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Review

Adenosine receptors and brain diseases: Neuroprotection and neurodegeneration ☆

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ABSTRACT

Adenosine acts in parallel as a neuromodulator and as a homeostatic modulator in the central nervous system. Its neuromodulatory role relies on a balanced activation of inhibitory A_1 receptors (A1R) and facilitatory A_{2A} receptors (A2AR), mostly controlling excitatory glutamatergic synapses: A1R impose a tonic brake on excitatory transmission, whereas A2AR are selectively engaged to promote synaptic plasticity phenomena. This neuromodulatory role of adenosine is strikingly similar to the role of adenosine in the control of brain disorders; thus, A1R mostly act as a hurdle that needs to be overcame to begin neurodegeneration and, accordingly, A1R only effectively control neurodegeneration if activated in the temporal vicinity of brain insults; in contrast, the blockade of A2AR alleviates the long-term burden of brain disorders in different neurodegenerative conditions such as ischemia, epilepsy, Parkinson's or Alzheimer's disease and also seem to afford benefits in some psychiatric conditions. In spite of this qualitative agreement between neuromodulation and neuroprotection by A1R and A2AR, it is still unclear if the role of A1R and A2AR in the control of neuroprotection is mostly due to the control of glutamatergic transmission, or if it is instead due to the different homeostatic roles of these receptors related with the control of metabolism, of neuron–glia communication, of neuroinflammation, of neurogenesis or of the control of action of growth factors. In spite of this current mechanistic uncertainty, it seems evident that targeting adenosine receptors might indeed constitute a novel strategy to control the demise of different neurological and psychiatric disorders. This article is part of a Special Issue entitled: "Adenosine Receptors".

Contents

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1. Introduction

The role of adenosine as an extracellular signalling molecule begun with the seminal observations by Szent-Gyorgy on the ability of purines to control the functioning of the heart [1]. This was later followed by a series of studies carried out by Rob Berne relating changes in the extracellular levels of adenosine with the function and dysfunction of this same organ (reviewed in [2]). The discovery that methylxanthines acted as antagonists of adenosine receptors [3] represented a crucial step to establish the idea that adenosine indeed acted as an extracellular signalling molecule operating selective receptors. One such methylxanthine is caffeine, the most widely consumed psychoactive drug worldwide, which was proposed to mostly act as an antagonist of adenosine receptors [4]. Given that caffeine mostly triggers phenotypic modifications related to brain function [4], a major emphasis was directed towards a better understanding of the role of adenosine receptors in the control of synaptic transmission, which were first described by Ginsborg and Hirst [5].

2. Double role of adenosine as a neuromodulator and as a homeostatic modulator

This short historical background is particularly important to stress the dual role fulfilled by extracellular adenosine in the nervous system. On one hand, as shall be detailed in the next section, adenosine has a particular role as a neuromodulator, controlling the flow of information through neuronal circuits. This function is rather restricted to the nervous system. However, it should always be kept in mind that adenosine also fulfils another more general role in all eukaryotic cells acting as a homeostatic modulator (see [6,7]). Thus, the extracellular levels of adenosine convey paracrine signals designed to coordinate metabolic activity in groups of cells forming a tissue, thereby allowing a trans-cellular coordinated response to changes in the workload of the tissue. This homeostatic regulatory role of adenosine also occurs in brain tissue, where adenosine fulfils a double role of neuromodulation as well as of homeostatic coordination and it is often difficult to disentangle both functions.

3. Effects of adenosine on brain function

Albeit there are four adenosine receptors (A1R, A2AR, A2BR and A3R), the higher density of A1R and A2AR in the brain, together with the generally modest impact on brain function of manipulations of A2BR and A3R function, has led to the idea that the impact of adenosine on brain function might mostly depend on the actions of A1R and A2AR [8].

The most evident effect of adenosine in neuronal circuits of adult mammals is to selectively depress excitatory transmission [9]. This occurs through the activation of A1R, which are located both presynaptically, postsynaptically and nonsynaptically [8]. This inhibition of excitatory, but not inhibitory [10–12], synaptic transmission is mostly due to presynaptic A1R [11,13–16], in accordance with the enrichment of A1R in synapses, mainly in excitatory synapses [17–19]. The mechanism of A1R-mediated inhibition of synaptic transmission is considered to rely on the coupling of A1R to the inhibition of N-type calcium channels (e.g. [20,21]) thus decreasing stimulus-evoked release of glutamate in central synapses (e.g. [9,22]). However, presynaptic A1R can also decrease miniature events in excitatory synapses and this effect was proposed to depend on a direct ability of presynaptic A1R to down-regulate the sensitivity of the release apparatus [15,16,23,24]. When considering more integrative properties of neuronal circuits, it is likely that the role of postsynaptic and nonsynaptic A1R might become of particular interest. Thus, A1R are located in the postsynaptic density [17], where they can influence the responsiveness to excitatory stimuli by a simultaneous control of N-type calcium channels and NMDA receptors [25,26]. A1R in neuronal cells are also located nonsynaptically where they control potassium current leading to neuronal hyperpolarization [27]. Finally A1R also have non-neuronal localizations modulating both astrocytic and microglia-related functions in brain tissue [28–30].

This prominent inhibitory role of adenosine in the control of 'basal' synaptic transmission (i.e. under conditions where synaptic plasticity is not engaged) has largely clouded the effect of A2AR in the control of brain function. This was further aggravated by the widespread idea that the localization of A2AR in the brain was restricted to the basal ganglia (e.g. [31]). Instead, A2AR are now recognised to display a widespread distribution in the brain [8] and are mostly located in synapses [32]. They seem to have limited impact on the control of 'basal' synaptic transmission but play a crucial role in controlling synaptic plasticity (reviewed in [33]). Thus, presynaptic A2AR can control the release of glutamate and play a major role in shutting down the profound A1R-mediated inhibition of synaptic transmission [34,35], which would otherwise preclude the possibility of enhancing synaptic efficiency upon increasing neuronal activity. Postsynaptic A2AR can control NMDA receptors [36–38], which provides a mechanistic basis to understand the observations that the pharmacological or genetic blockade of A2AR can attenuate long-term potentiation at different excitatory synapses [37,39]. A particularity of A2AR is their striking ability to undergo increases in expression and density upon noxious conditions (reviewed in [40]), both in neurons (e.g. [41]) as well as in glial cells [42]. Accordingly, A2AR can affect glial reactivity and control neuroinflammatory processes [43–47], in line with the key role of A2AR as a STOP signal of the immune-inflammatory system acting peripherally (reviewed in [48]). A2AR are also located in endothelial cells of brain capillaries, where they play an important role in controlling brain vascular function (reviewed in [49,50]). The scope of action and effects of A2AR may be considerably broader in view of their ability to heteromerise with different other G protein-coupled receptors, such as dopamine D2, metabotropic glutamate type 5 and cannabinoid CB1 receptors (for reviews see e.g. [51,52]).

It is also important to mention that both A1R and A2AR [53–55], as well as caffeine [56], can affect brain metabolism. It is still unclear to what extent this metabolic control in brain tissue is related to the neuromodulatory role of adenosine or represents a trait of the general homeostatic role of adenosine observed in different types of eukaryotic cells [57–60]. But this ability of adenosine receptors to control metabolic activity is expected to play a potentially relevant role in the control of both physiological and pathological brain adaptive changes, which are highly dependent on adequate metabolic support.

4. Role of adenosine in different brain disorders

In view of the involvement of glutamate-associated excitotoxicity in the aetiology of different brain disorders [61], the ability of adenosine A1R and A2AR to control excitatory transmission prompts considering this neuromodulation system as a putative therapeutic target to manage brain disorders. This interest is further bolstered by recurrent observations showing that the extracellular levels of adenosine are modified upon brain damage. Thus, albeit the extracellular levels of adenosine increase with neuronal activity [62], they increase to considerable higher levels when brain damage occurs [63]. This probably results from the increased use of ATP to attempt preserving cell viability, which leads to a disproportionally higher formation of adenosine (reviewed in [7]). Clearly, the clarification of the metabolic and cellular sources of extracellular adenosine is still unclear (discussed in [8]). However, the available data consistently shows that noxious brain stimuli enhance the extracellular levels of adenosine.

4.1. Ischemia

By analogy with the pioneering studies of Berne's group in the heart, hypoxic or ischemic conditions trigger a robust and sustained enhancement of the extracellular levels of adenosine in the brain parenchyma, *in vitro* brain preparations or cultured neurons (e.g. [64,65], reviewed in [63]). A major interest was focused on the potential role of A1R in the control of brain damage upon ischemia in view of the ability of these A1R to control several events that have been associated with ischemic damage, namely the control of calcium influx, the control of glutamate release, the control of membrane potential and the control of metabolism (reviewed in [66–69]). Indeed a role for A1R was confirmed; thus, either A1R agonists or the use of inhibitors of adenosine re-uptake or metabolisation (mainly through adenosine kinase but also through adenosine deaminase) generally tends to decrease the extent of ischemic brain damage ([70–73], reviewed in [69]). In contrast, the blockade of A1R generally tends to exacerbate ischemic brain damage (reviewed in [69]). However, these manipulations are only effective if made in the immediate vicinity (shortly, i.e. within circa 6 h, before or after the ischemic insult), whereas chronic manipulation of A1R function caused paradoxical effects [68,74].

