Adenosine A2A Receptor Antagonists in Neurodegenerative Diseases: Huge Potential and Huge Challenges

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Keywords: neuroprotection, astroglia and microglia, neuronal death, Alzheimer's and Parkinson's disease, human, clinical trials as topic, caffeine

BACKGROUND

In this opinion paper, we provide scientific-based reasons about the huge therapeutic potential of adenosine A2A receptor antagonists, and about the huge challenges to demonstrate efficacy in clinical trials, i.e., to provide data now required to approve a new medication by the regulatory bodies, such as U.S. Food and Drug Administration (FDA).

Adenosine is an autacoid present in all tissue and body fluids. Adenosine, whose extracellular concentration is controlled by producing/degrading enzymes and by nucleoside transporters, acts via four (A1, A2A, A2B, and A3) specific cell surface receptors that belong to the superfamily of G-protein-coupled receptors. For decades, adenosine receptors have shown promise as targets of medications for a variety of ailments. Until recently, however, the only approved medicine was adenosine itself, i.e., the endogenous agonist, to combat arrhythmias, such as paroxysmal supraventricular tachycardia (1–3). Prospects are changing as the first medication targeting selectively the adenosine A2A receptor has been approved few years ago in Japan. The recently approved drug is an antagonist, i.e., a receptor blocker (see later). A2A receptor antagonists show promise in neuroprotection, although for Huntington’s or Niemann Pick’s diseases it is suggested that antagonists may be detrimental and/or there is controversy on which is the efficacious intervention, i.e., receptor activation or blockade [see Ref. (4–9) and references therein].

POTENTIAL OF A2A RECEPTOR LIGANDS IN THE THERAPY OF NEURODEGENERATIVE DISEASES

At present, not only the A2A receptor (A2AR) is at the center stage for increasing the therapeutic tools in a variety of clinical indications, but this opinion paper focuses on the A2AR antagonists, which shows promise in immune-mediated control of cancer progression (10–13), in atrial fibrillation (14, 15), and in fighting against neurodegenerative diseases (see later). It is relevant that virtually all the selective A2AR antagonists whose toxicity has been tested in animal models are very safe. Safety has been confirmed in the clinical trials performed using different structures [e.g., Ref. (16, 17)]. Istradefylline (KW-6002) is one of the most studied antagonists; it is safe and efficacious in Parkinson’s disease. Accordingly, it was approved in Japan in 2013 for adjunctive treatment of Parkinson’s patients (under the Nouriast™) (18–20). To our knowledge, up to five clinical trials with different antagonists were or are being undertaken (18, 21), but none of them has yet got the approval by the U.S. FDA. In our opinion, the two main reasons of the difficulties in translating very promising preclinical assays into medications are (i) the tight requirements and (ii) the urgent

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Edited by:
Manuela P. Kaster,
Universidade Federal de Santa Catarina, Brazil

Reviewed by:
Filipe Marques Goncalves,
Albert Einstein College of Medicine, United States

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Specialty section:
This article was submitted to Neurodegeneration, a section of the journal Frontiers in Psychiatry

Received: 28 October 2017
Accepted: 19 February 2018
Published: 12 March 2018

Citation:
Franco R and Navarro G (2018) Adenosine A2A Receptor Antagonists in Neurodegenerative Diseases: Huge Potential and Huge Challenges. Front. Psychiatry 9:68. doi: 10.3389/fpsyt.2018.00068
need of efficacious approaches to assess neurodegeneration/neuroprotection in humans. It is commented in drug discovery forums that quite a number of current drugs could not pass today the tight requirements posed by the regulatory bodies. The issue of assessing how to measure the neuroprotective efficacy of a drug is commented later.

Parkinson’s and Alzheimer’s are the most extended neurodegenerative diseases in modern societies with high life expectancy (22, 23). With some exceptions of early-onset symptoms (24), age is the main factor for triggering the clinical symptoms (25–28). Whereas, Parkinson’s disease patients have successful dopamine-replacement therapies and other tools that may be used in the disease progression or to decrease the appearance of the medication side effects (29–31), Alzheimer’s disease patients have not yet got any really efficacious therapeutic drug/tool (32, 33).

