Adenosine A_{2A}-Receptor Antagonism and Pathophysiology of Parkinson's Disease and Drug-Induced Movement Disorders

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Key Words

Basal ganglia • Direct pathway • Dopamine • Extrapyrimal symptoms • Indirect pathway • Pharmacological agents • Parkinson's disease • Drug-induced movement disorders • Adenosine A_{2A}-receptor antagonism

Abstract

Parkinson's disease and drug-induced movement disorders (DIMDs) have commonalities in etiology based on impaired dopamine-based neurotransmission. Adenosine A_{2A}-receptor antagonism may provide a new mechanism through which these disorders can be managed. In the motor circuit, tonic output from the globus pallidus and substantia nigra regulates movement via opposing excitatory and inhibitory inputs to the cerebral cortex through the direct and indirect pathways. Increased activity of the direct pathway increases movement via an inhibitory effect on thalamocortical projection neurons; increased activity of the indirect pathway has the opposite effect. Regulation of these pathways is mediated primarily by reciprocal inhibitory interactions between dopamine and adenosine receptors on neurons of these pathways. Adenosine A_{2A} receptors are colocalized with dopamine D₂ receptors on the indirect pathway neurons, with A_{2A} activation opposing the effect of D₂ activation.

The A_{2A} receptors' role in the pathophysiology of Parkinson's disease and DIMDs is evidenced by the upregulation of A_{2A} receptors in patients with Parkinson's disease and patients receiving long-term administration of dopamine blockers. Further, A_{2A}-receptor antagonists are effective in reversing parkinsonian motor deficits and extrapyramidal symptoms in animal models of Parkinson's disease and DIMDs. Understanding the role of A_{2A}-receptor antagonism in the pathophysiology of Parkinson's disease and DIMD has therapeutic implications.

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Introduction

Movement disorders are associated with impairments in dopaminergic-related neurotransmission within the striatum. In particular, Parkinson's disease is characterized by a loss of dopaminergic neurons, whereas drug-induced movement disorders (DIMDs) – commonly referred to as extrapyramidal symptoms (EPS) – are associated with the nonselective blockade of dopamine receptors by pharmacologic agents (mainly antipsychotic drugs) within the striatum. Because of the link to dopamine depletion, treatment of Parkinson's disease has centered on various dopamine replacement strategies in-

cluding dopamine precursors, dopamine agonists, and agents that inhibit the metabolism of dopamine [1]. These agents, however, are associated with significant adverse events and long-term complications. EPS are often managed by the addition of anticholinergics, beta blockers, or benzodiazepines to antipsychotic treatment regimens; switching antipsychotics; or reducing the doses of antipsychotics, which may ultimately compromise treatment efficacy [2]. The incidence of EPS in patients treated with antipsychotics remains a significant cause of treatment discontinuation and nonadherence [3], and the extent to which EPS are responsible for treatment discontinuations may be grossly underestimated [4]. This article reviews the underlying pathophysiology of Parkinson's disease and DIMDs, highlighting the common pathways involved and the emerging role of the adenosine A_{2A} receptor as a potential target for the management of both disorders.

Motor Circuitry of the Basal Ganglia

Overall Circuitry

The basal ganglia consist of several anatomic structures, including the neostriatum (caudate nucleus, putamen), the globus pallidus [internal (GPi) and external (GPe) segments], the subthalamic nucleus (STN), and the substantia nigra [pars reticulata (SNr), pars compacta (SNc)]. These anatomic structures form segregated loops that control motor, associative, and limbic functions [5, 6]. The designation of these circuits is based on the function of the cortical areas from which they originate.

Although there is some uncertainty regarding the degree of separation between circuits and whether these circuits are closed or partially open, there is general agreement on their overall framework, and the organization of the intrinsic and extrinsic connections has been mapped [6]. In brief, the striatum and STN receive glutamatergic input from the cerebral cortex and thalamus and this information is relayed to the GPi and SNr, which then provide basal ganglia output to the thalamus and cerebral cortex [6]. Other basal ganglia projections connect with the centromedian and parafascicular thalamic nuclei of the thalamus as well as the pedunculopontine nucleus of the cortex.