This decreased function of brain A1R after ischemia is accompanied by a decreased density of brain A1R after ischemia (e.g. [75–77]) and is now thought to result from the desensitization of A1R; in fact, oxygen deprivation causes a rapid down-regulation of A1R function, which is dependent on the enhanced levels of adenosine and continuous activation of A1R (e.g. [78–81]). However, this loss of function of A1R after ischemic insults should not undermine the interest of A1R as a potential therapeutic target in ischemic conditions. In fact, the group of Detlev Boison provided exciting evidence supporting that an adequate control of the adaptive changes of adenosine metabolism, through the inhibition of adenosine kinase, could provide a novel strategy to bolster a sustained A1R activation [82,83]. These studies clearly illustrate that the adenosine modulation system should be seen as a whole and studied as a whole, being senseless to attempt separating the study of adenosine receptors from that of adenosine metabolism. These studies also provide an *in vivo* confirmation of the key role of the A1R as a gate-keeper of neuronal damage, acting as a hurdle for the initiation of brain damage upon noxious insults (discussed in [84]). The idea that A1R might indeed be crucial to define the threshold of sensitivity of the tissue to ischemic damage is further emphasised by the observation that A1R play a key role in the cascade of events that underlie ischemic preconditioning [85–88], the process by which a sub- or near-threshold ischemic insult sets a cascade of events (namely bolstering A1R function) that decreases damage to a subsequent more intense insult. Clearly an aspect that remains to be clarified is the mechanism by which A1R might control the impact of oxygen shortage on neuronal viability. Several groups directed their efforts towards exploring if this neuroprotection was associated with the function of synaptic A1R (e.g. [89–91]). However, the observation that A1R also prevent ischemia-induced cytotoxicity in non-neuronal tissues [57–60] might suggest that A1R-mediated control of ischemic damage could involve a more general mechanism common to neurons and other cell types.

Apart from this novel breath in the interest of indirectly manipulating A1R function (through inhibition of adenosine kinase) to control ischemic damage, most of the efforts are now being directed to the exploitation of the role of A2AR in the control of ischemic brain damage (reviewed in [40,92]). The involvement of A2AR in ischemic brain damage was described nearly in parallel by the group of John Phillis and that of Ennio Ongini at Schering-Plough; they first found, somehow serendipitously, that the blockade of A2AR afforded a robust protection against ischemic brain damage [68,93–95]. This was later confirmed in experiments carried out by Jiang-Fan Chen, showing that the genetic elimination of A2AR conferred a robust protection against ischemic brain damage [96]. Subsequently several studies in different brain preparations indeed confirmed that the pharmacological or genetic blockade of A2AR consistently decreased the infarted area and/or the outcome (neurological score) upon ischemic insults (see references in [40,92,97]).

Although the available data is strikingly consistent in indicating an important role for A2AR in the control of ischemia-induced brain damage, there are still several open questions before attempting any translational application of this idea. In fact, it still remains to be explored what is the time window of opportunity for the manipulation of A2AR, namely if blocking A2AR might solely be considered a prophylactic strategy or if it might also have some therapeutic potential (see discussion in [98]). Also, the clarification of the mechanisms underlying this ability of A2AR to control ischemia-induced neuronal damage should be tackled to ensure a sustained translational rationale; in fact, different manipulations in animal models have supported the possible participation of different mechanisms, either controlling glutamate release [99,100], central inflammatory processes and glial reactivity [42,101,102] or the permeability of the blood-brain barrier [103,104] and infiltration of peripheral myeloid cells [105]. However, the recent pioneering studies showing that caffeinol improves stroke recovery [106], as well as post-traumatic injury [107] are certainly an exciting (albeit certainly indirect) suggestion prompting further investigation of the potential therapeutic effects of A2AR blockade to manage the post-ischemic recovery of brain function.

4.2. Epilepsy

Epilepsy corresponds to a series of disturbances of neuronal firing, often accompanied by bursting encephalographic activity with the appearance of paroxysmal depolarisation shifts [108]. Seizures have traditionally been viewed as an imbalance between excitatory and inhibitory transmission in brain circuits, where hyper-excitation or hypo-inhibition would result in an abnormal repetitive firing of affected brain circuits [109]. The potential of adenosine as an anti-epileptic substance [84,110–113] has emerged on the basis of two parallel observations: first, A1R are enriched in excitatory synapses, where they inhibit glutamate release, decrease glutamatergic responsiveness and hyperpolarise neurons, all desirable actions to decrease the hyper-excitability associated with epilepsy; second, the levels of endogenous extracellular adenosine rise upon seizure activity [114,115], which could be taken as an indication that adenosine would play a key role as an endogenous anti-epileptic compound. Accordingly, a wealth of studies have confirmed that the acute administration of either agents enhancing the extracellular levels of adenosine (inhibitors of adenosine transporters or of adenosine metabolism) or agonists of A1R attenuated seizure and/or convulsive activity in different animal models; conversely, the acute administration of either non-selective antagonists of adenosine receptors (such as caffeine or theophylline) or selective A1R antagonists enhance the duration and severity of seizures and/or convulsions (reviewed in [84,110–113]). Thus, it seems evident that A1R effectively constitute a hurdle curtailing seizure activity, which is further confirmed by the ability of A1R to control the spreading of seizure activity [116] and the greater susceptibility of A1R knockout mice to epilepsy [116–118]. Interestingly, this A1R-mediated control of epilepsy has recently been proposed to be a possible link for the anti-epileptic effect of ketogenic diets [119].

However, several studies have now identified a decreased density and efficiency of synaptic A1R in models of epilepsy [17,18,120–122]. Thus, the A1R-operated inhibitory system seems to act as a continuously active gate-keeper or hurdle to avoid initiating a seizure-like event; once this hurdle is overtaken, then there is a desensitization of this A1R system. Furthermore, the long-term consumption of moderate doses of caffeine (0.3 g/L) was found to prevent neuronal damage in different models of epilepsy [123–125]. Thus, in spite of the ability of chronic caffeine

consumption to upregulate cortical A1R [56,126], the partial but chronic blockade of adenosine receptors by caffeine reveals a beneficial effect on seizure-induced neuronal damage. These observations prompt two conclusions. First, there seems to be a clear dissociation between the ability of A1R to control glutamatergic transmission and to control other features present in epilepsy, which was directly documented in the case of pilocarpine-induced seizures [127,128]. Secondly, there is a suggestion that, probably, the greatest contributing factor for decreased function of the endogenous A1R-mediated inhibitory system might be the lack of adequate adenosine receptor tonus, which might be a result of the modified purinergic metabolism [82,113], namely a long-term reduction of the extracellular levels of adenosine [17], due to the robust increase of the expression and activity of ADK mainly in astrocytes [129,130], which seems to be a key event in the re-adaptation of the adenosinergic system [113]. Thus, albeit there is a decrease in the density of presynaptic A1R, their activation may still be an attractive and effective manner to restraint subsequent seizure activity in model of chronic 'epilepsy,' as testified by robust evidence showing that A1R are still able to efficiently control chronic epileptic-like conditions [113] and even pharmaco-resistant forms of epilepsy [131]; this might be better achieved by manipulating ADK rather than directly activating A1R using A1R agonists since the latter have profound cardiovascular peripheral effects (e.g. [132]). Interestingly, since ADK seems to be mostly an astrocytic enzyme in the adult and diseased brain [113], this consideration of ADK inhibitors as novel candidate anti-epileptic drugs clearly shifts the main focus of epilepsy from neurons to astrocytes (reviewed in [84,133]).

As occurred for ischemia-induced neuronal dysfunction and damage, an increasing number of studies on adenosine modulation of epilepsy are now shifting their focus from the better characterized inhibitory A1R system, to concentrate on the possible role of facilitatory A2AR in the control of epilepsy (reviewed in [84]). Interestingly, upon chronic epilepsy there is a robust increase (over 200%) of the density of A2AR [18]. Albeit the impact of A2AR on the onset of seizure activity is still disputable (reviewed in [84,112]), recent elegant studies make it evident that the blockade of A2AR, either using genetic deletion of A2AR or selective A2AR antagonists [134–136] or non-selective antagonists such as chronic caffeine administration [134] can afford a robust protection against the seizure evolving severity. Furthermore, chronic caffeine administration or A2AR blockade effectively prevents neuronal damage following convulsions [123–125,137] and seems to be a general indicator of favorable prognosis in diseases involving neurodegeneration [138,139]. Thus, A2AR seem to control the evolution and consequences of seizures, both seizure-beget-seizure and seizure-induced neurodegeneration, although the mechanisms involved (glial or neuronal) still remain to be clarified (reviewed in [40,84,92]). Interestingly, the source of the adenosine proposed to preferentially activate A2AR (ATP-derived adenosine formed through the ecto-nucleotidase pathway; reviewed in [7,140,141]) is also modified in 'epileptic' rodents; thus, there is a lower release of ATP and a modified extracellular catabolism of ATP [17,142–145], but more importantly, there is an augmentation of the density and activity of ecto-5′-nucleotidase [17,144–147], which is often the rate-limiting step in the formation of adenosine from extracellular ATP [140,148]. Thus, there seems to be an upregulation of A2AR as well as of the source of adenosine activating them and A2AR blockade seems to afford beneficial effects in animal models of epilepsy.

