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Review

Role of adenosine A2A receptor antagonists in the treatment of Parkinson's disease

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ABSTRACT

In Parkinson's disease (PD), the traditional focus has been on bradykinesia, rigor and tremor, but non-motor symptoms such as gastrointestinal and sleeping disturbances, depression or cognitive deficits have gained increasing attention in recent times. Many of these non-motor symptoms respond but insufficiently to the classical, mainly dopaminergic, medication and thus substantially limit the quality of life of afflicted patients. This justifies searching for novel, effective and non-dopaminergic therapeutics. The adenosine A2A receptor antagonists were developed as just such a therapeutic option because adenosine A2A receptors are non-dopaminergic and are localized selectively in the basal ganglia. This introduces the additional possibility of modulating striato-thalamo-cortical loops. In 2013 an adenosine A2A receptor antagonist was already approved in Japan as an add-on to levodopa, and then in 2019 in the USA. In this review we hope to outline (1) the theoretical and mechanistic basics of this therapeutic approach as well as (2) the current data on its effectivity for both motor and non-motor symptoms and in addition (3) its potential neuroprotective effect.

KEYWORDS: Parkinson's disease, non-motor symptoms, adenosine A2A receptor antagonists.

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Introduction

Parkinson's disease (PD) induces a progressive neurodegeneration, which ascends upward from the dorsal vagal nucleus to locus coeruleus, and the substantia nigra and may throughout this course involve the basal forebrain and neocortical areas [1]. The decline of neurons in the substantia nigra which project to the striatum causes a deficiency of dopamine which essentially contributes to the cardinal symptoms of PD: bradykinesia, rigor, tremor and postural instability [2]. Thus the symptomatic therapy (via medication that either induces an increase in dopamine levels such as levodopa, dopamine agonists or inhibits its depletion) has constituted the backbone of Parkinson therapy [3]. After an initial honeymoon phase in which deficits respond well, increasingly higher doses of the medication are required in the course of the disease to attain symptom control while at the same time the therapeutic windows decline. This leads to increasing levels of limitations in daily life due to intermittent on and off phases with dyskinesia associated with vacillating between symptom aggravation and adequate motility [2].

Non-motor symptoms present a therapeutic challenge

In recent years non-motor symptoms of PD have been attracting increasing attention: Complaints of constipation, REM-sleep disturbance or hyposmia are often observed years in advance of the

manifestation of initial motor deficits. In the course of PD, pains, anxiety, depression and daytime drowsiness can come into focus and constitute a personally relevant, but nonetheless frequently under-diagnosed strain on the patients [4-6]. But in contrast to the motor deficits, the non-motor symptoms usually do not issue from a dopaminergic deficit but rather a deficiency in other neurotransmitters such as norepinephrine (due to degeneration in the Locus coeruleus), serotonin (degeneration of the Raphe) or acetylcholine (degeneration in the basal forebrain). This explains why non-motor complaints frequently only partially respond to the dopaminergic therapy [4, 7]. The number and the effectivity of treatment options for these non-motor deficits are generally limited such that here there is growing concern both among the patients as well as the attending medical practitioners [7]. In recent years the primarily non-dopaminergic therapeutic agents such as the selective adenosine A2A receptor antagonists have thus attracted more and more attention as potential therapy options for both non-motor and motor deficits [8, 9].

The physiological role of the adenosine A2A receptor and its influence on motor and non-motor complaints in PD