The motor circuit is the most well-described circuit because of its involvement in the pathophysiology of movement disorders (fig. 1) [5–8]. Several subcircuits that originate from the cortex and various premotor areas contribute, including postcommissural putamen and motor regions of the GPe, GPi, SNr, STN, and the ventro-

Fig. 1. Locomotor regulatory pathways [8]. A_{2A} receptors are highly expressed in medium-sized spiny GABAergic neurons of the indirect pathway and are predominately found at postsynaptic sites where they are thought to interact with colocalized D_2 receptors [69]. Presynaptic A_{2A} -receptor-mediated enhancement of striatopallidal GABAergic transmission has also been proposed [69]. Reprinted with permission from the American Association for Laboratory Animal Sciences.

anterior and ventrolateral nuclei of the thalamus (VA/VL). Overall, tonic output from the GPi/SNr regulates movement via input to the cerebral cortex that is channeled through the VA/VL, with increased basal ganglia output resulting in decreased movement and decreased output resulting in increased movement via disinhibition of neurons [5–8].

Direct and Indirect Pathways

The connection between the striatum and the output structures of the globus pallidus (i.e. GPi, SNr) is mediated by direct and indirect pathways [5–8]. The direct pathway is a monosynaptic inhibitory pathway that is mediated by gamma-aminobutyric acid (GABA), whereas the indirect pathway is a polysynaptic net excitatory pathway that includes the GPe and STN [6]. Input to the striatal neurons of the direct and indirect pathways comes from several sources in the cortex and the thalamus (direct pathway). Increased activity of the direct pathway results in increased movement via an inhibi-

Fig. 2. Distribution of A₁ and A_{2A} receptors in a human brain [11]. A₁ and A_{2A} receptors as visualized by positron emission tomography with [1-methyl-11C]8-dicyclopropylmethyl-1-methyl-3-propylxanthine and [7-methyl-11C]-(E)-8-(3,4,5-trimethoxystyryl)-1,3,7-trimethylxanthine, respectively. Reprinted with permission from Macmillan Publishers Ltd. [70].

tory effect on thalamocortical projection neurons, whereas increased activity of the indirect pathway results in the opposite effect (i.e. decreased movement due to disinhibition of these neurons). Balanced locomotion is mediated via the opposing excitatory and inhibitory effects of the direct and indirect pathways on the activity of the GPi and SNr. One model of movement suggests that increased striatal output via the direct pathway inhibits specific neurons within the GPi and SNr, resulting in a facilitation of movement [6, 8]. This ongoing movement is inhibited by a subsequent disinhibition of the same GPi and SNr neurons via input from the indirect pathway [6]. Regulation of the direct and indirect pathways is predominantly mediated by reciprocal inhibitory interactions between dopamine and adenosine receptors on neurons of these pathways [8]. Dopamine receptors in the motor circuit can be either excitatory (D₁) or inhibitory (D₂) [8]. The release of striatal dopamine decreases GPi and SNr activity via stimulation of the direct pathway (D₁ receptors in the SNc) and inhibition of the indirect pathway (D₂ receptors). Inhibition of dopamine release has the opposite effect (i.e. increased GPi and SNr activity).

Adenosine receptors play a prominent role in modulating dopamine receptors in the basal ganglia. Adenosine A₁ receptors have a relatively high expression in many areas of the brain (i.e. cortex, cerebellum, hippocampus, and dorsal horn of the spinal cord; fig. 2) [9–11]. Adenosine A₁ receptors are found in conjunction with D₁

receptors in the SNc of the direct pathway with no expression on neurons of the direct pathway [12–15]. This interaction mediates GABA release at the substantia nigra and nucleus accumbens and dopamine release in the striatum [9]. Activation of the adenosine A₁ receptor may also potentiate D₁ receptor desensitization [9].