4.3. Huntington's disease

Huntington's disease (HD) is an inherited neurodegenerative disorder caused by a mutation of the gene which encodes for the protein huntingtin [149]. Normal huntingtin, whose function is not completely known, is associated with vesicular membranes, microtubules and several proteins involved in synaptic function [150,151], suggesting that mutated huntingtin likely alters synaptic transmission in HD [152,153]. Several studies support the original idea of Wong and coworkers [154] that cortico-striatal glutamatergic deregulation should be involved in HD pathogeny. Indeed, mutated huntingtin induces glutamatergic dysfunctions, namely: i) increases glutamate release and decreases astrocytic glutamate clearance [155,156]; ii) increases expression and activation of NMDA receptors (for a review see [157]); iii) induces changes in NMDA receptor subunits [158–160]; and iv) triggers mitochondrial dysfunctions secondary to glutamate-induced toxicity or impaired energy metabolism [161,162], among others.

This major deregulation of this cortico-thalamic afferent glutamatergic input would be the primary cause of the hallmark of HD, which is the degeneration of the major striatal neuronal population, the GABAergic medium-sized spiny neurons (MSNs). MSNs are divided into two distinct classes based on different anatomical and pharmacological criteria, as well as by the segregation of adenosine and dopamine receptors: dynorphinergic MSNs co-expressing A1R and dopamine D1 receptors and enkephalinergic MSNs co-expressing A2AR and dopamine D2 receptors. Both MSN sub-classes are driven by cortico-thalamic glutamatergic excitatory inputs and their relative responsiveness is controlled by dopaminergic inputs from the substantia nigra pars compacta (SNc) [163], which determines the subsequent control of motor function. MSNs constantly receive inputs from cortical glutamatergic terminals, but remain hyperpolarized by mechanisms such as presynaptic inhibitory modulation in glutamatergic terminals, operated by A1R, D2 or GABA-B receptors among others [164–169] and postsynaptic inwardly rectifying K^+ channels [170], both preventing depolarization. Continued exposure to glutamate and persistent opening of NMDA channels, make MSNs vulnerable to excitotoxic damage. As deregulation of glutamate transmission occurs, morphologic and functional (plastic) synaptic changes take place, namely a down-regulation of inhibitory presynaptic receptors and a decrease of the area of the soma, dendrites and dendritic spines of MSNs (for a review see [171]); these changes have an impact on the number of functional K^+ channels responsible for the hyperpolarization of MSNs. Altogether, the referred changes contribute to depolarization at rest and amplification of excitatory inputs. Furthermore, as the postsynaptic area decreases, extrasynaptic receptors, which often display different functional properties from synaptic ones, become prominent. This is the case for NMDA receptors, which extrasynaptically worsen cell dysfunction eventually causing death [172].

The striatum is particularly rich in A1R and A2AR. Notably, the striatum has the highest density of A2AR in the brain [173,174], which supports the pathophysiologic relevance of A2AR in motor diseases. A2AR can be found presynaptically on the cortico-striatal glutamatergic afferents [175], where they modulate glutamate release [35,176], but are mainly located postsynaptically in MSNs [173]. Besides neurons, A2AR are also present in non-neuronal cells, such as endothelial and glial cells which allow a control of vasodilation and glial responses to injury and inflammation [177–179]. Several lines of evidence point towards a pathophysiologic role for adenosine A2AR in HD: 1) changes in A2AR gene, expression, density and signaling; 2) early vulnerability of MSNs selectively expressing A2AR; 3) physiologic role of A2AR in motor control; 4) ability of A2AR to control glutamatergic transmission; 5) A2AR involvement in neuroinflammation; 6) A2AR ability to regulate metabolism and mitochondrial functioning.

In spite of some controversy mainly due to observations in distinct animal models of HD (e.g. genetic versus toxin-induced models), different phases of the "disease," (pre-symptomatic versus symptomatic periods), most animal studies point towards changes in A2AR expression, density and/or signaling [180–183]. Moreover, recent evidence indicates that a polymorphism of the A2AR gene (ADORA2A) can influence the age of onset of HD patients [184]. As stated above, continued exposure to glutamate and persistent opening of NMDA channels, make MSNs vulnerable to excitotoxic damage, in particular those expressing A2AR, which receive more glutamatergic inputs from the cortex [185], further supporting a role for A2AR in HD physiopathology. Furthermore, the hyperkinetic phenotype of the disease seems to be due to the early loss of A2AR-expressing MSNs. Neuroprotective effects attributed to A2AR antagonists correlate well

with their ability to decrease glutamate levels [186,187] by preventing its release [188,189] or decreasing its release and enhancing its uptake by glial cells [190–193]. A2AR in glutamatergic synapses are also able to control the activation/expression of NMDA receptors [194,195], their subunit composition [196] and plastic changes in cortical glutamatergic inputs [174].

Whereas the presynaptic role of A2AR antagonists is increasingly accepted as neuroprotective, an effect mainly attributed to the modulation of glutamatergic transmission, the postsynaptic and extrasynaptic effects of A2AR blockade have been speculative and most studies favor A2AR agonists, rather than antagonists as protective agents in the particular case of the degeneration of MSNs. These results were attributed to the ability of A2AR antagonists to potentiate NMDA-mediated toxicity and to the ability of agonists to reduce NMDA currents in striatal MSNs [188,189,194,197,198].

The same controversy exists regarding metabolic compromise and mitochondrial dysfunction secondary to excitotoxicity in HD, where A2AR antagonists or genetic blockade of the receptor has been shown to be either protect or increase striatal MSN lesion [199–201]. The controversy further increases when considering that the compromise of the cortico-striatal pathway determines a decrease in the supply of trophic factors to the striatum, in particular brain-derived neurotrophic factor (BDNF), which plays an important role in the pathophysiology of HD [202]. It is well known that the ability of A2AR agonists can transactive the TrkB BDNF receptor, and are also able to regulate levels and effects of different neurotrophic factors, including BDNF [203]. These modulatory actions may be beneficial in terms of trophic support to degenerating neurons. However, BDNF exerts multiple cellular functions, including the potentiation of glutamate release [204] and sustaining neuroinflammation [43]. According to these observations and to the dual effects of BDNF, dependent on the activation of different receptors (p75 versus TrkB, see below), it is important to emphasize that trophic factors are not always “good” players in the neurodegenerative course of diseases. Thus, the enhancement of BDNF-mediated effects by A2AR agonists may also have deleterious effects. Finally, A2AR blockade is generally accepted as a protective strategy in the control of neuroinflammation in several degenerative conditions, including HD. However, the relative importance of A2AR-mediated contention of inflammation, in particular its *in vivo* relevance, still requires further investigation.

In conclusion, in spite of the established pathophysiologic role of A2AR in HD, it remains to be clarified if it is the activation or the blockade of A2AR that can bring about clinical benefits. The complexity of functions operated by A2AR in specific cellular and regional locations specifically in the striatum may suggest that neither stimulation nor blockade are beneficial or that both can be advantageous, depending on the time-frame of the disease taken into account. Thus, HD is a special case of a brain disorder where both A2AR agonists and antagonists have been shown to provide protection in animal models of HD.

4.4. Parkinson' disease

The etiology of Parkinson's disease (PD) is still ill-defined, in spite of the established influence of genetic and environmental factors. Independently of the trigger, protein misfolding and aggregation and mitochondrial dysfunction associated oxidative stress are important in PD pathogenesis (for a review see [205]). The pathologic hallmark of PD is the loss of dopamine innervation in the striatum and the subsequent degeneration of dopaminergic neurons from the SNc, even though the degenerative process extends beyond dopaminergic neurons [206]. Dopamine depletion attenuates the control of striatal circuits and, in particular, reduces the inhibitory tonus to MSNs selectively expressing A2AR [207], which characteristically become overactive. To balance early changes in inhibitory dopaminergic tonus, compensatory mechanisms, such as plastic adaptations in the cortico-striatal pathway [208–210], probably delay motor impairment and justify the existence of a pre-symptomatic period [211] preceding the gradual appearance of symptoms.

As occurs in HD, strong evidence highlights the critical role of A2AR in the pathophysiology of PD, namely: 1) the physiological role of A2AR in motor control; 2) the ability of A2AR to control glutamatergic transmission; 3) the increased A2AR-mediated activity in PD; 4) the eventual A2AR involvement in neuroinflammation, which is most evident in the substantia nigra; 5) the ability of A2AR to regulate metabolism and mitochondrial functioning. In contrast to the controversy around A2AR manipulation as a therapeutic approach in HD, A2AR antagonists are currently under clinical trials in PD patients, given their ability to control motor impairment and to confer neuroprotection, as suggested by the epidemiologic inverse relation between the consumption of caffeine (an antagonist of adenosine receptors) and the risk of developing PD [212,213].

Adenosine control of motor function is centered on the ability of A2AR to tightly control dopamine D2 receptor function, both at the level of intracellular signalling as well as by the formation of heteromers with D2 receptors (reviewed in [174], although these receptors form heteromers with different receptors, also functionally important in striatal physiology (see [214]). In fact, almost 20 years after the observation that adenosine receptor antagonists exert the same motor effects as dopamine receptor agonists (i.e. hyperlocomotion, see [215]), it was discovered that A2AR and D2 receptors co-localize [216–218], form heteromers [219,220] and alter each other's pharmacological properties such as affinity and desensitization [218,221]. A2AR and D2 receptors have antagonistic interactions not only at the membrane level but also at the intracellular signalling (reviewed in [174,222]). Thus, the net result of dopamine depletion in the striatum is an A2AR over-signalling resulting in typical hypokinetic symptoms of PD and blockade of A2AR became an attractive alternative (or adjunctive) to the dopamine-based therapeutic approaches.

