

Adenosine A_{2A} receptors in Parkinson's disease treatment

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Received: 7 May 2007 / Accepted: 17 March 2008 / Published online: 26 April 2008
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Abstract Latest results on the action of adenosine A_{2A} receptor antagonists indicate their potential therapeutic usefulness in the treatment of Parkinson's disease. Basal ganglia possess high levels of adenosine A_{2A} receptors, mainly on the external surfaces of neurons located at the indirect tracts between the striatum, globus pallidus, and substantia nigra. Experiments with animal models of Parkinson's disease indicate that adenosine A_{2A} receptors are strongly involved in the regulation of the central nervous system. Co-localization of adenosine A_{2A} and dopaminergic D2 receptors in striatum creates a milieu for antagonistic interaction between adenosine and dopamine. The experimental data prove that the best improvement of mobility in patients with Parkinson's disease could be achieved with simultaneous activation of dopaminergic D2 receptors and inhibition of adenosine A_{2A} receptors. In animal models of Parkinson's disease, the use of selective antagonists of adenosine A_{2A} receptors, such as istradefylline, led to the reversibility of movement dysfunction. These compounds might improve mobility during both monotherapy and co-administration with L-DOPA and dopamine receptor agonists. The use of adenosine A_{2A} receptor antagonists in combination therapy enables the reduction of the L-DOPA doses, as well as a reduction of

side effects. In combination therapy, the adenosine A_{2A} receptor antagonists might be used in both moderate and advanced stages of Parkinson's disease. The long-lasting administration of adenosine A_{2A} receptor antagonists does not decrease the patient response and does not cause side effects typical of L-DOPA therapy. It was demonstrated in various animal models that inhibition of adenosine A_{2A} receptors not only decreases the movement disturbance, but also reveals a neuroprotective activity, which might impede or stop the progression of the disease. Recently, clinical trials were completed on the use of istradefylline (KW-6002), an inhibitor of adenosine A_{2A} receptors, as an anti-Parkinson drug.

Keywords Parkinson's disease · Adenosine · Adenosine receptors · Dopamine receptors · Neuroprotection

Introduction

In Parkinson's disease, which belongs to the family of neurodegenerative disorders, the progressive damage of dopaminergic neurons in the substantia nigra is the cardinal pathophysiological event, which leads to a substantial reduction in the dopamine concentration in striatum. This reduction is responsible for the major symptoms of the disease, such as bradykinesia, muscular rigidity, and tremor. The clinical symptoms appear after approximately 60% of the dopaminergic neurons are damaged, 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 caeruleus. The eosinophilic inclusion bodies, called the Lewy bodies, occur in many damaged neurons. The etiology of Parkinson's disease is still unknown, although

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participation of environmental toxins, oxidative stress, and free radicals is postulated. Up to now, 11 types of familial Parkinsonism have been described. Of those, the mutation of the α -synuclein gene (PARK1) in chromosome 4 was identified first.

The major drugs used in the treatment are the dopamine precursor L-DOPA (L-3,4-dihydroxyphenylalanine) and dopaminergic receptor agonists. Other drugs are cholinolytic compounds; the catechol-O-methyltransferase inhibitors (COMT); drugs that increase the release of dopamine, such as amantadine, which is also an antagonist of glutaminergic receptors; as well as inhibitors of monoaminooxidase type B.

The agonists of D2/D3 dopaminergic receptors newly introduced into clinical use (e.g., pramipexole and ropinirole) reveal a 20–30 times greater affinity for D3 than D2 receptors. All of these drugs are highly efficient in early stages of the disease [1, 2]. However, long-term treatment with L-DOPA leads to its decreased efficacy and the occurrence of side effects, including dyskinesias, “on” phase shortening, occurrence of “on-off” syndromes and psychotic symptoms [1, 2]. The dopaminergic receptor agonists, especially at the beginning of the treatment, might cause the acute side effects, such as nausea and vomiting, while lowering the blood pressure. Their long-term use also results in lowering of the drug efficacy, development of dyskinesias, and progression of the disease [1]. It should be emphasized that all the drugs mentioned above act symptomatically and do not significantly impede the disease progression.