Adenosine A_{2A} receptors are highly expressed in the striatopallidal GABAergic neurons and olfactory bulb [9], and are colocalized with D₂ receptors in the basal ganglia on enkephalin-expressing output neurons of the indirect pathway [12, 13]. A_{2A} and D₂ receptors have reciprocal antagonistic interactions that regulate GABAergic neurons [16, 17]. Most evidence suggests that adenosine A_{2A}-receptor activation in the indirect pathway opposes the action of D₂ activation by means of an intramembrane interaction, whereas stimulation of D₂ receptors inhibits A_{2A}-receptor-induced activation of adenylyl cyclase [16]. Stimulation of A_{2A} receptors facilitates GABA release, whereas D₂-receptor stimulation inhibits GABA release in the globus pallidus. Conversely, inhibition of A_{2A} and D₂ receptors produces the opposite effects (i.e. inhibition and stimulation of GABA release, respectively) [17, 18]. There is some evidence, however, that A_{2A} and D₂ receptors may act synergistically, with D₂-receptor activation potentiating the effects of A_{2A} receptors under certain circumstances (e.g. presence of certain adenylyl cyclase isoforms, interruption of previous long-term exposure to D₂-receptor agonists) [16].

Pathophysiology of Parkinson's Disease

Parkinsonism is characterized by abnormalities in basal ganglia circuitry [5, 6]. The hallmark pathophysiologic abnormalities in Parkinson's disease are the loss of pigmented neurons in the substantia nigra and the presence of Lewy bodies (i.e. eosinophilic cytoplasmic inclusion bodies) [19]. Neuronal loss and Lewy body formation in other areas (e.g. locus coeruleus, pedunculopontine nucleus, raphe nucleus, dorsal motor nucleus of the vagus nerve, olfactory bulb, parasympathetic and sympathetic postganglionic neurons) further contribute to some non-motor symptoms associated with the disease [19].

The etiologic factors associated with Parkinson's disease appear to be multifactorial and include endogenous neurotoxins, lifestyle, and factors related to genetics and the environment [19]. Subsequent neuronal death results from a variety of mechanisms, which include mitochondrial dysfunction, oxidative damage, and impaired protein degradation (via proteasome and lysosome dysfunction) [19]. Mitochondrial dysfunction is evidenced by decreased activity of mitochondrial complex I proteins [20, 21] and a decrease in alpha-ketoglutarate dehydrogenase complex [22] in the substantia nigra of patients with Parkinson's disease. These biochemical changes are similar to those provoked in animal models of parkinsonism induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) [19]. Oxidative damage is evidenced by increased lipid peroxides [23], a decrease in reduced glutathione [24], and increased iron [25] in the substantia nigra of patients with Parkinson's disease. Oxidative stress is postulated to lead to the dissipation of mitochondrial membrane potential and the release of cytochrome c into the cytoplasm, resulting in an apoptotic cascade [19].

Aberrant protein degradation also appears to be an important factor in nigral neuronal death and is suggested by the presence of Lewy bodies, consisting of aggregated proteins (e.g. alpha-synuclein), and also by the observation that mutations in the *alpha-synuclein* gene are associated with autosomal dominant familial Parkinson's disease [26]. The aggregation of alpha-synuclein has particularly emerged as an important pathogenic factor in nigral neuronal death [19].

Degeneration of dopaminergic neurons within the substantia nigra is a slow progressive process that develops over many years [5]. Reduced dopamine levels in patients with Parkinson's disease result in an imbalance in the activity of striatal output pathways (i.e. imbalance in the direct and indirect pathways) [27]. Dopamine depletion causes striatonigral neurons of the direct pathway to become hypoactive and the striatopallidal neurons of the

indirect pathway to become hyperactive. This imbalance leads to an increased output from the SNr/GPi to the VA/VL, resulting in the hypokinetic symptoms that characterize Parkinson's disease [27]. Reduced dopamine levels have been linked to secondary morphologic changes, which include a reduction in the density of dendritic spines on striatal medium spiny output neurons (involved in corticostriatal transmission) and changes in the density, sensitivity, and subcellular locations of dopamine receptors within the striatum [5].