A2AR antagonists improve motor function in different rodent and primate models of PD, alone or co-administered with dopaminomimetic drugs, levodopa or dopamine agonists [223–227]. When administered after the onset of the most severe side-effect of levodopa, dyskinesia, A2AR antagonists have an additive beneficial effect upon motor disability and do not worsen dyskinesia [224,228–231]. These non-clinical studies culminated in clinical trials testing the A2AR antagonist istradefylline (KW-6002) in PD patients. There is only one inconclusive clinical report showing that istradefylline alone had no effect on motor dysfunction [232]. However, istradefylline co-administered with low doses of levodopa potentiates motor improvement, without worsening dyskinesia [233]. Further clinical studies involving patients in low-dose levodopa therapeutic schemes are needed in order to clarify the adjunctive potential of A2AR antagonists, since most results were assessed in patients under optimal levodopa doses and may underestimate the therapeutic potential of A2AR antagonists (for a review see [234]).

Currently, first line pharmacotherapeutical strategy in PD aims at restoring dopamine levels and/or effects, by the use of a dopamine precursor, dopamine agonists and inhibitors of enzymatic degradation of dopamine. These drugs, which mainly interfere with motor symptoms, have, at least, two limitations: long-term side-effects (in particular, motor disability, including dyskinesia) and inability to stop the ongoing degenerative process. In this regard, A2AR pharmacological or genetic blockade reduce dopaminergic cell loss and counteract striatal dopamine depletion, underpinning an effective neuroprotective role for A2AR, which mechanism has not yet been ascertained, but seem to be different from that mediating motor effects of these ligands [235–237]. As stated above, abnormal glutamatergic transmission may be implicated in PD pathogeny. Accordingly, the neuroprotective role attributed to A2AR blockade is also based on the ability of the receptor to increased glutamate release [7,174,188]. It was also suggested that neuroprotection by the A2AR antagonists may be related with the inhibition of glial activation [237] or with the inhibition of dopamine

metabolism by MAO-B [238]. In conclusion, neuroprotection by A2AR antagonism in PD likely results from the balance between a plethora of effects, which deserves detailed integrative analysis in order to clarify the clinical applicability of receptor manipulation.

4.5. Alzheimer's disease

Alzheimer's disease (AD) is the most common neurodegenerative disorder that affects the elderly. In fact, advanced age is the major risk factor for AD, as its incidence is around 1–2% in people with 60–64 years old, rising to about 30% in those aged 85 years old and older [239,240]; thus the increase of life-expectancy is transforming AD into a great health-care problem. AD is characterized by a progressive impairment of memory and other cognitive skills leading to dementia [240,241]. The neuropathological hallmarks of AD include (in order of relevance): i) selective synaptic and neuronal loss in several brain regions, including the cerebral cortex and hippocampus; ii) senile plaques, mainly composed of amyloid-β peptide (Aβ); iii) neurofibrillary tangles [242,243]. Currently, it is accepted that AD pathogenesis results from the imbalance between production and clearance of Aβ, which derives from the abnormal processing of the amyloid precursor protein (APP) at the β-secretase (BACE 1) and γ-secretase sites to produce Aβ fragments of 40 or 42 amino acids [244,245]. Moreover, the Aβ cascade hypothesis, postulates that soluble Aβ oligomers (particularly 12-mers), rather than the fibrillar forms, are responsible for the synaptic dysfunction and loss that underlie early memory impairment in AD [242,246]. Aβ oligomers build up into proto-fibrils and fibrils, giving rise to diffuse plaques that may evolve to neuritic plaques, also named senile plaques, which often have a dense amyloid core and are associated with clusters of activated glia cells (microglia and astrocytes) and dystrophic neuronal processes [243,247]. Synaptic degeneration, which is detectable already in patients with mild cognitive impairment (a prodromal state of AD), progresses during the course of AD [241,248] and in most early stages involves mechanisms of compensation before reaching a stage of decompensated function [249]. Synaptic dysfunction and loss in cortical regions, mainly in the neocortex and hippocampus, is an early change and the major structural correlate of cognitive deficits in AD, as supported by a variety of electron microscopic, immunocytochemical and biochemical studies on synaptic proteins markers in biopsies and autopsies of brain's patients (reviewed in [249]).

Adenosine, mainly through its action on A1R and A2AR, can control and integrate cognition and memory [250]. In the brain, A1R and A2AR are mainly located in synapses, controlling the release of neurotransmitters, such as glutamate and acetylcholine that are involved in memory and other cognitive processes [40,251]. Increasing evidence suggest that adenosine receptors change their pattern of localization and density in afflicted brain regions of AD [250]; however, the role of adenosine and its receptors in regulating the pathogenesis of this neurodegenerative disease remained weakly known. *Post-mortem* analysis of frontal cortex of AD patients showed that the total number (assessed by binding studies) and levels (determined by Western blot analysis) of A1R and A2AR are significantly increased in either early or advanced stages of this disease [252]. Moreover, a re-distribution of these receptors was found in the hippocampus and cortex of AD patients, such as an increased A1R immunoreactivity in neurons with neurofibrillary tangles and/or in dystrophic neurites of senile plaques and an upregulation of A2AR in glial cells [253]; however, the level of transcription of the A1R gene (measured by quantitative PCR) was similar in control and AD brain [253]. This study also analysed if other metabotropic receptors undergo changes in their cellular localization in the AD brain and found that no significant change was evident for several other metabotropic glutamate receptors [253]; this suggests that the re-distribution of adenosine receptors in AD brain may be a specific and relevant event. Furthermore, in a transgenic mice model of AD carrying the APP Swedish mutation (APPSw), it was also reported that the levels of A1R and A2AR are augmented as compared with non-transgenic mice [254]. However, it must be referred that autoradiography and binding studies performed in the 1990s showed that the density of A1R was reduced in the hippocampus of AD patients [255–257] and a loss of A1R was also observed in the hippocampus of patients with sclerosis-associated dementia [257]. A recent study using positron emission tomography (PET) and 8-dicyclopropylmethyl-1-[^{11}C] methyl-3-propylxanthine showed a significant reduction in A1R binding potential in the temporal cortex and thalamus of AD patients as compared with elderly normal subjects [258]. This reduction in the density of A1R is in agreement with the decrease of A1R density and efficiency in neurodegenerative disorder (reviewed in [40]).

Chronic stressful brain conditions also trigger the upregulation of A2AR, prompting the hypothesis that the manipulation of these excitatory receptors may control neurodegeneration [40]. Accordingly, numerous studies show that the modulation of A2AR could have neuroprotective effects in AD. Studies *in vitro* showed that A2AR antagonism prevents synaptic loss as well as neuronal death triggered by Aβ synthetic peptides [259,260]. However, the mechanisms of neuroprotection by A2AR antagonism against Aβ still remain to be fully characterized. It is known that A2AR can control the neurochemical consequences of enhanced production of free radicals [261,262] and glutamate excitotoxicity [40] and that adenosine receptors can affect neuronal primary metabolism [54,55], albeit the exact impact of the different adenosine receptor subtypes on astrocytic and neuronal metabolism remains to be established. This ability of A2AR to control mechanisms involved synaptic degeneration and subsequent neuronal death opens the possibility that A2AR antagonists might actually control this apparently reversible synaptic dysfunction (reviewed in [250]), which might be an effective strategy to arrest neurodegenerative diseases at their early stages before they evolve into overt irreversible neuronal loss [263].

Benefits for cognitive deficits in AD patients and AD animal models might be achieved by manipulating A2AR, since these receptors facilitate the synaptic mechanisms of memory and learning [250,264]. Some of the strongest evidence rely on the impact in different AD animal models of caffeine (the most widely consumed behavioral stimulant present mainly in coffee and tea), which, in non-toxic doses, acts as an antagonist of adenosine receptors, mainly of adenosine A1R and A2AR [4]. Maia and de Mendonça reported the fist retrospective epidemiological data showing that the incidence of AD was inversely associated with the consumption of coffee in the previous two decades of life [265]. An inverse relation between caffeine intake and age-related cognitive impairment was also noted in three other epidemiological studies [266–268]. Finally, a recent study also shows that coffee drinking at midlife is associated with a decreased risk of dementia/AD later in life [269]. A different drug, propentofylline, which acts as a mixed blocker of nucleoside transporters and of adenosine receptors [270], was also reported to afford beneficial effects on cognition, but not on activities of daily living, in patients with vascular dementia [271]. This evidence from human studies is concurred by results obtained in animal models of aging and AD; thus, there is evidence for a beneficial role of caffeine and/or selective A2AR antagonists in animal models of aging [272,273] and AD [141,254,259,274,275]. In AD transgenic mice (APPsw), a 6-month period of caffeine intake (0.3 g/L) alleviated the cognitive deficits found in these mice, and restored the levels of soluble Aβ [254]. Furthermore, in cultured neurons from these AD mice, caffeine also reduced the production of $A\beta_{1-40}$ and $A\beta_{1-42}$ peptides [254], whereas propentofylline attenuated tau phosphorylation [276]. Likewise, acute caffeine administration to both young adult and aged AD transgenic mice rapidly reduces Aβ levels in both brain interstitial fluid and plasma, whereas long-term oral caffeine treatment to aged AD mice provided not only sustained reductions in plasma Aβ, but also decreases in both soluble and deposited Aβ in hippocampus and cortex [277]. Delayed memory deficits caused by intracerebral administration of Aβ were prevented by either caffeine or selective A2AR antagonists [33,259,275]. Moreover, it was shown that, in A2AR