So far there is no efficient strategy to counteract the progressive death of the dopaminergic neurons of the substantia nigra [3]. Experiments have shown that dopamine, MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), or oxidation products of 6-hydroxydopamine (6-OHDA) might be responsible for the neuron death [4–6]. Therefore, the search continues for new drugs for alleviating the disease that do not cause dyskinesias and reveal a long-term clinical efficacy. It is expected that new drugs would also impede or stop the disease progression by a neuroprotective action.

Adenosine, dopamine, and their receptors in CNS

All sub-types of adenosine receptors, i.e., A_1 , A_{2A} , A_{2B} and A_3 , have been detected in the central nervous system (CNS). These receptors are glycoproteins that cooperate with the G proteins [7–9].

Adenosine A_1 and A_{2A} receptors are characterized by high affinity for adenosine, while A_{2B} and A_3 receptors show significantly lower affinity for adenosine. Activation of adenosine A_1 receptors occurs at 0.3–3 nM concentration of adenosine, adenosine A_{2A} receptors at 1–20 nM, while

adenosine A_{2B} or A_3 receptor activation requires an agonist concentration larger than 1 μ M [7]. Therefore, under physiological conditions, concentration of extracellular adenosine (ectoAdo) between 0.3–1.000 nM is high enough to activate the adenosine A_1 and A_{2A} receptors. Receptors with a low affinity to the agonist require higher concentration of the extracellular nucleoside. Such elevated concentrations of ectoAdo, exceeding the highest physiological level of 1 μ M, are detected in tissues during hypoxia [7].

A_1 receptors are coupled with the subfamilies $G_{i(1-3)}$ and G_o of G proteins. They inhibit the adenylate cyclase activity. Activation of these receptors results in the opening of several types of potassium channels and closing of some calcium channels [7–10].

Adenosine A_{2A} and A_{2B} receptors are coupled with G_s proteins, which in turn activate adenylate cyclase, causing the elevation of the cAMP level in cells [7]. It is still unclear if the activation of the adenosine A_{2A} receptor leads to different results than the stimulation of the adenosine A_{2B} receptors. However, both subtypes differ in location and pharmacological properties. In CNS, the adenosine A_{2B} receptor is widely spread, while adenosine A_{2A} receptors have been found only in the dopaminergic regions of the brain.

Adenosine A_3 receptors are not as well known as the others. It is known that stimulation of that receptor leads to the formation of inositol triphosphate (IPA3) and consequently to an increase in calcium concentration in cells. The adenosine A_3 receptors are abundant in the brain, but their amount is significantly lower than that of other adenosine receptors [7, 9].

The adenosine receptors are bound to the cell membranes of neurons, glia cells, and endothelial cells of the brain blood vessels [7–9]. In the brain, A_1 is the most abundant type of adenosine receptor. It occurs in the neuron synaptic membranes of such brain structures as the brain core, hippocampus, cerebellum, spinal cord, thalamus, and striatum [7–10]. Small amounts of mRNA of the adenosine A_{2B} receptor have been found in such brain structures as the brain core, hippocampus, cerebellum, thalamus, hypothalamus, and striatum. In turn, the presence of mRNA of the adenosine A_3 receptor was detected in the rat hippocampus, thalamus, and hypothalamus [7].

The adenosine A_{2A} receptors are abundant in striatum and other nuclei of the basal ganglia, as well as in nucleus accumbens and olfactory bulb, where they are always colocalized with the dopaminergic D2 receptors. However, presence of adenosine A_{2A} receptor was not detected in striatal neurons expressing D1 receptors, substance P, and dynorfin [10]. In the rat brain, small amounts of mRNA of that receptor have been detected in the brain core, hippocampus, cerebellum, thalamus, and hypothalamus [7, 10]. Few adenosine A_{2A} receptors involved in modulation

of neurotransmission related to γ -aminobutyric acid (GABA), acetylcholine, or glutamate are localized on neurons of nucleus caudatus and pulvinar [3]. In striatum, adenosine A_{2A} receptors are localized mainly postsynaptically (70%), but also presynaptically (23%), on the neuron body (3%), and on glia cells (3%).

