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*Review Article*

# Adenosine A2 Receptor: Novel Target for the Management of Parkinsonism

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**Abstract**

The cellular and regional distribution of adenosine A2A receptors in basal ganglia that are richly innervated by dopamine, and their antagonistic role towards the stimulation of dopamine receptors, have positioned A2A receptor antagonists as an attractive nondopaminergic target to improve the motor deficits of PD. Adenosine receptors are G protein-coupled receptors (GPCRs). In the CNS, adenosine A2A receptors are highly enriched in striatopallidal neurons where they form functional oligomeric complexes with other GPCRs such us the dopamine D2 receptor. Formation of balanced A2A/D2 receptor oligomers is essential for correct striatal function. The A2A receptor activation reduces the affinity of striatal D2 receptor for dopamine and the blockade of A2A receptor with specific antagonists facilitates function of the D2 receptor. Thus, it may be postulated that A2A receptor antagonists are pro-dopaminergic agents. Therefore, A2A receptor antagonists will potentially reduce the effects associated with dopamine depletion in Parkinson's disease (PD). Accordingly, this category of compounds have recently attracted considerable attention as potential therapeutic agents for PD as they have shown potential effectiveness in counteracting the motor dysfunctions and also displayed neuroprotective and anti-inflammatory effects in animal models of PD.

## 1. INTRODUCTION

Parkinson's disease (PD) is a debilitating neurodegenerative disorder that affects approximately 1% of the population worldwide over the age of 55 and is associated with motor symptoms including tremor, muscle rigidity, bradykinesia, gait abnormalities and postural instability[1]. The clinical course of PD is not limited to motor symptoms. A variety of non-motor symptoms and disorders are common and significantly affect the quality of life[2-5]. Depression, Anxiety (including panic attacks), Psychosis, Apathy, Hypersexuality, Binge eating, Obsessional behavior, Daytime somnolence, Insomnia, Vivid dreams, Dysphagia, Hypersalivation, Xerostomia, Orthostatic hypotension, Olfactory dysfunction are the non motor symptoms of PD[6-8]. The progressive damage of dopaminergic neurons in the substantia nigra is the cardinal pathophysiological event that leads to a substantial reduction in the dopamine concentration in striatum. The clinical symptoms appear after approximately 60% of the dopaminergic neurons are destroyed, and the dopamine concentration in the striatum drops by about 80%. The neuronal degeneration is observed especially in the ventralis region of the pars compacta, substantia nigra, and locus ceruleus. The Lewy bodies occur in many damaged neurons. The etiology of PD is still unknown, although involvement of environmental toxins and free radicals is postulated. Till now, 11 types of familial Parkinsonism have been reported. Of those, the mutation of the α-synuclein gene (PARK1) in chromosome 4 was first identified[9]. No treatment with established efficacy in preventing or slowing the progression of neurodegeneration in PD is currently available and development of such treatment is of utmost importance. PD patients often develop psychotic symptoms that severely affect the quality of life. Although current medication of PD provides good benefit for number of years, long-term treatment still remains inadequate. Continued neuronal degeneration can lead to the emergence of dementia or problems that can cause substantial disability.

There is a need for medications that can slow the underlying progression of degeneration, improve motor fluctuations and PD symptoms in early disease without inducing dyskinesia and 'off' time in advanced disease. Due to these limitations of current therapy, an intense search for new medications is going on to treat PD. Now days, attention has been given on non-dopaminergic therapies, mainly adenosine A2 receptor antagonists[10]. A2A receptor antagonists have proven to be efficacious in animal models of PD and in clinical studies[11]. This review will focus on the role of adenosine and its receptors in the pathophysiology of PD and the role of various novel adenosine antagonists and adenosine receptor antagonists as potential therapy for the treatment of PD.

## 2. PATHOPHYSIOLOGY OF PD

The pathogenesis of PD has not been fully elucidated, and it may have multiple causes, including genetic risk factor. Among patients with PD, 10-15% has a family history[12]. Features of Parkinsonism emerge when more than half of the dopaminergic nerve terminals in the straitum are gone[13].The gliosis that develops involves the hyperplasia and hypertrophy of the astrocytes. Gliosis also leads to the formation of scars. In almost all patients with sporadic PD, one or multiple Lewy bodies are discovered in the cytoplasm of some of the dopaminergic neurons that still remain[14-16].