Pathophysiology of DIMDs

Drugs with dopaminergic-blocking properties (e.g. antipsychotics) are associated with DIMDs. EPS can be acute or tardive (i.e. late developing). Acute EPS (e.g. dystonia, akathisia, parkinsonian symptoms) typically develop within hours, days, or weeks of treatment with an antipsychotic, whereas tardive syndromes (e.g. tardive dyskinesia, tardive dystonia, tardive akathisia, parkinsonism) are delayed, developing only after months or years of treatment [28].

Acute dystonia is a postural distortion caused by sustained contraction of voluntary muscles (e.g. hyperpronation of the arms, wrist flexion, plantar flexion of the feet, adductor spasm of the thighs, protrusion of the tongue) [28]. Acute dystonias typically occur very early (i.e. within the first week) after the initiation of dopamine antagonists, with increased dosage and younger age associated with increased risk [29]. Tardive dystonia is distinguished from acute dystonia by the nature of the muscle contractions (persistent vs. transient for acute dystonia) and by the onset of occurrence (after prolonged therapy vs. days for acute dystonia) [28]. Tardive dyskinesia, a different side of the spectrum to which tardive dystonia belongs, consists of involuntary choreatic movements, rather than more fixed, postural problems that can affect any part of the body but are usually initiated in orofacial muscles (i.e. lips, mouth, or face) with symptoms generally beginning after several months of antipsychotic therapy [28]. Akathisia is characterized by motor restlessness (i.e. repetitive movements of legs and feet) and subjective restlessness (unease, distress, dysphoria). Akathisia can manifest acutely (soon after initiating or increasing dose), tardively (during long-term therapy and unrelated to dose), or after neuroleptic dose reduction or withdrawal [28]. Drug-induced parkinsonism is characterized by bradykinesia (impaired voluntary motor activity), tremor (of low frequency and wide amplitude and primarily affecting the hands), and rigidity (increased resting muscle tone manifesting as 'cog-

wheel' and 'lead-pipe' rigidity). The symptoms have an insidious onset, typically beginning after several weeks of therapy [28].

Although the exact mechanism of EPS remains unknown, dopamine receptors appear to have an important role. Animal models suggest a relationship between D₂-receptor occupancy by antagonists and the development of EPS, with approximately 70% occupancy of D₂ receptors by antipsychotics being associated with EPS development [30]. Threshold levels of striatal D₂-receptor occupancy linked to the development of EPS (roughly 80%) also have been demonstrated in human imaging studies [31, 32]. In one study, drug-induced EPS were most common in patients whose striatal/frontal cortex ratio for D₂-receptor occupancy was <1.2 [32].

The role of dopamine receptors in the pathophysiology of EPS is further supported by the differing pharmacologic profiles of antipsychotics [28]. Differences in EPS potential between antipsychotics are believed to be due to differences in D₂-receptor antagonism, speed of dissociation from the D₂ receptor, selectivity for limbic versus striatal D₂ receptors, and activity at other receptors (e.g. serotonergic, muscarinic) [28]. Therefore, older, high-potency D₂-blocking agents (e.g. haloperidol) are particularly associated with increased EPS risk [28, 33]. In general, atypical antipsychotics have a decreased potential for EPS relative to conventional antipsychotics, which may be related to a variety of factors including looser binding of atypical antipsychotics to D₂ receptors, a more balanced receptor profile [i.e. binding other nondopaminergic receptors (serotonergic receptors)], and decreased striatal dopamine-receptor sensitivity [33]. However, the risk of antipsychotic-induced EPS is dose dependent and varies among drugs in the atypical and conventional classes of antipsychotics [28].