The dopaminergic receptors are classified into two sub-families:

1. D1 sub-family (D1-like), which consists of D1 and D5 receptors
2. D2 sub-family (D2-like), with receptors D2, D3 and D4

The dopaminergic receptors are built with about 400 amino acids and contain seven α -helices participating in ligand binding [11]. Signal from the activated receptor is transmitted to the effector proteins via G proteins. The dopaminergic cells are grouped into the dopaminergic system pathways. The most important is the pathway linking substantia nigra and striatum (nigrostriatal), which produces 75% of the brain dopamine and participates in the regulation of motor activity. Other pathways are the mesolimbic pathway, which participates in the regulation of emotional and cognitive functions, as well as mesocortical and tubero-infundibular pathways [11].

For fulfilling the functions of dopamine, the simultaneous stimulation of D1 and D2 receptors is necessary, a process called obligatory synergism. Agonists of D1 and D2 receptors not only enhance their action, but neither of them is efficient separately when used in the presence of the antagonist of the other receptor [11].

It is important that in striatum the dopaminergic D1 and D2 receptors occur on different neuron populations [12]. The majority of D1 receptors are localized on the direct pathways between striatum and substantia nigra (direct striatonigral pathway) [13]. However, co-localization of D2 and adenosine A_{2A} receptors occurs only on the indirect pathways between striatum, globus pallidus, and substantia nigra (indirect striato-pallido-nigral pathway) [14].

Functions of adenosine and dopamine in CNS

The neurochemical and behavioral research reveals that stimulation of pathways between striatum, globus pallidus, and substantia nigra leads to improved mobility. These results indicate a synergism between stimulation of D2 receptors and inhibition of adenosine A_{2A} receptors [14].

In 1970 it was found that adenosine participates in regulation of signal transmission in the extrapyramidal system [15]. Currently it is known that adenosine A_{2A} receptors participate in the antagonistic interaction between adenosine and dopamine and could affect the mobility independent of D2 receptors [10]. Activation of adenosine

A_{2A} receptors in animals results in sedation and catalepsy, reduces the normal mobility resulting from activation of the dopaminergic receptors, and lowers the affinity of agonists for the dopaminergic D2 receptors [16]. The presynaptic adenosine A_{2A} receptors occur in the glutaminergic endings of the core-striatum pathway of the GABA-ergic neurons or interneurons, where their activation leads to glutamate release. Biochemical and electrophysiological research revealed that adenosine A_{2A} receptors modulate the GABA-ergic transmission in striatum and globus pallidus [17]. Activation of adenosine A_{2A} receptors in striatum inhibits the GABA release and GABA-ergic transmission, while in globus pallidus it enhances the GABA-ergic transmission via the cAMP-dependent mechanism [1, 18]. In striatum, the adenosine A_{2A} receptors occur also in the cholinergic interneurons, where they modulate the activity of A and C kinases, and consequently stimulate acetylcholine release [19]. Therefore, in striatum, an activation of adenosine A_{2A} receptors, resulting in lower transmission depending on dopamine, disturbs the balance of neurotransmission described above. The progressive degeneration of neurons of striatum and substantia nigra, occurring in Parkinson's disease, causes a decrease in the stimuli inflow, and consequently results in the pathological disorders of mobility called hypertonic-hypokinetic syndrome, characteristic of Parkinson's disease.

New possibilities for treatment of Parkinson's disease, including the design of new antipsychotic drugs free from the extrapyramidal side effects, are indicated by results showing that CGS 21680, the agonist of the adenosine A_{2A} receptor, decreases the affinity of D2 receptors for dopamine in human striatum [20–22].

