140]. Development of bivalent drugs (able to bind to two receptors simultaneously) to target A2A-D2 heteroreceptor complexes acting on A2A and DA D2 receptors may be a good therapeutic approach in the future. Heterobivalent drugs offers the opportunity to target the orthosteric sites of the receptors in the heterodimer with a higher affinity and a higher specificity versus corresponding homomers and reduce the dose required for therapy and, accordingly, the side effects [20].

Adenosine A2A receptor antagonists may also involve direct or indirect actions at microglia and inflammatory
processes. Pre-treatment of slices from 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-injected mice with preladenant facilitates the ability of activated microglia to respond to tissue damage [141]. The nonselective A1/A2A adenosine receptor antagonist caffeine and the selective A2A receptor antagonist (KW-6002) had anti-inflammatory potential in a rat model of lipopolysaccharide (LPS)-induced neuroinflammation [142].

The Role of A2A Receptors in Synucleopathy

Increased striatal A2A receptor expression was observed as an early pathological event in PD and increased A2A receptor expression was detected after hippocampal injection of α-synuclein in mice [143, 144]. A2A receptor-knock out mice showed resistance against α-synuclein induced insults [145]. A2A receptor antagonism restrained hyperactivation of NMDA-glutamate receptors and decreased the aggregation of α-synucleins [146]. Based upon these results, A2A receptors seem to have role in the pathological process of synucleinopathy [111].

### P2 Receptor-Mediated Signalling in PD

P2 ionotropic and metabotropic receptors are widely expressed in basal ganglia and in various cell types, such as neurons and astrocytes [87, 147, 148]. 6-Hydroxidopamine (6-OHDA) induced lesions of nigral dopaminergic neurons generate a significant decrease in the expression of P2X and P2Y receptor proteins from striatal spiny neurons and GABAergic interneurons, thus confirming the involvement of P2 receptors and extracellular ATP in the striatal circuits [87]. P2Y1 and P2X1-4, 6 receptor protein subtypes are expressed in dopaminergic neurons with co-expression of P2X1 with DA D1 receptors, therefore stimulation of P2 receptors by ATP induces an increased release of DA in the striatum [149–152]. In a neuronal cell model, extracellular ATP induced a significant increase in intracellular

| Compounds                  | Mechanism of effect | Models                        | Published | Results                                                   |
|----------------------------|---------------------|-------------------------------|-----------|-----------------------------------------------------------|
| KW-6002 (istradefylline)   | A2A receptor antagonism | PD patients                  | 2003      | Improved PD motor scores when added to low-dose l-DOPA    |
| KW-6002 (istradefylline)   | A2A receptor antagonism | LPS treated rats             | 2013      | Enhanced therapeutic effect of l-DOPA                     |
| Caffeine                   | A2A receptor antagonism | LPS treated rats             | 2013      | Reduced motor impairment                                 |
| Preladenant                | A2A receptor antagonism | MPTP treated mice            | 2014      | Enhanced therapeutic effect of low doses of l-DOPA       |
| 8-Ethoxy-9-ethyladenine    | A2A receptor antagonism | 6-OHDA lesioned rats         | 2015      | Enhanced effect of low doses of l-DOPA without increased dyskinesia |
| SCH 58261                  | A2A receptor antagonism | A2A receptor knockout mice, SH-SY5Y cells | 2015      | Decreased α-synuclein aggregation, prevented neuronal death |
| ZM 241385                  | A2A receptor antagonism | A2A receptor knockout mice, SH-SY5Y cells | 2015      | Decreased α-synuclein aggregation, prevented neuronal death |
| Preladenant                | A2A receptor antagonism | PD patients                  | 2017      | Failed (was not superior to placebo in phase III clinical trial |
| Vipadenant                 | A2A receptor antagonism | PD patients                  | 2009      | Failed (was not superior to placebo)                      |
| Tozadenant                 | A2A receptor antagonism | PD patients                  | 2017      | Failed in phase III clinical trial (induced agranulocytosis) |
| NF449                      | P2X1 receptor antagonism | H4 cells                     | 2015      | Prevented α-synuclein aggregation                          |
| A-438079                   | P2X2 receptor antagonism | 6-OHDA lesioned rats         | 2010      | Prevented depletion of DA in striatum                      |
| BBG                        | P2X2 receptor antagonism | 6-OHDA lesioned rats         | 2014      | Reverted dopaminergic neurons loss in substantia nigra     |
| BBG                        | P2X2 receptor antagonism | BV2 microglia cells          | 2015      | Decreased ROS production induced by α-synuclein           |
| PPADS                      | P2X2 receptor antagonism | SH-SY5Y cells                | 2017      | Prevented abnormal calcium influx induced by α-synuclein   |
| AZ 11645373                | P2X2 receptor antagonism | SH-SY5Y cells                | 2017      | Prevented abnormal calcium influx induced by α-synuclein   |
| AP4A                       | P2Y2/P2Y4 antagonism   | 6-OHDA lesioned rats         | 2003      | Reduced dopaminergic neurons loss                         |
| MRS2578                    | P2Y4 receptor antagonism | SH-SY5Y cells                | 2017      | Delayed neuronal loss                                     |