It is considered that the pathogenesis of PD involves several major interacting pathways. A mitochondrial dysfunction of various origins was first shown to lead to the development of oxidative stress and a cell energy insufficiency. Similarly, immune mechanisms identified in PD cause oxidative damage, but were also postulated to give rise to apoptosis through more direct mechanisms. Another important pathway is related to the abnormal aggregation of proteins. Glutamate excitotoxicity has additionally been implicated in striatal cell death in PD[17]. The various events involved in the pathogenesis of PD have been described in the flow chart.

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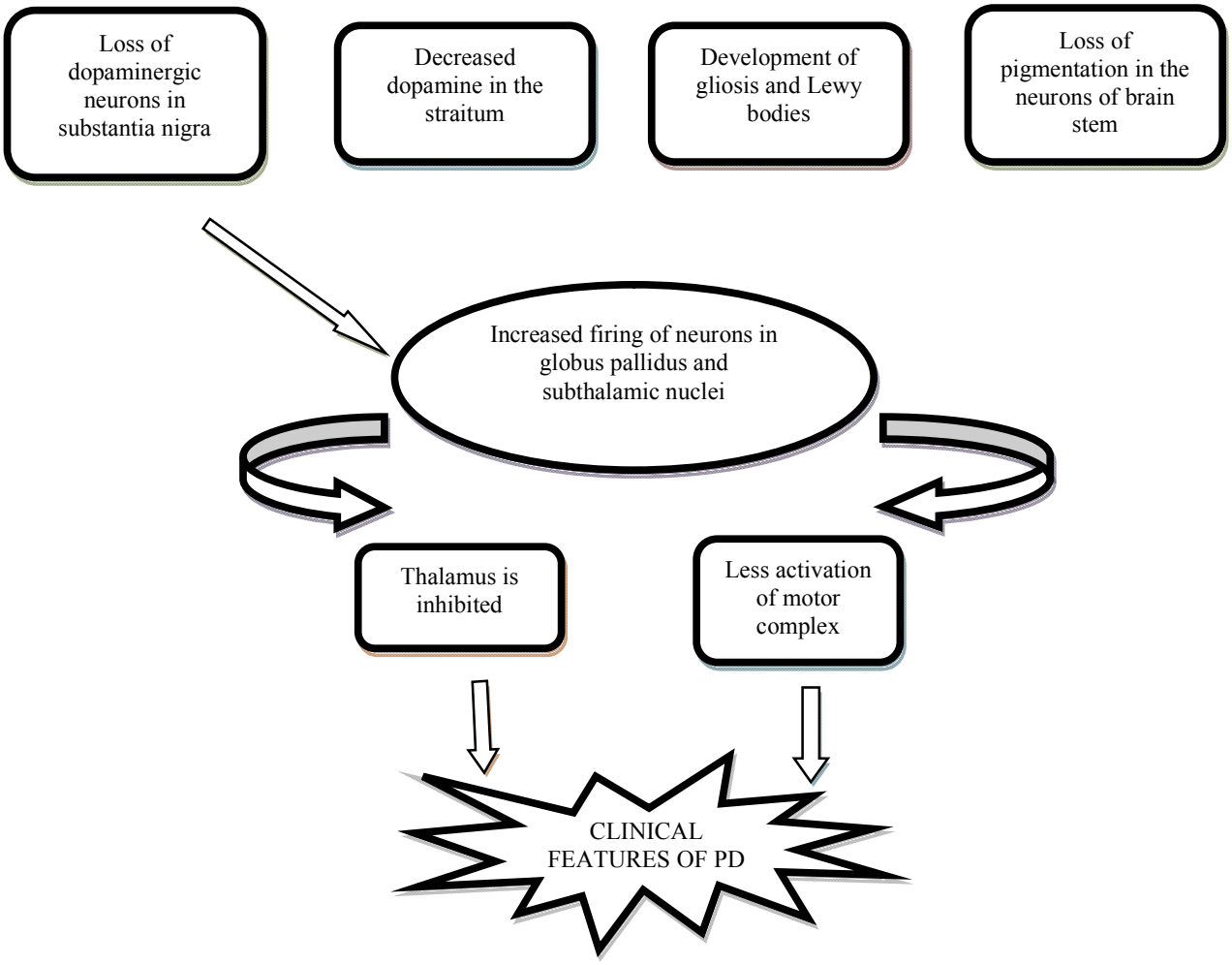