knockout mice, the intracerebral administration of $A\beta_{1-42}$ did not cause cognitive deficits or synaptotoxicity [259]. Although it was reported that A1R density is increased in afflicted brain regions of AD patients [252,253] and that A1R can also control the production of soluble Aβ *in vitro* [253], the protective effects of caffeine in AD animal models are not mimicked by antagonists of A1R but rather by antagonists of A2AR [33,259,260,275]. These data further strength the idea that caffeine affords a prophylactic benefit on memory performance through its action on A2AR, which were found to be upregulated in cortical regions both in AD animals models [254] and AD patients [252,253]. A recent study also found that caffeine might actually be able to revert the pre-installed working memory deficits and the pre-existing considerable Aβ burden in aged AD transgenic (APPSw) mice [274]. Caffeine and/or the selective blockade of A2AR are also effective in reverting other experimental conditions of mnemonic impairment (reviewed in [250]). In fact, our group recently reported that a single convulsive episode in the early life of rats causes a delayed memory deficit in adulthood accompanied by a glutamatergic synaptotoxicity that was prevented by caffeine or A2AR antagonists [278]. Likewise, caffeine also prevented both the memory impairment as well as the loss of synaptic markers caused by an experimental model of diabetes [56]. The chronic use of a low dose of caffeine also prevents short-term memory deficits and early long-term potentiation in acutely (24 h) sleep-deprived rats [279]. The memory impairment and synaptotoxicity associated caused by a protocol of chronic unpredictable stress were also prevented by either chronic caffeine consumption or A2AR antagonists or genetic deletion of A2AR [280]. In both rodents and humans, the acute memory impairment caused by the administration of scopolamine (an antagonist of cholinergic muscarinic receptors) was found to be prevented by caffeine [281,282], prompting the hypothesis that adenosine receptors might also correct cholinergic hypofunction associated with memory impairment (but see [283]).

Taken together, the above discussed evidence strength the idea that both caffeine and A2AR antagonists can act as a cognitive normaliser, rather than as a cognitive enhancer, and thus the blockade A2AR may be a novel promising prophylactic and/or therapeutic option to manage the precocious phases (synaptic loss and cognitive impairment) of AD (reviewed in [250]). Furthermore, the ability of caffeine and A2AR antagonists to control memory dysfunction under different pathological conditions indicates that A2AR may impact on memory preservation in general rather than affecting selectively pathogenic mechanisms of AD. However, our knowledge about the role of adenosinergic system, mainly of adenosine receptors, in AD pathogenesis and associated memory loss still needs to be detailed to afford a better understanding of the therapeutical potential of the adenosine neuromodulation system in AD (discussed in [98]).

4.6. Depression

Depressive disorders are frequent forms of psychiatric conditions estimated to become the second leading cause of disability by the year 2020 [284]. The difficulty to understand the neurobiological basis of depressive disorders, together with the inadequacy of currently available treatments, contributes to the significant health burden associated with this disease (reviewed in [285]). In the past three decades, systematic epidemiological studies have highlighted a relationship between caffeine intake and specific psychiatric symptoms (reviewed by [33,286]). These data are the strongest piece of evidence linking the adenosinergic system in modulation of mood, since caffeine, at non-toxic doses, acts as an antagonist of A1R and A2AR [4,287]. However, studies trying to clarify the mechanisms underlying antidepressant action and animal models designed to unravel the neurobiological basis of depression also point to a role for adenosine receptors in the regulation of mood.

Caffeine intake is so common, in different time-schedules and different doses, that is difficult to determine, from the epidemiological point of view, how it affects the evolution of psychiatric disorders. The literature is complex, with both positive [267,288–290] and negative [291–293] effects being suggested. The consumption of low to moderate doses (<6 cups/day) is well known to increase energy and attention and to decrease cognitive failures (reviewed in [264]), depressive symptoms and risk of suicide [267,294]. However, in large amounts, caffeine can act as a trigger of psychiatric symptoms, from anxiety to depression and even psychosis in both normal and vulnerable subjects [295]. Conversely, a variety of mood related symptoms are also triggered upon withdrawal from regular caffeine consumption, including anxiety, irritability, sleepiness, dysphoria, nervousness or restlessness [296–300]. More recently, compromised adenosine transport due to variation in nucleoside transporter gene SLC29A3 was suggested to enhance susceptibility to depression in women [301].

The effect of the adenosine neuromodulation system in depression is complex, especially due to its ability to modulate several other neurotransmission systems, such as dopaminergic, glutamatergic and serotoninergic as well as the corticotrophin system [302–306]. Adenosine and its analogues were shown to cause a depressant-like response in behavioral despair models [307–309], an effect that was prevented by the administration of classical antidepressants [310]. In contrast, other studies showed an antidepressant effect associated with adenosine administrated both systemically and centrally [311–313].

The strongest evidence supporting the relation between adenosine and depression in preclinical models came from manipulation of A2AR. Available data suggests that A2AR antagonists might be novel antidepressants compounds (reviewed in [141]). The main evidence sustaining this hypothesis relies on the observation that the genetic depletion of A2AR results in an antidepressant-like phenotype in animal models [314,315]. In addition, A2AR blockade relieves the early hippocampal modifications induced by stress [316], one of the major environmental factors favoring the implementation of depressive states [317].

It is important to highlight that different therapeutic strategies currently used to manage depressive disorders also have effects related to the adenosine system. Tricyclic antidepressants such as nortriptiline, chlorimipramine or desipramine can bind to adenosine receptors [318] and dose-dependently reduce the activity of ecto-nucleotidases and, expectedly, the levels of extracellular adenosine in cortical synapses [319]. In addition, both electroconvulsive therapy and sleep deprivation cause an increase of adenosine concentration and of A1R activation [28]. In conclusion, although at this stage the relation between adenosine and depression is still circumstantial, it seems evident that the adenosinergic system is able to modulate mood states by functioning as a normalizing system, and both too high or too low levels of activation can cause a failure in the organism to adapt and a predisposition to disease [320].

4.7. Bipolar disorders

The first account for a purinergic dysfunction in bipolar disorders can be attributed to Kraeplin (1921) when exploring the association between manic symptoms and purinergic metabolism (uric acid excretion, hyperuricemia and gout) [321]. Later, an increased excretion of uric acid during initial phase of remission from manic episode and an enhanced purinergic turnover was observed during mania [322]. The efficacy of the xanthine oxidase inhibitor allopurinol to improve patients with mania seems to support that a dysfunction of the purinergic system might be associated with this disease [323,324]. In addition, historical reports describe that lithium, an effective antimanic agent, was primarily used to treat disorders related to a dysfunction in purinergic metabolism (gouty diseases) [325].

The purinergic system has also been proposed to be involved in the kindling phenomena, a valuable model to explain the pathological activation, increase of energy and recurrence of maniac episodes, typical components of the bipolar illness (reviewed in [326]). The kindling phenomena stimulate the release of adenosine and adenosine receptor agonists have anti-kindling properties, attributed to the activation of A1R [327]. Caffeine and aminophyline (two non-selective adenosine receptor antagonists) have 'mania-like' stimulant effects and significantly increase kindled seizure duration and induce a persistent state of arousal [328,329]. Caffeine also seems to exacerbate manic symptoms [330] and heavy caffeine intake appears to contribute to worsen the course of seasonal bipolar disorder [331]. The convulsive behavior in kindled rats was also demonstrated to cause a long-term decrease of A1R density accompanied by an increased density of A2AR in the cortex and hippocampus [17,18]. The decrease of A1R functioning has been associated with an increase in intracellular cAMP levels, G_S proteins expression, calcium influxes and protein kinase C activation and all these abnormalities in second messenger systems and intracellular pathways are also relevant signals associated with bipolar disorders (reviewed by [332]). In contrast, the role of A2AR in psychotic events still remains unclear (reviewed in [320]), albeit a recent study analyzing variations in the exons and exon–intron boundaries of the ADORA2A gene in methamphetamine dependent/psychotic patients suggested that the ADORA2A gene could be a vulnerability factor for the psychotic consequences of methamphetamine dependence [333].

The anti-convulsant and anti-kindling mechanism of action of carbamazepine, a drug used primarily in the treatment of epilepsy and bipolar disorder, seems to include an adenosinergic modulation [334], basically by an action on A1R [335,336]. Additionally, carbamazepine treatment induces an upregulation of A1R in brain cells that express low basal levels of A1R [337] and the protective activity of carbamazepine is potentiated using the adenosine receptor agonist APNEA, acting through A1R [338]. Therefore, it is reasonable to suggest that the antimanic effects of some mood stabilizers might be associated in part with the effects operated by the adenosine neuromodulation system, mostly through actions operated through A1R.

4.8. Schizophrenia

Schizophrenia is a neurodevelopmental disorder with both genetic and environmental components that comprises three distinct symptom clusters: positive symptoms (delusions, agitation, hallucinations), negative symptoms (blunted affect, anhedonia) and cognitive dysfunction (executive function deficits and working memory dysfunction) (for review see [339]). Currently, schizophrenia is best explained by the dopamine and glutamate hypotheses. However, adenosine receptors can control both dopaminergic and glutamatergic systems [69,214], and its neuromodulation role supports the newly proposed adenosinergic hypothesis of schizophrenia, which constitute a link between the two other hypotheses [340].