The list is not comprehensive and is restricted to studies mentioned in the article. For further references, see [111, 113].
α-synuclein levels, which was the result of lysosome dysfunction caused by P2X7 receptor activation [153].

Many data have implicated the role of P2X7 receptor in PD. P2X7 receptor antagonism with A-438059 or Brilliant Blue G (BBG) prevented DA deficit in the striatum and 6-OHDA-induced hemiparkinsonian behavior [154, 155]. However, P2X7 receptor deficiency or inhibition did not promote the survival of dopaminergic neurons in rotenone and MPTP induced animal models of PD [156]. It is presumed that there is a massive release of ATP during cell death in the lesioned striatum and substantia nigra, which activates cell death pathways via purinergic receptors and is able to activate further purinergic subtypes [20]. Permanent purinergic receptor activation and ATP release seem to play a key role in the neuronal death, which exacerbates α-synuclein aggregation in PD [87]. The accumulation of α-synuclein might overwhelm the capacity of intracellular protein-degradation mechanisms and induce neuroinflammation, which creates a positive feedback loop promoting the degeneration of dopaminergic cells [7]. α-Synuclein-induced intracellular free calcium mobilization in neuronal cells depends on the activation of purinergic P2X7 receptors. In the same study, activation of P2X7 receptors lead to ATP release with the recruitment of the pore forming protein pannexin1, whilst α-synuclein decreased the activity of extracellular ecto-ATPase which is responsible for ATP degradation [157]. Stimulation of the microglial P2X7 receptor by extracellular α-synuclein increased oxidative stress, which was prevented with the use of P2X7 receptor antagonist [158].

DA neurotransmission has been linked to calcium signalling. There is data that P2Y1 receptor is involved in the regulation of calcium signalling [159]. Neurodegeneration induced by 6-OHDA in nigrostriatal dopaminergic neurons was reduced by pretreatment with diadenosine tetraphosphate (AP4A, an endogenous diadenosine polyphosphate) possibly through an anti-apoptotic mechanism and the activation of P2Y1 and P2Y4 receptors [160]. Recently, expression levels of P2Y6 receptor in PD patients younger than 80 years were higher than healthy controls and multiple system atrophy (MSA) patients and P2Y6 receptor could thereby be a potential clinical biomarker of PD. P2Y6 receptor was also upregulated in LPS-treated microglial cells and involved in proinflammatory cytokine release through UDP secretion [161]. Another study showed that expression of P2Y6 receptor on neuronal SH-SY5Y cell is associated with the progression of oxidative stress and cell death induced by 1-methyl-4-phenylpyridinium (MPP+) [162]. In vivo, LPS induced microglial activation and delayed neuronal loss was prevented by selective inhibition of P2Y6 receptor with MRS2578 [163]. Based on these studies P2Y6 receptor subtype seems to be involved in the process of neuroinflammation in PD and blocking UDP/P2Y6 receptor signalling could reverse these pathological processes [161].

Conclusion

In many data, many data confirm the involvement of purinergic signalling pathways in PD. Modulation of purinergic receptor subtypes, the activity of ectonucleotidases and ATP transporters could be beneficial in the treatment of PD. Antagonism of A2A, P2X1, P2X7 and P2Y6 receptor subtypes is a promising weapon against PD via various ways: reducing l-DOPA induced dyskinesia, influencing neuroinflammation, preventing α-synuclein aggregation, reducing microglia activation. Development of new bivalent compounds to target A2A-D2 heteroreceptor complexes, which are orally bioavailable and can cross the blood–brain barrier could be a potential therapeutic tool. In addition, multi-target compounds targeting self-amplifying circuits controlled by purinergic and non-purinergic receptors could be a viable strategy to obtain the desired disease-modifying effect [164]. Additional studies and better quality PD animal models are required for the deeper understanding of underlying unknown pathological processes in PD and the role of purinergic signalling in it.

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