**Fig.1:** Pathophysiological events in parkinson's disease

**3. ONGOING PHARMACOLOGICAL APPROACHES FOR THE TREATMENT OF PD**

Since the discovery of levodopa as a treatment for PD, additional treatments, with fewer long-term side effects such as dyskinesia and with a better pharmacokinetic profile than the short half-life of levodopa (1–2 hours), have been developed. Over the last decade this search has been further motivated by discoveries in the understanding of the pathological mechanisms underlying PD. Available PD treatment options largely improve motor symptoms rather than being neuroprotective, but there is an indication that some agents may fulfill both objectives[18]. Current pharmacological management of the motor symptoms of PD relies mainly on dopamine precursors (levodopa), dopamine agonists (DAs), enzyme inhibitors of monoamine oxidase B (MAO-B) and catechol-O-methyltransferase (COMT), and amantadine, which is an N-methyl-D-aspartate antagonist[19].

**4. ADENOSINE RECEPTOR AS A NOVEL TARGET FOR THE TREATMENT OF PD**

Neurotransmitters other than dopamine are recognized as having modulatory roles within the basal ganglia and can influence the basal ganglia dopaminergic system to alter the activity of direct and indirect pathways. Numerous nondopaminergic neurotransmitter systems have been implicated in the mechanisms that contribute to the motor features of PD. It is now well established that neurotransmitter systems other than dopaminergic system, like glutamatergic, cholinergic, noradrenergic, GABAergic, opioidergic, histaminergic, serotonergic and adenosinergic, are affected in the pathogenesis of PD. Nondopaminergic neurotransmitter systems are thus targets for the development of novel therapies for motor symptoms and motor complications in PD[20]. Many research centers are conducting research on new forms of currently used drugs (e.g. Duodopa, XP21279, IPX066), new drugs of already known groups (e.g. safinamide-a MAO-B inhibitor), medicines that suppress side effects of L-DOPA (e.g. AFQ056, fipamezole), and, finally, compounds with a novel mechanism of action (e.g. PMY50028, A2A receptor antagonists). A lot of scientific reports have indicated an important role of A2A receptors in the regulation of the central movement system, so a new group of compounds – selective antagonists of A2A receptors (e.g. istradefylline, preladenant, SYN115) – have been developed and their potential use in PD has been examined. Clinical studies of A2A receptor antagonists have shown that this group of compounds can shorten off periods and at the same time they do not worsen dyskinesias in patients with PD[21].