Use of A_{2A} receptor antagonists in the experimental models of Parkinson's disease

The milestone in the research on Parkinson's disease was the design of an animal model in primates, treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). MPTP is converted by the B-type monoaminooxidase into MPP⁺ (1-methyl-4-phenylpyridine), which is selectively captured by the dopaminergic neurons. MPP⁺ inhibits the activity of complex I of the mitochondrial respiratory chain, decreases the ATP synthesis and enhances the formation of superoxide radicals, which form the toxic peroxonitrites in a reaction with nitric oxide. These processes lead to the aggregation of α -synuclein in neurons of the substantia nigra [23, 24]. Another animal model of Parkinson's disease was developed by an administration of methamphetamine (MTH). Administration of MTH decreases the number of dopaminergic cells in substantia nigra and the dopamine level in striatum and reduces the activity of

tyrosine hydroxylase. The other frequently used animal model is obtained by an injection of 6-hydroxydopamine into the forebrain bundle, which produces lesions of the nigro-striatal pathway in rats [3, 25, 26].

Xanthine derivatives-antagonists of the adenosine A_{2A} receptors

In 1994, selective antagonists of the adenosine A_{2A} receptors were synthesized. Their application in the animal models revealed that these compounds might be useful in treatment of Parkinson's disease [27]. The xanthine derivatives KF17837 and KW6002 (istradefylline), which are antagonists of the adenosine A_{2A} receptors in nanomolar concentrations, reveal almost 70 times higher selectivity for A_{2A} than for adenosine A_1 receptor. It was shown that the selective adenosine A_{2A} receptor antagonists (SCH 58261, KF17837, and istradefylline) in animals decrease the symptoms of catalepsy caused by administration of haloperidol, symptoms of akinesia caused by reserpine, and the anti-cataleptic action during administration of L-DOPA [1]. The action of the selective adenosine A_{2A} receptor antagonists in alleviating symptoms of Parkinson's disease was shown in the original animal model of that disease [28, 29]. In that research, istradefylline lowered the extrapyramidal mobility disorders caused by MPTP in monkeys.

Bara-Jimenez et al. [30] reported that istradefylline, either separately or co-administered with L-DOPA in a permanent intravenous infusion in the optimal dose, did not affect the progression of extrapyramidal syndrome. However, its co-administration with small doses of L-DOPA caused 36% greater efficacy of anti-Parkinson response and 45% decrease in dyskinesias caused by the optimal doses of L-DOPA. All basic symptoms of Parkinson's syndrome, in particular a passive tremor, were reduced after the procedure. Moreover, istradefylline increased the efficacy of L-DOPA by prolongation of its average half-life by 47 min, without any symptoms of toxicity [30].

In the animal experiments, Golembiowska et al. [31] had shown that inhibition of adenosine A_{2A} receptor in striatum after L-DOPA administration intensified the dopamine release from neurons. Therefore, the adenosine A_{2A} receptor antagonists, by increasing the therapeutic efficacy of L-DOPA, might have a positive effect even in the early stages of Parkinson's disease.

Oral administration of istradefylline in the animal model of Parkinson's disease induced in monkeys by MPTP improved mobility for 11 h [32], which was identical to that of healthy animals, while L-DOPA caused hyperkinesia. Moreover, the use of istradefylline for 21 days did not cause dyskinesias, which appeared during treatment with L-DOPA. Co-administration of istradefylline and L-DOPA

increased the anti-Parkinson activity by 30% and did not cause dyskinesias. These results suggest that istradefylline could be efficiently used in monotherapy in patients with the early form of Parkinson's disease. In patients who reveal significant mobility disorders, istradefylline can improve the anti-Parkinson activity of L-DOPA, while not causing dyskinesias. In patients with advanced Parkinson's, istradefylline reduced the "off" time. The most frequent among rarely observed side effects was nausea, usually occurring at the beginning of the treatment and disappearing in 10 days. The only significant side effect was the elevated concentration of lipase observed in five patients (7.4%) [32].

In the animal model of the disease induced by MPTP, istradefylline administered with L-DOPA or with the D2 receptor agonist quinpirole reveals not only the additive anti-Parkinson activity, but also does not intensify dyskinesias [1].