Still, the delay between dopaminergic blockade and the onset of symptoms suggests the mechanism is not strictly related to a hypodopaminergic state [34]. Dopamine-receptor hypersensitivity is the most frequently proposed pathophysiologic mechanism behind the development of acute dystonia and tardive dyskinesia [33]. For acute EPS, cholinergic/dopaminergic neurotransmitter system imbalances and serotonergic receptors (especially 5-HT₂ receptors) also appear to play a critical role [35].

The postsynaptic dopamine-receptor hypersensitivity hypothesis suggests that long-term dopamine-receptor blockade by antipsychotics, which is clinically associated with parkinsonism, results in adaptive phenomena that increase the sensitivity to dopamine agonists [36].

The hypersensitivity hypothesis is supported by the observations that tardive dyskinesia is associated with chronic dopamine-receptor blockade and that increasing dopaminergic blockade suppresses tardive dyskinesia [33, 36]. In particular, long-term administration of antipsychotics is associated with an increase in D₂ receptors and a supersensitivity of D₁ receptors [37]. In this theory, dyskinesia results from an imbalance between D₂- and D₁-receptor function, with a shift toward a predominance of D₁ receptors. This shift has been linked to a dose-dependent increase in drug-induced jaw movement in rats [38].

GABAergic dysfunction, resulting in a decrease in GABA inhibitory tonus in the basal ganglia, has also been proposed as a mechanism of antipsychotic-induced tardive dyskinesia [33, 36]. In animal models, neuroleptics produce a decrease in GABA turnover; a reduction in glutamic acid decarboxylase activity (a rate-limiting enzyme of GABA synthesis) in the substantia nigra, globus pallidus, and STN; and a decreased number of striatal neurons [39]. There is a correlation between an increase in GABA-A-receptor density in the SNr of haloperidol-treated rats and vacuous chewing movements [40]. In addition, patients with tardive dyskinesia have an increase in oculomotor distractibility, which is mediated by GABAergic nigral efferent tracts, compared with patients with schizophrenia without tardive dyskinesia [41]. These data suggest that hypofunction of GABA-mediated inhibitory tonus in the substantia nigra is important in the pathophysiology of DIMDs.

The loss of striatal cholinergic neurons, induced by the prolonged neuroleptic-induced overactivation of striatal cholinergic neurons, has also been proposed as a mechanism of tardive dyskinesia [42]. Evidence for this includes the observation that prolonged haloperidol treatment in rats leads to cholinergic cell loss in areas of the striatum that are related to oral movements [43].

Excitotoxicity due to overactivation of glutamate receptors or oxidative stress, or both, has been proposed as a possible mechanism of DIMDs. Animal models of DIMDs and Parkinson's disease suggest that disturbances in glutamate homeostasis leading to increased extracellular levels is associated with apoptosis of dopaminergic neurons in the substantia nigra and the development of dyskinesias [44–46]. Further, long-term administration of haloperidol in rats has been shown to increase levels of lipid peroxidation and decrease levels of reduced glutathione and antioxidant enzymes (i.e. catalase, superoxide dismutase) [47, 48].

The Role of Adenosine A_{2A} Receptor in Parkinson's Disease and DIMDs

Patients with Parkinson's disease have altered adenosine A_{2A}-receptor expression in the basal ganglia, suggesting a pathogenic role for these receptors. In a post-mortem study of patients with Parkinson's disease, a 2.95-fold increase was observed in A_{2A}-receptor density in the putamen compared with healthy subjects, whereas no difference was observed between groups in D₂-receptor density or affinity [49]. Another autopsy study demonstrated that patients with Parkinson's disease and dyskinesia who were treated with levodopa had increased levels of A_{2A} receptors and corresponding messenger RNA compared with levodopa-treated patients without dyskinesia [50]. This suggests that increased A_{2A}-receptor expression is due to a long-lasting pathologic adaptive alteration and is consistent with the observation that levodopa-induced dyskinesias are not easily reversible [50].