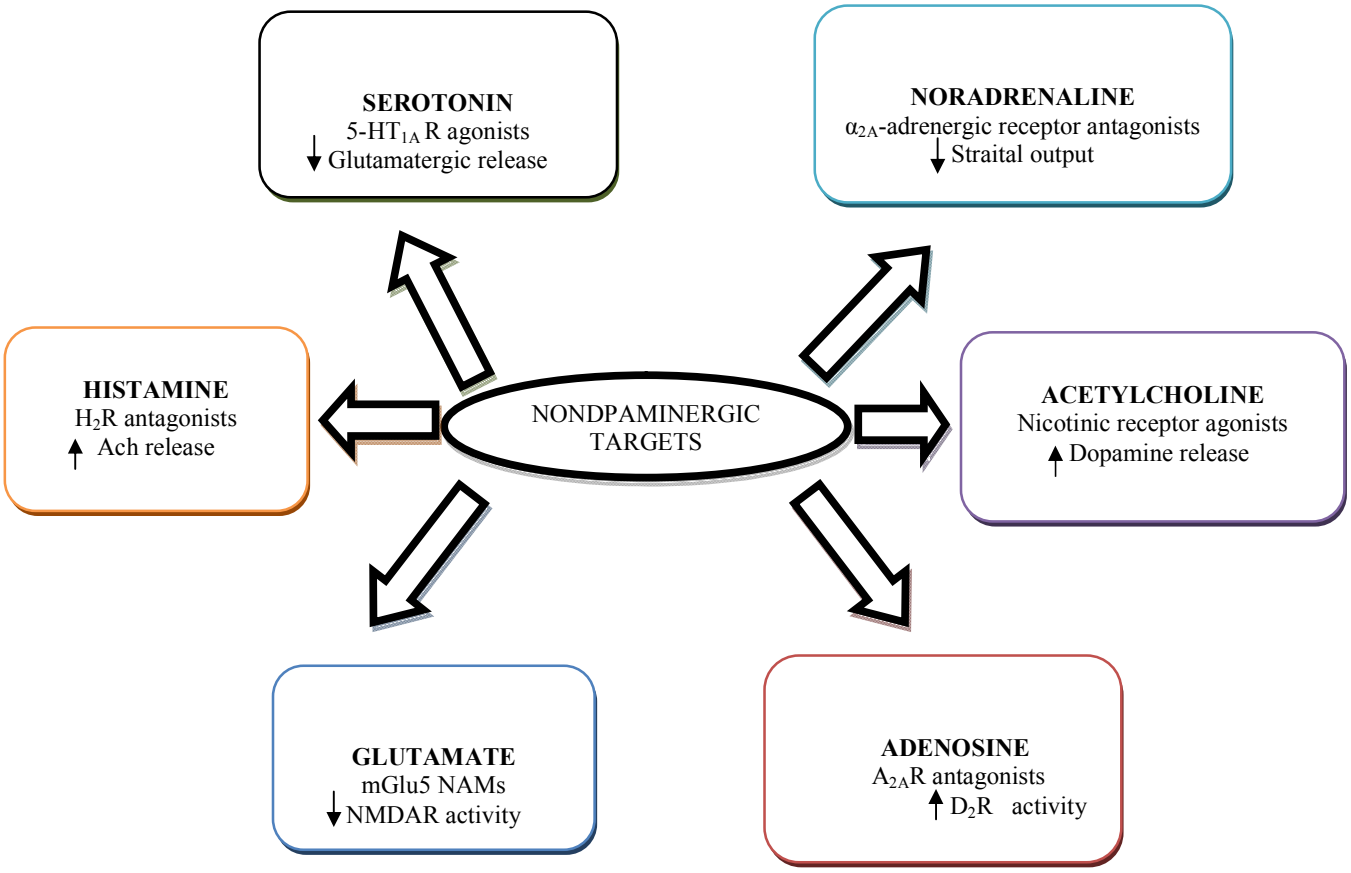


**Fig. 2:** Nondopaminergic neurotransmitter systems involved in the motor features of PD.

## 5. ROLE OF ADENOSINE RECEPTORS IN THE PATHOGENESIS OF PD

A2A receptors are present in medium to high concentrations in several basal ganglia (BG) nuclei and may therefore be capable of influencing motor activity by acting at different BG levels. This feature renders A2A receptors particularly attractive for modulation of dopamine receptor functions in PD[22]. These receptors modulate dopamine transmission by opposing D2-receptor activity. The D2 pathway is an indirect pathway that promotes suppression of unnecessary movement[23]. A2A receptor mRNA expression has shown to be elevated in the brains of dyskinetic patients with PD[24]. Adenosine mediates its actions by means of the activation of specific GPCRs, for which four subtypes (A1, A2A, A2B, and A3) have been identified[25]. These receptors have distinctive pharmacological profiles, tissue distributions, and effecter coupling, and their functions in the CNS have been extensively studied[26].Within the human CNS, A2A receptors are located almost exclusively in the striatum, nucleus accumbens, and olfactory tubercle and may serve specific integrative roles, such as in the coordination of motor behavior or the psychiatric function. A2A receptor in the striatum is located predominantly on the γ-amino–butyric acid and enkephalin-containing medium spiny neurons (GABA/ENK-MSN) that form the indirect output pathway extending from the striatum to the globus pallidus (GPe)[27]. Loss of dopaminergic neurons in the substantia nigra pars compacta (SNc) reduces the normal inhibition of the nigrostriatal pathway on the GABA/ENK-MSN, resulting in an increase in the excitability of the indirect pathway. The changes in the activity of its efferent targets, is considered to be the pathophysiological hallmark of PD[25]. It has been found that A2A receptor stimulation increases the excitability of the GABA/ENK-MSN, via A2A receptors expressed primarily on medium spiny neurons. Therefore, blockade of striatal A2A receptors results in a decrease in the excessive activation of the indirect pathway and may provide an alternative, non-dopaminergic approach to achieving symptomatic relief of PD[28]. There is a growing body of evidence suggesting that adenosine A2A antagonists are potential agents for a novel type of anti-PD therapy[29].