Role of other antagonists of the adenosine A_{2A} receptors in Parkinson's disease treatment

Recently, during the research on the anti-malaria drug mefloquine, Weiss et al. [33] discovered that a fragment of its molecule is an adenosine A_{2A} receptor antagonist. Based on that observation, they synthesized more than 2,000 different adenosine A_{2A} receptor antagonists. In particular VER-6947 and VER-7835 in vivo reversed the locomotorial disorders caused by the D2 receptor antagonist haloperidol [33]. In rats with brain damage induced by 6-OHDA infusion in the medial forebrain bundle, behavioral research was conducted with the use of the adenosine A_{2A} receptor antagonist SCH 58261 and the threshold dose of L-DOPA. Long-lasting or periodically interrupted administration of SCH 58261 (5 mg/kg) combined with L-DOPA (3 mg/kg) caused a stable turning behavior of animals, while treatment with L-DOPA resulted in sensitized turning behavior [25]. Wardas [34] showed the synergic action of L-DOPA and SCH 58261 in decreased muscular rigidity induced in rats by reserpine. Another study showed that these compounds significantly decreased the tremor in rats [35]. Also, in rats the A_{2A} receptor antagonists DMPX, KF17837, and istradefylline cancelled catalepsy caused by haloperidol or reserpine. Contrary to L-DOPA, the long-term administration of selective adenosine A_{2A} receptor antagonists does not result in dyskinesias or lack of response in Parkinson's disease models induced by 6-OHDA and MPTP.

Latest results show that ST1535 administered alone enhanced the exploratory behavior and produced a dose-related increase in ipsilateral rotation in unilaterally 6-OHDA-lesioned rats. Injection of ST1535 combined with high dose of L-DOPA caused significant contraversive

rotation but did not alter the rotational response produced by L-DOPA alone [26]. ST1535 administered alone produced a dose-related increase in the locomotor activity and tended to reverse the motor disability in MPTP-treated common marmosets. A similar effect was observed after treatment with a threshold dose of L-DOPA [36]. Another adenosine A_{2A} receptor antagonist, arylpiperazine SCH 420814, orally administered in rats with haloperidol-induced catalepsy revealed good pharmacokinetic properties and excellent in vivo activity [37].

Nonselective antagonists of adenosine A_1 and A_{2A} receptors

The indirect evidence of adenosine A_{2A} receptor involvement in regulation of motor behavior is the observed improvement in mobility after treatment with caffeine and theophylline, nonselective antagonists of the adenosine A_1/A_2 receptors [38]. This suggests that drinking concentrated coffee might improve the mobility of patients with Parkinson's disease. However, the opinions on that are contradictory. The epidemiological research indicates that these patients usually do not drink coffee. It was found that even a single administration of caffeine might increase the neurotoxicity, as measured by both the activity of tyrosine hydroxylase and the dopamine concentration in striatum [39]. However, the long-term administration of caffeine inhibits the neurotoxicity caused by MTH and MPTP [3, 39]. That might be explained by either inhibition of adenosine A_{2A} receptors or an increased amount of adenosine A_1 receptors in striatum [39].

Two large prospective epidemiological studies were performed. The 30 years of follow-up data for a group of 8,004 men revealed that higher dietary intake of caffeine significantly lowered incidence of PD [40]. Research by Ascherio et al. [41] on two cohorts of men and women further supported the protective effect of caffeine against a risk of PD in men, while for women the effect was U-shaped. Theophylline also decreases symptoms of Parkinson syndrome and elongates the “on” phase in patients with the advanced form of Parkinson's disease [42].

So far, there has been a lack of reliable research indicating changes in the adenosine level in the CNS of patients with Parkinson's disease. There are, however, few reports suggesting changes in the amount of adenosine receptors in these patients. Post-mortem tests of patients treated with dopaminergic drugs, reported by Hurley et al. [43], revealed changes in the amount of adenosine A_{2A} receptor mRNA in the nucleus caudatus and pulvinar, as well as in the substantia nigra. One could only guess that similar effects could occur in untreated patients. Calon et al. [44] suggested that long-lasting treatment with L-DOPA results in an intensified synthesis of adenosine A_{2A}

receptors in the pathway between striatum and substantia nigra, and occurrence of dyskinesias in Parkinson's disease patients. In our opinion, the therapeutic effect might depend not only on the change in the ecto-adenosine concentration or the amount of the adenosine receptors, but also might be linked to the disturbed ratio between adenosine and dopamine level, since the therapeutic effect is achieved by simultaneous use of the adenosine A_{2A} receptor antagonists and D2 receptor agonists.