Extracellular adenosine (which originates in the dephosphorylation of adenosine triphosphate, adenosine diphosphate and adenosine monophosphate) functions as a ubiquitous excitatory neuromodulator in the nervous system and is released by both neurons and glia cells. It modulates the release of dopamine, serotonin, acetylcholine, GABA, adrenaline and noradrenaline [10-13]. Adenosine receptors are sub-classified into the four subtypes: A1, A2A, A2B and A3 [14]. While A1, A2B and A3 receptors are expressed almost ubiquitously in the brain, A2A receptors are localized mainly in the striatum and to a lesser degree in the Nucleus accumbens, the Tuberculum olfactorium and the Globus pallidus [8, 15]. In the striatum they are limited to the medium spiny neurons and together with the D2 receptors (likewise expressed on these cells but in an inverse mode of action) they modulate the GABAergic inhibitory striato-pallidal loops which play an essential role in the development of motor and non-motor deficits [8, 16]. Adenosine is furthermore involved in the management of the sleep-wake cycle and modulates the cortico-striatal release of glutamate by means of the A2A receptors and thereby has direct influence on synaptic plasticity [17, 18]. The symptomatic therapeutic approach derives from the blockade of these receptors through the expression of A2A receptors in key regions for PD with modulation of several transmitter systems

Influence of A2A receptor antagonists in motor behavior

Motor performance is subject to regulation through activity of the basal ganglia loop. Special importance in PD adheres to (1) the striato-nigral pathway, the direct pathway, (which is regulated by dopamine D1 receptors) as well as to (2) the striato-pallidal (or indirect) pathway which functions antagonistically. Whereas the direct pathway supports the expression of motor behaviour (“Go”), the indirect pathway suppresses undesired movements (“No-Go”) [19, 20]. In PD the progressive decline of the nigral dopaminergic neurons leads to an increasing loss of dopamine which then causes an imbalance with (1) lower excitatory levels in the direct pathway and (2) increased inhibitory activity in the indirect pathway [21]. In summary, a reduction in activity in loops which support movement (Go) and an increased level in loops inhibiting movement (No-Go) occur simultaneously [22-24].

The activation of the striatal A2A receptors leads to a reinforcement of the “No-Go” signal by means of (1) an increased level of excitability of the indirect path in parallel with (2) a reduction in D2 activity [18, 24]. In PD an upregulation of the striatal A2A receptors has been described which is particularly distinct in patients with levodopa-induced dyskinesia [25]. The therapeutic mode of action of A2A receptors is especially based on the functional, receptor-mediated, dual excitatory modulation of the striato-pallidal GABAergic system and thus attenuates the pathologically strong “No-Go” signal [24]. This has been corroborated in the 6-OHDA model of Parkinson in rats (as opposed to non-lesioned animals) in which an increased level in GABA in the Globus pallidus externus was found which was

subsequently reduced after applying the A2A receptor antagonist istradefylline [26]. After administering levodopa in addition to an A2A receptor inhibitor, thus causing an additional stimulation of the D1 (direct) and D2 (indirect) receptors, a functional normalization of the basal ganglia loop can at least theoretically result (Figure 1) [24].

In monkeys treated with MPTP the administration of A2A receptor antagonists (in addition to levodopa or dopamine agonists in sub-therapeutic doses) induced a reduction in motor deficits without increasing the dyskinesia already present. This indicates, first, a reinforcing effect for the dopaminergic therapy, but secondly it suggests a possible extension of the therapeutic window through the A2A receptor antagonists [27-29].

In recent years medications such as istradefylline, tozadenant or preladenant have been introduced. They possess a high degree of selectivity and affinity and block adenosine A2A receptors. The positive effect on motor deficits which has been observed in animal models has been confirmed in numerous clinical studies. The combined administration of A2A receptor inhibitors with L-Dopa or D2 receptor agonists amplifies the therapeutic effect of these preparations and reduces off time [30-45]. In multicenter, double-blind, placebo-controlled studies with altogether more than 3,000 participants, istradefylline (as an add-on for dopaminergic medication) reduced the daily off time of the patients [34-39, 46-48]. In an open study with 14 participants a positive effect was observed for freezing of gait (as measured with the Freezing of Gait Questionnaire) [49]. The most frequent side effects were involuntary muscle twitching (dyskinesia), dizziness, constipation, nausea, hallucinations and insomnia [50, 51]. Serious side effects were not observed [52].