## 6. PHARMACOLOGICAL MODULATION OF ADENOSINE PATHWAY INPARKINSON'S DISEASE

### 6.1 Istradefylline (KW-6002)

It is a xanthine-derivative, was the first selective A2A receptor antagonist to enter the clinical trial, seeking an indication in PD[22]. It is considered nondopaminergic because of the lack of effects on dopamine receptors and dopamine-metabolizing enzymes. It is a new antiparkinsonian drug that can be added as a new treatment option to current PD therapy[30]. In experimental parkinsonian animals, istradefylline, when used in combination with levodopa, exhibited an add-on effect on motor control without worsening levodopa-induced dyskinesia[31]. The improvement in motor function without a worsening of dyskinesia is highly significant as it differentiates istradefylline from the known effects of dopaminergic treatments (dopamine agonists, MAO-B inhibitors, COMT inhibitors) used to reduce OFF time in PD. The results also revealed that istradefylline did not abolish the priming for dyskinesia induced by a high dose l-DOPA but suppressed the expected dyskinesia response to l-DOPA[32]. Istradefylline is the most studied, with results available from five phase II[33] and two phase III[34] randomized control trials. These trials demonstrated that istradefylline was safe, well tolerated and provided reduction in off-time in l-dopa-treated PD patients with motor fluctuations. An application for marketing istradefylline in Japan has been filed; however, potential for approval elsewhere still remains unknown[30].

**6.2 Preladenant (MK-3814; SCH-420814)**

It is a second-generation A2A receptor antagonist under investigation for the treatment of PD[35]. It is derived from SCH-58261, a pharmacological tool used to specify the A2A receptor subtype. Preladenant is intended for PD treatment, either as monotherapy or as an adjunct to levodopa therapy. It has higher affinity and greater selectivity and has shown an equivalent effect in improving OFF time in a double-blind, placebo-controlled trial[36]. Preladenant has completed a phase II clinical trial and a phase II extension study assessing its effect on PD related dyskinesia and its associated safety profile. It is currently undergoing three phase III clinical trials and one phase III extension study comparing its effect against placebo or rasagiline on PD related dyskinesia, PD symptoms and its associated safety profile[37]. Based on the results from randomized, double- blind trials, preladenant appeared to balance efficacy and tolerability[36]. In animals bearing severe disease, potentiation of L-DOPA by preladenant showed an improvement in motor function with a significant increase in the ON Time. The profile of preladenant was quite different from that of a dopaminergic agent, as nausea, vomiting, hypotension or any CNS events were not recorded up to the maximal dose tested[38].

**6.3 Vipadenant (BIIB014, also known as V2006)**

This compound is a a triazolo[4,5-d] pyrimidine derivative with high affinity for A2A receptor. A number of preclinical studies examining Vipadenant in PD experimental models have been performed in order to assess the in vivo activity of Vipadenant as an anti-Parkinsonian drug[38]. It has been observed that Vipadenant produced the same magnitude of anti-Parkinsonian effect as L-DOPA, against disability, with an equivalent duration of action, but less dyskinesia[39]. The pharmacological efficacy and safety of Vipadenant as anti-Parkinsonian drug has been investigated by two clinical Phase II trials. No clinically significant abnormalities have been observed in vital signs, electrocardiography (ECG), safety laboratory or cognitive function tests[40, 41]. It has been reported that Vipadenant was well tolerated in both clinical trials in Phase II: in combination with L-DOPA, in late-stage PD patients, and as monotherapy in early-stage PD patients[42,43].