Several indirect findings suggest that adenosinergic activity might be deficient in schizophrenia. Presynaptically, the increased in dopamine turnover [341] and release [342] in schizophrenia are consistent with a loss of A1R-mediated inhibitory tonus on the dopaminergic system. A1R antagonists cause a potentiation of amphetamine-induced locomotion [343] and dopamine release in the nucleus accumbens [344] while adenosine receptor agonists display antipsychotic-like profile [345–347]. Evidence of altered adenosinergic activity in schizophrenia includes the upregulation of striatal A2AR [348], which could be compensatory to low adenosinergic activity [340], as well as the clinical improvement of schizophrenic patients with dipyridamole and allopurinol, two pharmacological agents enhancing adenosine activity [324,349]. The blockade of adenosine receptors by caffeine might exacerbate positive symptoms and a reversal of caffeine-induced behaviors is observed by antipsychotics [345,350]. In addition, theophylline (a non-selective adenosine receptor antagonist) [351], as well as A2AR knockout mice have a reduction in the startle habituation, a measure of sensorimotor gating disrupted in patients with schizophrenia [352]. Regarding the dopaminergic involvement in schizophrenia, it is noteworthy that activation of A2AR reduces the effectiveness of dopaminergic D2 receptor signalling (both affinity and intracellular effects, see review in [174]), being the probable mechanism underlying the antipsychotic-like profile of adenosine agonists [353].

Genetic studies also support the adenosine hypofunction hypothesis of schizophrenia. A single-nucleotide polymorphism of the A2AR gene on chromosome 22q12-13 was found to increase schizophrenia susceptibility [354,355]. In addition, studies using a transgenic mouse model overexpressing adenosine kinase, demonstrated that the decrease in adenosine levels in the forebrain could lead to the emergence of behavioral endophenotypes implicated in schizophrenia and abnormal response to psychostimulants [356]. A functional polymorphism of adenosine deaminase (G/A genotype) associated with low adenosine deaminase activity, was also found to be less frequent in schizophrenic patients [357]. In addition, A1R polymorphisms may also represent good candidate markers for schizophrenia research and were found to be involved in the pathophysiological mechanisms of schizophrenia in Japanese populations [358].

The adenosinergic hypothesis was further refined by neurodevelopmental data showing that A1R can mediate the neurotoxicity in early stages of brain development, leading to an excessive adenosine release and to primary brain changes. These events would lead to an adenosine inhibitory deficit through a partial loss of A1R that may emerge as reduced control of dopamine activity and increased vulnerability to excitotoxic glutamate action in the mature brain (reviewed in [359]).

According to the glutamate hypothesis, NMDA receptor blockade can give rise to behavioral dysfunction and psychotic-like behavior, while co-agonists of the NMDA receptors, such as D-serine and glycine, improve cognition and negative symptoms in schizophrenia [360,361]. A1R and A2AR agonists have both been shown to prevent behavioral and EEG effects induced by NMDA receptor antagonists [362,363], and the function of NMDA receptors can be modified by both A1R and A2AR [25,36,37,364,365]. Furthermore, both A1R and A2AR control the evoked release of glutamate in the striatum [35,176]. Conversely, the activation of the NMDA receptors increases the adenosine tone [366], while inhibition of NMDA receptors leads to a reduction of adenosine release [367]. Importantly, the psychostimulant effects of NMDA receptor antagonists are largely abolished by genetic inactivation or pharmacological blockade of A2AR [368,369], supporting the idea that modulation of adenosine receptors may rebalance the hypofunction of NMDA receptors in models of schizophrenia.

Finally, it was observed that the ability of clozapine (an atypical antipsychotic, and to a lesser extent haloperidol) to induced c-fos expression is blocked by A2AR antagonists [370] and this antipsychotic also affected the key pathway of formation of ATP-derived adenosine acting on A2AR, the ecto-nucleotidase pathway [356].

4.9. Phobia

Fear is an adaptive response to potentially dangerous (external and internal) stimuli. However, when disproportional in intensity, chronic, irreversible, or not associated with any genuine risk, it may be symptomatic of a debilitating anxious state (i.e. phobia, panic attacks or generalized anxiety disorder) [371,372]. Panic and phobic disorders are the most frequently diagnosed anxiety disorders, associated with significant psychosocial morbidity [373,374].

A strong link between the adenosine modulation system and the control of fear processing and anxiety is suggested by several types of studies, namely: i) animal models designed to mimic anxiety traits; ii) epidemiological studies with caffeine, both in normal subjects and in patients in anxiety disorders; iii) gene linkage studies in humans (reviewed in [320,375]). However, the role of adenosine receptors in

specific anxiety disorders, like phobia, is still to be defined. Studies with caffeine consumption by phobic patients are rare, especially in comparison to research on caffeine consumption among patients with other anxiety disorders like panic disorder. A study from Boulenger and Uhde [376] showed that panic disorder patients have increased sensitivity to caffeine and its consumption appears to be more strongly linked to generalized anxiety symptoms than to 'phobic-anxiety' symptoms. The work from Uhde [377] also showed that anxiety symptoms are not made more severe by caffeine consumption in social phobics and that caffeine consumption in social phobic individuals does not differ from the general population. In addition, no differences in electroencephalographic activity of patients with panic disorder versus control subjects were observed after oral administration of caffeine [378]. On the other hand, another study reported that caffeine can induce panic attacks in both panic disorder and social phobic patients following consumption of a dose of 480 mg [379]. It was also demonstrated that caffeine ingestion per se does not appear to reduce fear extinction at least in some specific phobias, whereas changes in caffeine consumption, during learning or recall tests, can enhance the return of fear in spider phobia [380].

Another line of evidence that indicates a possible role for the adenosinergic system in anxiety-related conditions derives from polymorphism analysis of the A2AR gene. It was observed that there is a significant association between self-reported anxiety after caffeine administration and two linked polymorphisms of the A2AR gene, the 1976 C>T and 2592 C>T polymorphisms [354,355]. Likewise polymorphisms of the A2AR gene were also observed to be associated with the incidence of panic disorder and agoraphobia [381–384]. A genetic variation of the A2AR gene was also found to influence sympathetic indicators of anxiety-related disorders in blood-injury phobia, further supporting a role for the adenosinergic system in the pathogenesis of anxiety disorders [385].

5. Neuroprotection and neuroregeneration

Current pharmacotherapy of neurodegenerative diseases is focused on symptomatic relief and eventually on neuroprotective temptative approaches. These strategies delay neuronal death, but do not consider the regeneration of damaged neurons. Neuronal survival is necessary, but not sufficient for complete structural and functional recovery after injury or after the onset of pathogenic triggers of disease. Thus, besides neuroprotection, it is crucial to ensure that local environment around the lesion site has the appropriate conditions for re-innervation of degenerated regions. Neurotrophic factor-mediated actions and neurogenesis are innate self-repair mechanisms of the nervous system, although limited and inefficient to completely recover all damaged neurons. We will now briefly summarize the potential for the involvement of adenosine receptors in neurogenesis and in the modulation of trophic factor-mediated regenerative effects.

5.1. Interaction with growth factors

There are several actions by which trophic factors could provide important therapeutic benefits in neurodegenerative diseases, including their ability to promote survival of specific neuronal populations exposed to an injury, i.e. neuroprotection. Neuroprotective effects of trophic factors are well illustrated by animal studies where these molecules are administered prior to an insult (e.g. MPP^+, 6-OHDA); just to mention a couple of examples, brain-derived neurotrophic factor (BDNF) or glial cell line-derived neurotrophic factor (GDNF), administered after neurotoxins decrease the extension of neuronal loss [386–394]. A second mechanism resulting in therapeutic benefits is the restoration of function, i.e. neuroregeneration. Far beyond their roles during development, trophic factors are able to regulate axonal and dendritic outgrowth, *de novo* synapse formation, cell proliferation and survival of adult neurons [395–405].

The adult mammalian brain is unable to efficiently promote reparative actions, in particular axonal regeneration, mainly due to the low intrinsic ability of adult neurons to regrow axons, but also due to the restricted supply of appropriate trophic factors and to the presence of inhibitory molecules controlling this process [406]. Thus, axonal damage characteristic of several degenerative conditions often results in persistent functional deficits. Axonal regrowth can occur by collateral sprouting from intact neurons into denervated areas or by regenerative growth of injured neurons to re-establish connections with target areas. Several trophic factors are able to induce this kind of restorative actions, as well as to interact with effectors, such as cyclic adenosine monophosphate (cAMP) and overcome inhibitory action induced by growth inhibitory molecules [407].

Since the discovery of the ability of A2AR to transactivate the main BDNF receptor, TrkB [408], intense research has focused on the effects of adenosine on the release and on the short-term effects of trophic factors [204,409–412]. Considering the established functional interaction between A2AR and trophic factors, some authors argue that A2AR agonists may be beneficial in degenerative conditions (discussed in [203]). However, to date, there are no studies in pathological conditions, i.e. in animal models of degenerative diseases to support the idea. Clearly, the fact that trophic factors are mostly considered to be survival promoting factors casts some concern on the potential harmful effects of long-term use of A2AR antagonists to manage neurodegenerative disorders. However, the observation that the consumption of caffeine (an adenosine receptor antagonist) is not only essentially safe but provides global beneficial effects in different neurodegenerative disorders, clearly argues against potential detrimental effects resulting from long-term consumption of A2AR antagonists and seriously dampens the physiopathological relevance of this trans-activation between A2AR and TrkB receptors.