Although the precise role of A_{2A} receptors in DIMDs is unknown, long-term administration of haloperidol has been shown to upregulate A_{2A} receptors in rat striatum [51]. In a study by Parsons et al. [51], the effect of haloperidol was selective for A_{2A} receptors compared with other adenosine-receptor subtypes. There was a correlation between the degree of antipsychotic-induced A_{2A}-receptor upregulation and D₂-receptor upregulation [51]. Notably, atypical antipsychotics had no effect on A_{2A}-receptor density in this study [51]. Adenosine A_{2A} receptors may play a role in GABA neurotransmission, and A_{2A} receptors have been shown to mediate the release of GABA in the striatum [52].

Results of studies evaluating adenosine A_{2A}-receptor antagonists in animal models of Parkinson's disease and DIMDs suggest an important role for adenosine. Adenosine A_{2A}-receptor antagonists inhibit motor deficits induced by dopamine antagonists, such as catalepsy and suppressed locomotion [47, 48, 53–57]. Consistently, adenosine A_{2A}-receptor antagonists inhibited the motor disability induced by dopaminergic neurotoxins (i.e. 6-hydroxydopamine, MPTP) [27, 58, 59]. A_{2A}-receptor antagonists are effective in relieving parkinsonian muscular rigidity and tremor, as evidenced by suppression of haloperidol-induced rigidity [60] and inhibition of haloperidol- and pimozide-induced tremulous jaw movements [55, 56, 61]. In one study, motor effects of A_{2A}-receptor antagonism were accompanied by an inhibition of pimozide-induced increased expression of *c-Fos* in the VL neostriatum, the striatal area most closely associated with tremulous jaw movements [61]. Other studies indicated that A_{2A}-receptor antagonists inhibited haloperidol-induced oxidative damage [47] and reversed haloperidol-

related impairment of decision-making in the T-maze choice procedure (a possible model of antipsychotic-induced anhedonia) [62]. Selective A_{2A}-receptor antagonists also have demonstrated efficacy in the treatment of Parkinson's disease as adjunctive therapy [1, 12, 63], although nonselective A_{2A}-receptor antagonists (e.g. theophylline) have demonstrated less encouraging results [64].

Several studies in monkeys have demonstrated that adenosine A_{2A}-receptor antagonists have little propensity for inducing dyskinesia and can alleviate DIMDs in various models. For example, the adenosine A_{2A}-receptor antagonist, istradefylline (KW-6002), induced little or no dyskinesias in levodopa-primed MPTP-treated marmosets [59]. In an animal model of tardive dyskinesia, A_{2A}-receptor antagonism inhibited haloperidol-induced orofacial dyskinesia (e.g. vacuous chewing movements, tongue protrusions, facial jerking) [47, 48]. Haloperidol-induced EPS in *Cebus apella* monkeys closely approximates neuroleptic-induced acute and tardive EPS in humans and has been widely used as a model for assessing this syndrome [65–67]. The A_{2A}-selective antagonist, preladenant (SCH412348), has been found to delay or prevent the onset of EPS in this model in a dose-dependent fashion [65]. This agent has been shown to inhibit EPS induced by atypical antipsychotic agents (i.e. risperidone, aripiprazole, olanzapine, quetiapine) in haloperidol-sensitized *Cebus apella* monkeys [68].

Conclusions

Although the pathophysiology of movement disorders is complex, movement is fundamentally controlled by a balance between the excitatory and inhibitory effects of the direct and indirect pathways of the motor loop within the basal ganglia. The dramatic symptomatic response produced by dopaminergic agents in the treatment of Parkinson's disease has resulted in a focus on the role of dopamine in the pathophysiology of Parkinson's disease. However, other neurotransmitter systems are becoming increasingly recognized. The localization of adenosine A_{2A} receptors within the basal ganglia and its extensive interaction with dopaminergic systems suggest a unique role for A_{2A}-receptor blockade in the pathophysiology of movement disorders. This understanding has implications for the treatment of Parkinson's disease and DIMDs. A_{2A}-receptor antagonists have the potential to be effective for the treatment of Parkinson's disease and DIMDs, while potentially avoiding some of the adverse events (i.e. dyskinesias) associated with dopaminergic therapies.

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