Adenosine receptor signaling in the brain immune system

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Abstract

The brain immune system, which consists mainly of astrocytes, microglia and infiltrating immune cells, is quiescent normally, but it is activated in response to pathophysiological events such as ischemia, trauma, inflammation and infection. Adenosine is an endogenous purine nucleoside that is generated at sites that are subjected to these 'stressful' conditions. Adenosine interacts with specific G-protein-coupled receptors on astrocytes, microglia and infiltrating immune cells to regulate the function of the immune system in the brain. Although many of the effects of adenosine on immune-competent cells in the brain protect neuronal integrity, adenosine might also aggravate neuronal injury by promoting inflammatory processes. A more complete understanding of adenosine receptor function in the brain immune system should help develop novel therapeutic ways to treat brain disorders that are associated with a dysfunctional immune response.

Adenosine regulates brain function in health and disease

The purine nucleoside adenosine is a modulatory substance that is studied by researchers from different biomedical areas because of the plethora of its actions on organs and tissues. Probably one of the most widely recognized effects of adenosine is its ability to control CNS functions in both physiological and pathophysiological conditions. Adenosine interacts with four receptors (A_1, A_{2A}, A_{2B} and A_3 receptors) [1,2], which are seven-membrane-spanning proteins that couple to heterotrimeric G proteins to access several intracellular signaling pathways. Although adenosine is present at low concentrations in the extracellular space, metabolically stressful conditions increase dramatically its extracellular levels. Physiological, tonic stimulation of adenosine receptors by extracellular adenosine and adenosine receptor activation following modest increases in extracellular adenosine concentrations have important roles in the modulation of many brain functions, most notably the regulation of sleep and arousal, locomotion, anxiety, cognition and memory [3]. In this regard it is noteworthy that several mechanisms have been proposed to explain the stimulant effects of caffeine, but antagonism of adenosine receptors is most likely to account for the primary mode of action [4]. By contrast, the metabolic stress associated with hypoxia, ischemia, trauma and excessive neuronal firing elicits large increases in the concentration of extracellular adenosine, which has an important role in controlling subsequent tissue damage. Although the actions of extracellular adenosine are mainly protective, it is an imperfect endogenous neuroprotective agent because, in some scenarios, adenosine receptor stimulation further aggravates tissue damage [5,6]. These

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injurious effects are caused mainly by activation of A_{2A} receptors and they appear to manifest in a delayed fashion [5].

The protective and regenerative functions of adenosine after acute injury are several-fold [5, 6]. Immediately following the onset of harmful stimuli, activation of A_1 receptors by adenosine exerts a potent, presynaptic, feedback-inhibitory effect on the release of injurious excitatory neurotransmitters, mainly glutamate. At the same time, adenosine hyperpolarizes the postsynaptic membrane, restrains activation of NMDA receptors and limits Ca^{2+} influx, which prevents the generation and propagation of excitatory action potentials, another A_1 receptor-mediated effect. A more delayed protective pathway involves isolating the damaged tissue by an astrocytic scar and potentiating the astrocytic support of neurons [7]. Finally, in the long term, adenosine might be instrumental in ridding the affected tissue of dead cells and debris by inducing microglial proliferation and phagocytosis. Furthermore, there is indirect evidence that adenosine might help to complete tissue remodeling after injury by promoting angiogenesis and, thus, facilitating the replacement of dysfunctional blood vessels [8].

The early protective effects of adenosine, which appear to target mainly neuronal cells, are the subject of several recent reviews [9–12]. In this review we focus on the delayed actions of adenosine, which are both protective and harmful. These involve mainly the modulation of immune events that follow injurious insults such as metabolic, traumatic, and either acute or chronic inflammatory conditions. First, we discuss the mechanisms by which extracellular adenosine concentrations increase during metabolic stress in the CNS. Second, because cells of the immune system in the CNS, including astrocytes, microglia and infiltrating macrophages, are key players in the delayed modulatory effects of adenosine subsequent to tissue injury, we provide an insight into how adenosine modulates the function of these cell types. Finally, we address the issue of how a better understanding of regulation of the CNS immune response by adenosine might lead to improved therapies for ischemic, inflammatory and degenerative diseases.