It is also important to emphasize that trophic factors may also be deleterious rather than only protective or restorative. This is the case for BDNF, which is synthesized as a precursor protein often involved in neuronal death. Furthermore, mature BDNF and the precursor protein activate two different receptors (TrkB and p75), both of them existing as full-length or truncated forms. The activation of each receptor isoform by precursor or mature BDNF often results in opposite actions in terms of cell survival or death [413,414]. And it still remains to be explored if adenosine receptors (or caffeine consumption) might be able to influence the detrimental effects of abnormal signalling by growth factors. Therefore, it is of utmost importance to clarify the functional interaction between adenosine and trophic factors in animal models of degenerative diseases to effectively grasp if the manipulation of adenosine receptors might be envisaged as a novel reaparitive strategy based on the control of the action of growth factors.

5.2. Neurogenesis

Adult neurogenesis, a process by which new neurons are generated from neural stem or progenitor cell populations in limited areas of the brain [415–420], is indicative of an intrinsic ability of the nervous system to self-repair, but is limited and unable to reverse the ongoing neuronal loss charactering neurodegenerative diseases. Both *in vitro* and *in vivo*, newly formed neurons express classical neuronal markers [421–424] and exhibit morphologic and physiologic characteristics of intrinsic neurons, such as excitability-related electrophysiologic properties and formation of functional synaptic connections [423].

Neurogenesis throughout life may be important in processes such as learning and memory [425–427] and changes in neurogenesis have been associated with neurological diseases. For instance, depression is causally related with declining neurogenesis in the hippocampus [428,429]. Accordingly, antidepressant drugs promote *de novo* adult neurogenesis and block stress-induced decrease of neurogenesis [430] and neurogenesis blockade compromises the efficacy of antidepressants

in mice behavioral paradigms [431,432]. Some lines of evidence suggest that neurogenesis is impaired in neurodegenerative diseases, such as PD, HD and AD [433–438] but is enhanced following stroke [439,440]; curiously, after stroke, a certain degree of recovery is observed in patients over time.

In normal or disease conditions, neurogenesis involves four general cellular events: i) proliferation of stem/progenitor cells; ii) migration of stem/progenitor cells into different areas of the central nervous system; iii) differentiation into specific neuronal cell types; iv) integration in the established neuronal circuitry. Stem/progenitor cells with undifferentiated self-renewal and multipotent features reside in two major areas: subventricular zone (SVZ) along the walls of lateral ventricles [419,441] and the subgranular zone (SGZ) of the dentate gyrus of the hippocampus [422,442–444]. The newborn neurons generated in these germinative areas migrate to the olfactory bulb (OB) [445,446] and to the granule cell layer (GCL) of the dentate gyrus [421,447], respectively, where they differentiate and incorporate into the pre-established circuitry.

There is increasing evidence that purinergic signalling pathways are involved in mammalian adult neurogenesis (for a review see [448]). Interestingly, there are only few reports on the role of caffeine in adult neurogenesis [449–451], in spite of several findings favoring the potential involvement of adenosine in the process, namely: 1) the tissue non-specific form of alkaline phosphatase (TNAP), an enzyme which hydrolyzes extracellular nucleotides to nucleosides, including adenosine from extracellular ATP [452] has a selective localization in the SVZ, including its extension into the OB [453], in spite of the lack of activity in the neurogenic dentate gyrus of the hippocampus [454]; furthermore, TNAP co-localize with a marker for immature and migrating neurons and cells of the adult SVZ, doublecortin [453]; 2) ecto-5′-nucleotidase, the major enzyme involved in the extracellular formation of adenosine [455] is present in the adult OB and is involved in lesion-induced sprouting within the adult dentate gyrus [146]; 3) functional adenosine receptors were identified in neurosphere cells (*in vitro* cultured neuron stem cell aggregates) cultured from the adult mouse SVZ [456]; these cells predominantly express A1R and A2BR and A1R agonists (but not A2AR agonists), are able to increase the proliferation of these cells in a time- and concentration-manner [457]; 4) the complexity of behavioral and biochemical effects of adenosine in the central nervous system; for instance, caffeine influences locomotor activity, which has been shown to increase neurogenesis in the dentate gyrus [458]; at higher doses, caffeine also influences anxiety and stress, both associated with depressed adult neurogenesis [459,460]; indirectly, the vasocontrictive effects of caffeine could alter the vascular neurogenic niche in the brain [461] and modify adult neurogenesis; adenosine signalling has been shown to potentiate BDNF signalling in the hippocampus, which has been established as an important factor modulating the survival of adult-born hippocampal neurons and implicated in exercise-induced survival of adult-born neurons [462]; 5) caffeine does not affect the differentiation or the long-term survival of precursor cells, but influences their proliferation in the adult hippocampus in a time- and dose-dependent manner: extended moderate-high doses of caffeine depress (20–25%) proliferation in the dentate gyrus and higher doses increase (50%) proliferation [449,451].

Surprisingly, very little is known concerning adenosine effects upon adult neurogenesis. This apparent lack of interest may be due to the strong evidence for the involvement of nucleotides in the control of neurogenesis. More integrative experimental design, analyzing multiple and interactive mechanisms may unmask a possible role of adenosine in adult neurogenesis. Wentz and Magavi [451] proposed that caffeine may be considered a slow-onset modifier of neurogenesis, and that its contribution is probably related to habituation or adaptation to caffeine, which presumably induces compensatory changes in systems where it influences biochemical effects and alters activity, such as cortical, thalamic and striatal neurons.

It is also possible that homeostasis requires a limited supply of the factors for sustained adult neurogenesis. More specifically, considering the first results on the inhibitory effect of neuroinflammation upon neurogenesis [463,464], adenosine involvement in the control of neuroinflammation (and in particular, A2AR-mediated control of neuroinflammation) could be a potential mechanism by which neurogenesis is suppressed in neurodegenerative diseases. However, more recent studies conceive neuroinflammation as having a dual role in neurogenesis [465,466] and, thus, further studies are needed in order to test this hypothesis.

6. Concluding remarks

This more detailed review on the available evidence relating the adenosinergic system and different neurological and psychiatric disorders highlights the potential of manipulating the adenosine receptor neuromodulation system as a novel strategy to manage brain disorders (Fig. 1). However, in spite of this potential interest, it is also clear that a long road lies ahead to attempt confirming the effectiveness of manipulating this system to obtain some clinical benefit in the management of brain disorders. There are obvious and immediate questions related to the how and when to manipulate the adenosine system.

As a way of conclusion there seem to be a parallel benefit of manipulating both A1R and A2AR. Overall, it seems that A1R effectively act as a hurdle contributing to increase the threshold to initiate neurodegenerative processes and the relevance of A1R seems to decrease upon continuous activation. Since A1R function has not yet been shown to revert or arrest ongoing brain damage, it is expectable that bolstering the activation of A1R will be of little interest to control the death of brain tissue once the insult has begun its damaging effects. However, since all neurodegenerative processes are evolving conditions, targeting A1R activation may be of real interest if one considers that it may control the spreading of neurodegeneration; likewise, bolstering A1R activation may also be of interest when the time-span between the initial impact of the insult and the initiation of the neurodegenerative process is large, i.e. when the initial damaging insults sets a cascade of modifications that allow for compensatory mechanisms to delay more permanent and irreversible damage. The work of Detlev Boison has largely set the stage to provide a tentative answer to the question of how to manipulate A1R function: instead of using A1R agonists (which cause profound peripheral effects), it seems more effective to control the activation of A1R by enhancing the endogenous adenosine levels through inhibition of the activity of adenosine kinase. Albeit promising, the mechanisms, long-term consequences and potential drawbacks of this strategy still have to be explored. Thus, it is still not known how the inhibition of adenosine kinase changes the extracellular levels of adenosine (in the brain parenchyma and also in synapses), if it causes long-term changes in adenosine metabolism (as occurs for long-term effects related with the continuous activation of A1R with A1R agonists) and if it causes changes in the expression, density and subcellular localization of both A1R and A2AR. Also, given that adenosine metabolism takes place intracellularly and the neuroprotective actions of adenosine have been shown to depend on the action of extracellular adenosine on A1R, there is a clear need to better comprehend the transport of adenosine across cell membranes through nucleoside transporters, which may become an eventually more tempting target that adenosine kinase. There is also the question of providing a mechanistic rationale for this A1R-mediated neuroprotective effect of adenosine kinase inhibitor. Thus, it seems an established fact that bolstering A1R affords neuroprotection; however, the mechanism(s) underlying A1R-induced neuroprotection is still unclear (see [84] for a detailed discussion). Finally, the possible negative impact of manipulating adenosine kinase still remains to be explored (see [356]). But the main message here is that the inhibition of adenosine kinase affords an evident benefit in experimental models of