Neuroprotective activity of antagonists of the adenosine A_{2A} receptor

Research on the role of adenosine receptors in treatment of Parkinson's disease indicates that the therapeutic effect of their antagonists could be linked to the neuroprotective action. The increased release of the stimulating transmitters might play a crucial role in the death of neurons resulting from excitotoxicity. Therefore, it should be concluded that drugs inhibiting glutamate release might be efficient in the treatment of neurodegenerative diseases [45, 46]. Both adenosine A_1 and A_{2A} receptors play an important role in neuroprotection.

Chen et al. [46] showed, in an animal model of PD induced by MPTP, that the neuroprotection is caused by inactivation of adenosine A_{2A} receptor with caffeine.

A similar effect is achieved with the use of several other adenosine A_{2A} receptor antagonists (SCH58261, KW-6002) or by genetic inactivation of adenosine A_{2A} receptor expression. In rat models of Parkinson's disease induced by 6-hydroxydopamine (6-OHDA), a significant neuroprotective effect was achieved by oral administration of KW-6002, an antagonist of adenosine A_{2A} receptor [3]. On the other hand, inhibition of adenosine A_1 receptors with 8-cyclopentyl-1,3-dipropylxanthine did not protect neurons. Therefore, the neuroprotective action is coupled to the blockade of adenosine A_{2A} and not A_1 receptors.

Neurons of knockout mice with no adenosine A_{2A} receptors revealed lower resistance to hypoxia and damage caused by MPTP. The pharmacological inhibition of adenosine A_{2A} receptors prevented the neurotoxicity induced by administration of cholic acid into striatum [45]. The strongest neuroprotection was achieved by simultaneous activation of adenosine A_1 receptors and inhibition of adenosine A_{2A} receptors. That results from the opposite action of A_1 and A_{2A} receptors during release of glutamate and aspartate [2]. During inhibition of A_{2A} receptors, the main mechanisms responsible for the neuroprotection include dilation of the blood vessels, inhibition of blood platelet aggregation, and decrease in the amount of neutrophils [47]. There are several other mechanisms for the neuroprotective action of the adenosine A_{2A} receptor antagonists, such as a decrease in the microglia activation

and/or decreased release of cytokines (TNF- α , IL-1 β) [2]. Interactions between both types of the adenosine receptors suggest that the adenosine action mediated by adenosine A_1 receptors might be weakened when accompanied by adenosine A_{2A} receptor activation. Stimulation of the A_{2A} part of heteromeric adenosine A_1/A_{2A} receptor, present in the hippocampus or striatum synaptosomes, decreases the agonist binding by A_1 receptors, therefore lowering their ability to inhibit the excitability and synaptic transmission in hippocampus. As a result, low concentrations of adenosine inhibit the release of glutamate, which is involved in neurotoxicity, while high concentrations stimulate its release [48].

Re-uptake of glutamate by neurons and glia cells is the main mechanism for maintaining or lowering the extracellular concentration of that neurotransmitter. In striatum, activation of adenosine A_{2A} receptors results in an increased concentration of extracellular glutamate, while the adenosine A_{2A} receptor antagonists inhibit glutamate release from cells [49]. It was found that the selective antagonists of adenosine A_{2A} receptor prevent damage of the hippocampus neurons caused by forebrain hypoxia in gerbils and rats and decrease the size of the brain stroke region in the model of focal ischemia during occlusion of the middle cerebral artery [49]. Similarly, use of selective adenosine A_{2A} receptor antagonists (SCH 58261, ZM 241285, and CSC) decreased the region of brain damage by the kainic, kinurenic and cholic acids [2]. The adenosine A_{2A} receptor antagonists affect the adenosine receptors located on the presynaptic membrane, but do not influence the effects of the stimulation of NMDA receptors [45]. It was found that large doses of SCH 58261 can cause peripheral symptoms such as lowering the blood pressure, which leads to a decrease in brain blood flow and further stimulation of the glutamate release.