Clinical manifestation of Parkinson’s disease occurs when a significant number of nigral dopamine-producing neurons have disappeared. Natural aging leads to 18% of loss of tyrosine hydroxylase-positive neurons in the nigra, whereas the degree of denervation in patients is very wide, going from 50 to 90%, even shortly after diagnosis (34). In this study in post-mortem samples, the authors state: “with several of the short-duration subjects showing comparable, severe loss of tyrosine hydroxylase-positive neurons to that seen in subjects 20 years, post-diagnosis” (34). The idea behind the use of A2AR antagonists in this disease is the adenosine-dopamine antagonism (35–37) in the striatum, where the expression of A2ARs is highest in the whole mammalian body (38). Therefore, dopamine-replacement therapy may be potentiated by the blockade of the A2AR. Indeed, Nouriast™ may serve to achieve efficacy of dopamine-replacement therapies at lower levels of dopaminergic drugs, such as levodopa. But the key point is that whereas levodopa is not neuroprotective, several preclinical assays indicate that A2AR antagonists show neuroprotective effects [see Ref. (39–42)]. Moreover, transgenic A2AR animals are more resistant to neurodegeneration induced by either 1-methyl-4-phenyl-1,2,3,6-tetra-hydropyridine (MPTP)-induced nigral lesion or focal cerebral ischemia (43–46). Further to those preclinical results, epidemiological studies showed that caffeine, which is a mixed/non-selective adenosine receptor antagonist, decrease the risk of suffering from Parkinson’s or from Alzheimer’s diseases [(47, 48); see Ref. (49) and references therein for review]. In summary, one challenge for the progression of A2AR antagonist into approved drugs is to demonstrate neuroprotection in humans, for instance to decrease the death rate of nigral dopaminergic neurons.

CHALLENGES IN DEVELOPING NEUROPROTECTIVE A2AR ANTAGONISTS

The two sides of drug action, i.e., addressing symptoms and disease progression, should be considered for any drug type (A2AR antagonists in this article). Whereas in the case of Parkinson’s disease, the targets of antagonists in adjunctive treatments of dopamine-replacement therapies are A2AR receptors in neurons, the A2A receptor containing targeted cells in the MPTP model of Parkinson’s disease that could be responsible for the neuroprotective action could not be determined in transgenic animals with cell-type-specific (conditional) deletion of the receptor (46). In this scenario, and based in convergent and wide experimental evidence, we consider that the role of the A2A receptor expressed in microglia should not be neglected. Hence, another challenge is to select (for a given disease) the receptor to be targeted, but also the cell where the receptor must be targeted and/or when the receptor of a given cell (neuron or glia) must be targeted to afford neuroprotection. Years ago, we found a relevant A2AR-related side result on studying gene expression in samples from Alzheimer’s patients. Genomics-relevant results were upregulation in samples from patients of the Kv3.4 voltage-gated potassium channel (51) and of the adenosine A1 receptor (52). Interestingly, when we moved to perform immunostaining
in the cerebral cortex and hippocampus from necropsies of Alzheimer’s disease (AD) patients, we confirmed the upregulation of the adenosine A2A receptor concomitant with a change in the pattern of expression. The receptor was found inter alia in degenerating structures, i.e., in both dystrophic neurites and neurons exhibiting neurofibrillary tangles. Whereas, specific mRNA expression in the assayed brain areas was not different from that found in control samples, the microglial expression of the protein was negligible or absent in control samples but was evidently expressed in microglial cells in both the cerebral cortex and the hippocampus of patients (52).

Function of immune cells in the periphery and of microglia in the CNS is regulated by the A2AR. Due to the extensive work of M. Sitkovsky’s and other laboratories devoted to targeting adenosine receptors to combat cancer, the already promising immunotherapy to combat certain tumor types, may be enhanced by the blockade of A2AR expressed in immune cells (10–12). Provided that ATP is degraded to adenosine in oxygen partial deficiency and/or cell death occurring in degenerating environments, increased adenosine levels activate upregulated microglial A2A Rs. Therefore, an obligate drug discovery approach is to target those cells and those receptors that promote M2-skewed microglial responses.

We highlight microglia as the most likely cell type to be targeted (for neuroprotection) by A2AR antagonists. Straightforward data in different models, support the view that A2AR activation in glia drives neuroinflammation and, therefore, the selective blockade of this receptor may be neuroprotective (40, 53–58). We think that more experimental effort is required to define when and how A3A,R antagonists may achieve conversion from M1-skewed (proinflammatory) to M2-skewed (neuroprotective) microglia, something that requires control of the production of cytokines/chemokines, interferon-gamma, etc. [see (59) for review]. Intrinsically to any transformation, in this case into M1 or into M2 cells, there is a time window of opportunity whose starting point and duration should be also explored. In other words, when to start the application of the intervention and when it is too late.

We would like to end this paper with a further opinion, which A3A,R antagonists may “conceptually” be the new beta-blockers (β-adrenergic antagonists) whose therapeutic potential is vast from cardiovascular problems to asthma.

**AUTHOR CONTRIBUTIONS**

The two authors participated in the conceptual design of this opinion article. RF did literature search. The two authors contributed to the writing and carefully checked English spelling/grammar.

**FUNDING**

Partially supported by grant BFU-2015-64405-R from Spanish Ministry of Economy and Competitiveness (may include EU FEDER funds).

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**Conflict of Interest Statement:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.