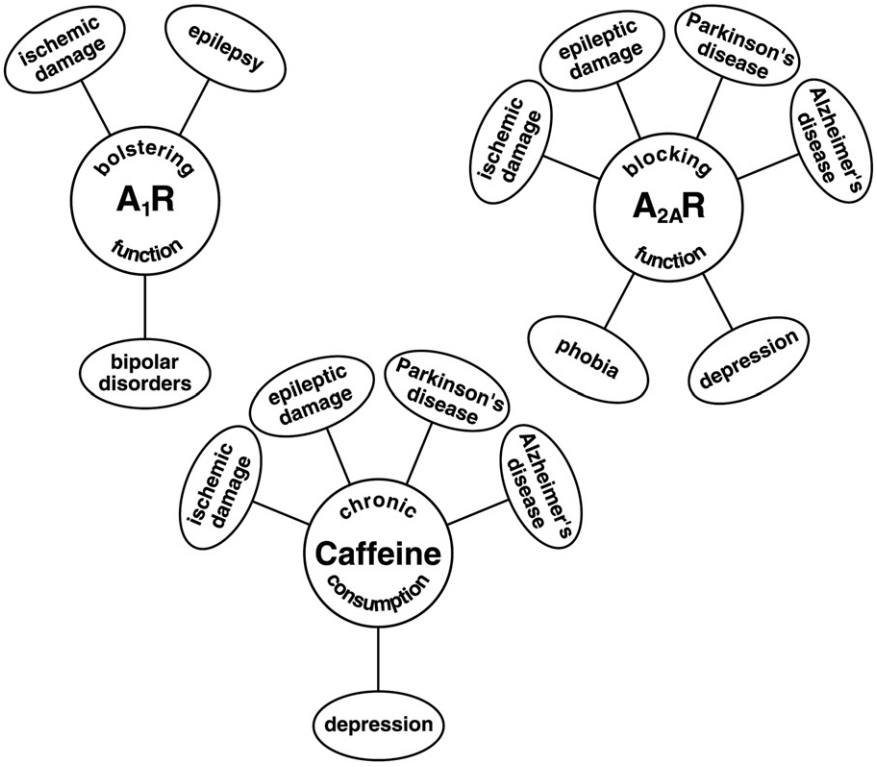

Fig. 1. Proposed impact of different manipulations of the adenosine neuromodulation system to control both neurological and psychiatric disorders.

brain ischemia and epilepsy. Whether one may provide a proof of concept for a similar neuroprotective potential of adenosine kinase inhibitors in other brain disorders still remains to be explored. Furthermore, in relation to the translational potential of this strategy, there is the clear need to explore the biochemistry of adenosine kinase and the neurochemical impact of its inhibition in human tissue, especially in view of the existence of polymorphisms of adenosine kinase in humans that may be associated with different susceptibility to brain disorders.

The other 'competing' view on the impact of the adenosine neuromodulation system on brain damage is centered on the role of A2AR, namely on the ability of A2AR blockade to attenuate the burden of most brain disorders (Fig. 1). The last years have witnessed a substantial increase in the number of reports documenting the ability of the pharmacological or genetic blockade of A2AR to attenuate brain damage caused by different insults. However, the underlying mechanisms are still to be unravelled, and there seems to be nearly as many possible mechanisms as researchers dedicated to the subject (see [84] for a detailed discussion of putative mechanisms operated by A2AR to control brain damage). It should also be noted that there are some reports suggesting that in some particular models it seems to be the activation rather than the blockade of A2AR that seems to afford neuroprotection. This mostly occurs in models involving the degeneration of striatal neurons; this strengthens the idea that postsynaptic A2AR in striatal medium spiny neurons are clearly an 'aberrant' population of A2AR: these receptors make the striatum the brain region with the largest density of A2AR, but these A2AR display properties often opposite of these displayed by other A2AR (e.g. [369]) and, therefore, should not be used as models of A2AR functioning in the brain but solely as models of what they are, i.e. controllers of signal processing in medium spiny neuron that are not related to neuroprotection. In view of our surprisingly scarce knowledge on the physiological role(s) of A2AR in the central nervous system, it is not surprising that we are still at a stage of phenomenological rather than mechanistic understanding of the impact of A2AR on the complex processes of brain dysfunction and evolving damage associated with different brain disorders. The role of A2AR in the control of brain damage is further complicated by the plasticity of its expression and its promiscuity in terms of recruitment of intracellular signalling pathways, which leads to the hypothesis that the newly expressed A2AR upon brain insults (see [8] for a review on the changes of A2AR expression and density upon brain damage) may fulfil roles different from constitutively expressed A2AR. And certainly without this fundamental supportive information, we currently lack a rationale to logically sustain any proposal on when and how to manipulate A2AR function to attempt controlling the demise(s) of brain disorders. There is another question of particular importance when considering the translational interest of A2AR: we still know surprisingly little about A2AR in the human brain, either in terms of its pharmacological properties, localization, function(s) and modifications upon brain disorders. And this is crucial information to evaluate the extent to which animal models are representative of the role of this receptor in the human brain.

This summary, the potential and current uncertainties related with the interest of manipulating either A1R or A2AR, leads to an obvious question related to the role of adenosine (the actual endogenous ligand) in the control of brain disorders. Clearly the arguments that both A1R activation and A2AR blockade may afford benefits in the control of brain disorders means that adenosine plays a double role in the control of brain disorders. There are two parallel groups of questions that need to be considered. First, from the intervention point of view, the obvious suggestion should be to link both strategies in a common framework. This would mean that the most powerful neuroprotective strategy targeting the adenosine neuromodulation system should be based on a combined inhibition of adenosine kinase with a blockade of A2AR, as previously proposed [40]. But this should require prior investigation of the impact of A2AR blockade on adenosine metabolism (i.e. does it affect the expression or activity of adenosine kinase or of adenosine transport?) and, conversely, on the impact of the inhibition of adenosine kinase on the expression, density, localization, transducing systems and functions of A2AR. The second major and most fundamental question is related to our current lack of knowledge on the metabolism of adenosine: thus questions such as

activity- or pathology-related fluctuations of the extracellular levels of adenosine remain unanswered and the subcellular localization of all the players controlling these extracellular adenosine levels in brain tissue also remains unexplored. In fact, knowing when, where and how the extracellular levels of adenosine are changing in different definable extracellular domains in the brain parenchyma (synaptic, neuronal-astrocytic, astrocytic-vascular or astrocytic-microglia domains) as well as in endothelial cells forming brain barriers or in infiltrating myeloid cells, seems of fundamental important to allow predicting the impact of manipulating the adenosine modulation system.

The last concluding remark is related to the knowledge gathered from the impact of caffeine consumption on brain disorders. From the superficial point of view, there is an (apparently) easy conclusion that can be drawn: the chronic consumption of moderate doses of caffeine seems to afford a prophylactic benefit since it decreases the incidence of most brain disorders (Fig. 1). The situations seem clearer in animal models (see [250]) than in humans, where most studies have evaluated the consumption of coffee, which is certainly rich in caffeine but where numerous other active compounds are present. The effects of caffeine have largely been interpreted as resulting from an effect on the adenosine neuromodulation system. In fact, the neuroprotective effects of caffeine seem to be mimicked by A2AR blockade in different animal models of brain disorders (reviewed in [250]). However, the observation that either chronic caffeine consumption or A2AR blockade afford neuroprotection cannot be taken as a demonstration that chronic caffeine intake is acting through A2AR blockade to afford neuroprotection and the fact that the two manipulations cause the same overall effect makes it particularly difficult to actually demonstrate a causal link. The question of how caffeine is acting to afford neuroprotection is particularly tricky to discuss since we still do not know the actual levels of caffeine in the brain parenchyma upon its chronic consumption (see [467] for a discussion on the available data) nor do we know how the chronic caffeine consumption affects the expression density and function of A1R and A2AR nor the extracellular metabolism of adenosine. Finally, it should be kept in mind that, although the available evidence supports that adenosine receptors should be the main targets of caffeine [4,8], there is evidence that caffeine can affect different other molecular targets with different efficiency such as phosphodiesterases, GABA-A receptors and controllers of intracellular calcium stores, just to name a few. And most of these alternative targets are actually constituted by different isoforms and it is currently unknown if caffeine differently affects each of the isoforms, and whether they play different roles in the control of brain damage. This question is particularly pertinent for humans, where we simply lack reliable information on the pharmacodynamic of caffeine in brain tissue. Thus, although there is a tentative global impression that the prophylactic effects of caffeine can be taken as evidence for a role of the adenosine neuromodulation system in the control of brain disorders there still seems to be several open question to firmly secure this conclusion.

The impact of caffeine on brain disorders also opens another pertinent question related to the usefulness of targeting the adenosine neuromodulation system to manage brain disorders. Both the consumption of caffeine as well as the blockade of A2AR have proved efficient when administered before the insults triggering brain damage. Thus, they have been suggested to afford a prophylactic benefit; they have not been broadly shown to provide a benefit once the damage is progressing, i.e. they have not been shown to display therapeutic effects. To a large extent, the same occurs for A1R, which manipulation only affects brain damage if carried out in the temporal vicinity of the perturbing insult, albeit the manipulation of adenosine kinase was shown to actual revert the phenotype in an animal model of epilepsy [131]. Thus, it should be carefully evaluated if the proposal to target the adenosine neuromodulation system to manage brain disorders should focus on prophylaxis or also on treatment of these brain conditions.

In summary, the current status of knowledge on the potential interest of the adenosine neuromodulation system is rather exciting. Albeit there are several open questions that demand careful attention, the general impression is that there is a great potential to further explore this system to develop novel strategies to control both neurological and psychiatric brain disorders.

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