Neuroprotective action of adenosine is also confirmed by analysis of the effect of adenosine deaminase and adenosine kinase inhibitors in the MHT model, as well as the influence of the adenosine transport inhibitors on the dopamine release and long-lasting neurotoxic effects of MHT [50]. In the 6-OHDA and MPTP models of brain damage, istradefylline and KF18446 revealed the neuroprotective action by inhibiting the adenosine A_{2A} receptors [3].

Summary

Immunohistochemical research revealed that neurons localized in the basal ganglia have high amounts of adenosine A_{2A} receptors, which are located mainly on the indirect striato-pallido-nigral pathway between the striatum, globus pallidus, and substantia nigra. The animal models of Parkinson's disease proved that adenosine A_{2A} receptors

are involved in the regulation of CNS. In striatum, adenosine A_{2A} receptors are co-localized with D2 dopaminergic receptors, which creates the possibility of an antagonistic interaction between adenosine and dopamine. Also, activation of adenosine A_{2A} receptors inhibits the release of GABA and the GABA-ergic transmission, while enhancing the GABA-ergic transmission in globus pallidus via the cAMP-dependent mechanism.

So far, the changes in the amount of adenosine in the brains of patients with Parkinson's disease have not been detected. Only a few results suggest changes in the amount of the adenosine receptors in that disease. Despite that, it seems that the largest improvement in the mobility of patients with Parkinson's disease could be achieved by simultaneous activation of the dopaminergic D2 receptors and inhibition of adenosine A_{2A} receptors. In the animal models of PD, in which the symptoms were induced by administration of MPTP to the basal ganglia, the reversibility of the motor dysfunction was shown with the use of selective adenosine A_{2A} receptor antagonists, such as istradefylline. That compound had proven effective, administered both in an intravenous infusion or orally. It was reported that the adenosine A_{2A} receptor antagonists might improve mobility when used both in monotherapy and co-administered with L-DOPA and agonists of the dopaminergic receptors. In the combination therapy, the use of these compounds will allow a reduction in the dose of co-administered L-DOPA and reduced side effects. Use of adenosine A_{2A} receptor antagonists does not cause the dyskinesias found in monotherapy or in the combination therapy with L-DOPA and with agonists of the dopaminergic receptors. In the additional treatment, the adenosine A_{2A} receptor antagonists could be used in both moderately and significantly advanced forms of Parkinson's disease. The long-lasting administration of adenosine A_{2A} receptor antagonists did not lead to tolerance or occurrence of side effects as is characteristic of the long-term use of L-DOPA. Inhibition of adenosine A_{2A} receptors not only decreases mobility disorders, but also reveals the neuroprotective effect, as shown in different animal models. Since adenosine A_{2A} receptors are also located in the limbic system, hippocampus, and amygdala, these compounds might also be helpful in psychic disorders, especially those with fear and depression symptoms. The occurrence of these symptoms in patients with Parkinson's disease might be an additional indication for usage of the adenosine A_{2A} receptor antagonists.

Clinical perspectives

The adenosine A_{2A} receptor antagonist istradefylline entered the preclinical tests as an adjunct in the L-DOPA

therapy in Parkinson's disease patients [32, 51]. Recently, phase II and III clinical studies with istradefylline were completed [52] in North America and the European Union in Parkinson's disease patients who are experiencing "wearing-off phenomenon" while taking L-DOPA alone, or while taking L-DOPA with other Parkinson's disease medications. More than 1,200 patients affected by Parkinson's disease participated in these tests. The research revealed that istradefylline is well tolerated by the majority of patients. It does not activate dyskinesias and other changes in mobility, which have been observed during dopaminergic adjunctive therapies. Istradefylline reduces the "off" time, and patients remain in the longer "on" phase with symptoms of nontroublesome dyskinesia. Another advantage is that istradefylline and arylpiperazine might also be administered orally based on home diaries [32, 37]. Due to its nonmotor and nondopaminergic action, istradefylline might also be used as a drug in the treatment of neuropsychiatric symptoms occurring in Parkinson's disease. In summary, istradefylline might become an important drug that delays, decreases, or reverses symptoms of Parkinson's disease. Also the neuroprotective action of istradefylline on dopaminergic neurons is very important and promising for its future applications.

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