Two clinical studies confirmed a synergistic effect for tozadenant with dopaminergic medications in

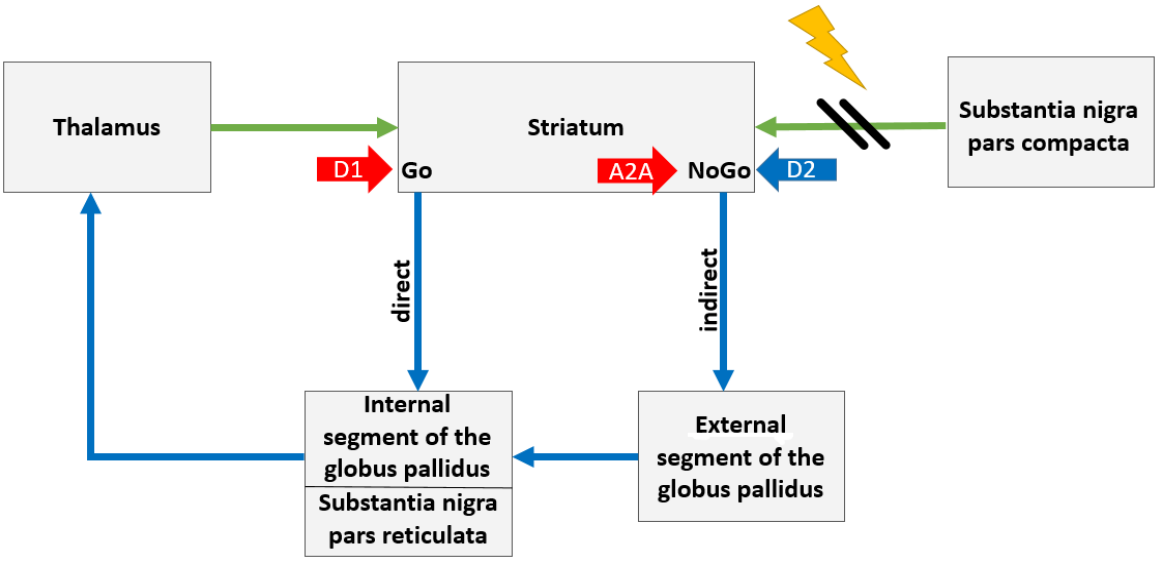

Figure 1. Schematic representation of the basal ganglia-thalamic-cortical loop with the pathways involved in PD focusing on the direct Go and - indirect NoGo pathway. The green arrows represent excitatory glutamatergic connections and the blue inhibitory GABAergic connections. The thick arrows represent the targeted receptors in drug therapy for Parkinson's disease. While the function of the direct Go pathway is restored after administration of dopamine via D1 receptors, the restored dopaminergic D2 stimulation is still opposed by a pathologically increased A2A receptor effect. Only the additional administration of an A2A receptor blocker leads to a reconstitution of the basal ganglia loop. The yellow lightning visualizes Parkinson's disease-related nigrostriatal degeneration. A2A, adenosine A2A receptor activation; D1, dopamine D1 receptor activation; D2, dopamine D2 receptor activation. Adapted from [21, 24].

Parkinson patients [45, 53]. Further work, however, was discontinued due to undesirable events during the development phase [52]. In a placebo-controlled phase IIb study preladenant reduced the off time in patients [54], but in the subsequent phase III studies the results could not be consistently confirmed. In two studies in which preladenant was administered as monotherapy, it could not be shown to be superior to placebo. The most frequent side effects were found to be dyskinesia and obstipation.