**6.4 ST-1535**

It is a 9H-purine derivative possessing preferential affinity for human A2A receptors. ST-1535 showed a good anti-Parkinsonian activity in different experimental models of PD in rodent and non-human primates[44]. Another important report showed that ST-1535 was effective, in antagonizing specific motor deficits induced by dopamine neuron degeneration, even without L-DOPA combined administration, suggesting that this drug would be effective as a monotherapy in the PD treatment. In order to ascertain the safety and tolerability, randomized, double-blind study in healthy humans was performed. There were no hematological, biochemical or urinary laboratory abnormalities of clinical concern[45]. ST-1535, being able to block the functionality of both A2A and A1 receptors, ameliorates the cognitive function in an animal model. The antagonism of A1 receptors by ST-1535 might improve the dopamine release that progressively is reduced in PD patients.

**7. NEUROPROTECTIVE ACTION A2A RECEPTOR ANTAGONISTS: OFFERING ADDITIONAL BENEFIT**

Research on the role of adenosine receptors in treatment of Parkinson's disease indicates that the therapeutic effect of adenosine receptor antagonists could be linked to the neuroprotective action. The augmented release of the stimulating transmitters might play a crucial role in the death of neurons resulting from excitotoxicity. Therefore, drugs inhibiting glutamate release might be efficient in the treatment of neurodegenerative diseases[46]. Both adenosine A1 and A2A receptors play an important role in neuroprotection. The neuroprotection caused by inactivation of A2A receptor with caffeine has been noticed in an animal model of PD. A similar effect has been observed with the use of several other A2A receptor antagonists (SCH58261, istradefylline)[47].

**8. NONSELECTIVE ADENOSINE A1 AND A2A RECEPTORS ANTAGONISTS**

The indirect evidence of adenosine A2A receptor involvement in regulation of motor behavior is the observed improvement in mobility after treatment with caffeine and theophylline, the 2 nonselective antagonists of the adenosine A1/ A2 receptors[48]. The long-term administration of caffeine inhibits the neurotoxicity, either by inhibiting the adenosine A2A receptors or by increasing the amount of adenosine A1 receptors in striatum[9]. Based on epidemiologic studies, it has been observed that caffeine intake is faintly linked with a lower risk of PD[49]. In addition, the weak effects of caffeine in achieving symptomatic relief in patients with PD have also been occasionally reported[50]. Neuroprotection by caffeine is supported by demonstration of reduced nigrostriatal degeneration in PD animal models[51]. Two open-label studies examined caffeine and PD motor symptoms. The first study found that a subgroup of PD patients with freezing of gait benefited from treatment with caffeine. Larger and longer trials will be required to confirm the benefits of caffeine on the motor symptoms in PD[20].

**9. CONCLUSION**

The advancement of non-dopaminergic therapies for PD has attracted much attention in recent years. A2A receptor antagonism is a promising nondopaminergic treatment for PD. The evolution of new highly selective A2A receptor antagonists, and their anti-parkinsonian responses in animal models of PD, has provided a rationale for clinical trials to assess the therapeutic potential and the safety profile of these agents in PD patients. Pharmacological blockade of A2A receptor attenuates the death of dopaminergic neurons, and A2A receptor antagonists are also being investigated as potential neuroprotective agents. Till date, the clinical research regarding A2A antagonists and their potential utilization in PD therapy continues to evolve between drugs just or previously discontinued (preladenant and vipadenant), new derivatives in pipeline (tozadenant, PBF-509, ST1535, ST4206 and V81444) and the relatively old drug istradefylline, which has finally been licensed in Japan. All these compounds have been shown to possess a good safety profile and be well tolerated and are effective in attenuating the off-time, without worsening troublesome dyskinesia, and in strengthening the on-time with a mild increase of non-troublesome dyskinesia, in patients at an advanced stage of PD treated with L-DOPA. Moreover, early findings suggest that A2A antagonists might also be efficacious as monotherapy in patients at an early stage of PD.

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