Influence of the A2A receptor antagonists on depression

In addition to improving motor behavior under A2A receptor antagonists there are indications that depressive disorders presenting in PD can also be improved on. Thus, administering caffeine (as a naturally occurring, non-selective, competitive A1 and A2 receptor antagonist) in a rat model leads to an increased release of dopamine and glutamate in the Nucleus accumbens [13]. In a mouse and rat model administering istradefylline both as monotherapy and as in combination with sub-therapeutic doses of antidepressants, administering istradefylline led to a reduction of depressive behaviors [55-58]. In an open study of 12-week duration with 30 Parkinson patients the positive results confirmed those in the animal experiments. Thus, after administering istradefylline a significant improvement could be seen in the Snaith-Hamilton Pleasure Scale Japanese version (SHAPS-J), the Apathy Scale and the Beck Depression Inventory (BDI), independent of motor impairment. This suggests that the antidepressive effect was not only due to the improvement in motility but to some other mechanism, for example the release of dopamine and glutamate in the Nucleus accumbens [59].

Influence of A2A receptor antagonists on daytime sleepiness

Adenosine modulates sleep rhythm and is released when the body has been awake for a longer length of time [60]. The sleep-promoting effect of adenosine is mainly mediated by A2A receptors, which has been demonstrated in animal experimentation and in the corresponding A2A knock-out models. Thus the A2A agonist CGS21680 induces sleep in wild type and A1A knock-out mice, but not in A2A knock-out mice [61]. Contrariwise, the wake-promoting effect of caffeine fails to appear in A2A receptor knock-out mice [62]. In two different smaller open studies with 14 and 22 patients an improvement in daytime drowsiness (as measured by the Epworth Sleepiness Scale) was observed although night sleep (as measured by the PD sleep scale) was not disrupted [49, 63].

Influence of A2A receptor antagonists on cognitive deficits

Treatment options for cognitive deficits in PD are limited in number and are based on medications that were developed for forms of dementia, such as rivastigmine [64]. In a mouse model it was shown that A2A receptors are involved in the development of cognitive deficits and that, vice versa, the application of A2A receptor antagonists does in fact lead to an improvement in performance in several cognitive domains, in particular memory and goal-directed behavior [65-68]. The secondary analysis of a placebo-controlled study with altogether 40 patients revealed no significant difference between istradefylline und a placebo in the Stroop Test, Trail Making Tests (Part A), or CVLT-II. A significant improvement was only observed for the Trail Making Test Part B Error Scale in the istradefylline group [32] so that, in summary, in spite of highly promising data from the animal model no reliable conclusions as to the effect of A2A receptor antagonists in humans can yet be made.

Influence of A2A receptor antagonists on neuroprotection

Caffeine intake is associated with a lower risk of PD on a population basis, but this effect is weaker in women than in men and, in the mouse model, is reversed by estrogen [69-71]. The influence of caffeine on the rate of progression is less clear: While a prospective study with 79 patients and a four-year follow-up demonstrated an association between stronger caffeine consumption and a slower rate of progression, this effect could not be confirmed in two larger studies (n = 413 and n = 1549) with a follow-up of one or five years [72-74]. In an animal model the administration of selective A2A receptor antagonists induced

a decrease in neurodegeneration in the Substantia nigra, pars compacta in rats after being treated with rotenone. Further possible neuroprotective effects have been described in animal models [75, 76]. Human clinical studies which could positively demonstrate neuroprotection as a result of treatment with these A2A receptor antagonists are not yet available to date. The difficulty lies in the fact that studies on neuroprotection theoretically would best be initiated on patients with an increased risk for Parkinson's who have however not yet been diagnosed with the disease and who would then be subjected to a long-term treatment regimen [76]. The potential neuroprotective effect of the A2A receptor antagonists is of course intriguing, but not yet sufficiently studied scientifically.

An outlook

The A2A receptor antagonists represent an important, novel therapy option in PD and favourably influence not just motor impairment but also alleviate non-motor symptoms. Intriguing topics involve possible neuroprotective effects, as indicated by animal experimentation, as well as the possibility of positive effects on cognition, which should be examined in clinical studies with PD patients.

CONFLICT OF INTEREST STATEMENT

NS is a speaker for Abbvie and WJ is a speaker and advisor for Abbvie, Bial, Desitin, UCB, and Zambon.

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