Adenosine metabolism in the CNS

Physiological actions of adenosine result almost exclusively from activation of cell-surface adenosine receptors and the stimulation of downstream intracellular pathways. Processes that are related to the generation, release, cellular uptake and metabolism of adenosine determine its bioavailability at receptor sites [1,2]. There are two sources of extracellular adenosine: release of adenosine from the intracellular space via specialized transporters; and extracellular conversion of released adenine nucleotides (ATP, ADP and AMP) by a cascade of ectonucleotidases that includes CD39 (also known as nucleoside triphosphate dephosphorylase) and CD73 (also known as 5′-ectonucleotidase) [13–15]. Virtually all cell types in the CNS contribute to the accumulation of extracellular adenosine. The cellular sources of adenosine, however, vary with the stimulus that evokes its release. For example, during high-frequency neuronal activity and seizure, neurons are likely to release large quantities of ATP [16,17], which can be converted to adenosine via CD39 and CD73. By contrast, glial elements might also constitute a source of extracellular adenosine following episodes of ischemia and hypoxia [18,19]. Ischemia promotes the intracellular accumulation of adenosine because ATP is dephosphorylated to adenosine by the metabolic enzyme 5′-nucleotidase and, at the same time, the activity of the salvage enzyme adenosine kinase, which performs the rephosphorylation of adenosine, is suppressed [20]. When adenosine reaches high concentrations inside the cell, it is expelled into the extracellular space by bidirectional, equilibrative, nucleoside transporters [18,19,21]. It has been demonstrated recently that high extracellular concentrations of both ATP and adenosine are elicited by treating hippocampal slices with the pro-inflammatory cytokine interleukin 1β (IL-1β) [22]. Although the release of ATP and adenosine in response to IL-1β depends on both glutamate receptor activity and

tetrodotoxin-sensitive Na^+ channels, the exact cellular source and mode of release of ATP and adenosine is unknown. Ischemia, head injury, seizure activity and inflammation induce rapid increases in extracellular adenosine concentrations to 30–100-times that of the resting concentration [23]. Whereas resting extracellular adenosine concentrations in the brain are 30–300 nM [24], it can reach 10–50 μM following 15-min ischemia [25]. Adenosine bioavailability is limited by its catabolism to inosine by adenosine deaminase. Conventional thinking is that inosine lacks biological activity, however recent studies document that it has potent neuroprotective and anti-inflammatory effects [26,27]. Inosine is degraded further to the stable end-product uric acid, which has anti-inflammatory properties and, as such, is a potential candidate agent for the treatment of multiple sclerosis [28].

Adenosine modulates the development of a neuroprotective astrocyte phenotype

Astrocytes are the major population of glial cells in the CNS and they have several important physiological properties that are related to CNS homeostasis. In response to noxious stimuli to the CNS, astrocytes undergo a process of proliferation, morphological change (hypertrophy of cell bodies, thickening and elongation of astrocytic processes) and increase the expression of glial fibrillary acidic protein [29]. This process, which is termed astrogliosis, is associated with enhanced release of growth factors and neurotrophins that support neuronal growth but might also lead to the formation of neuronal scars [29]. Another important aspect of astrocyte activation is that cells acquire immunocompetence, which is associated with enhanced production of inflammatory cytokines, increased expression of major histocompatibility complex II and augmented production of free radicals [30].

Astrocytes express all four subtypes of adenosine receptor, stimulation of which modulates various astrocyte functions. The best-studied aspects of the regulatory effects of adenosine are its effects on cell proliferation, survival and death (Figure 1). Adenosine acts at high-affinity A_1 receptors to reduce astrocyte proliferation [31]. This indicates that in physiological situations in which A_1 receptor expression is high, there might be tonic inhibition of astrocyte proliferation. By contrast, increased occupancy of A_{2A} receptors, which is expected to occur following upregulation of this receptor secondary to hypoxia, trauma and inflammation [5], increases astrocyte proliferation and activation [32,33]. This indicates that adenosine might be a key factor in inducing astrogliosis following ischemic events. Engagement of the low-affinity A_{2B} receptor increases reactive astrogliosis in cells pretreated with tumor necrosis factor α (TNF-α) but not in naïve cells [34]. Stimulation of the other low-affinity adenosine receptor type, the A_3 receptor, induces apoptosis in astrocytes [35–37]. Von Lubitz [23] has proposed that astrocyte death that is induced during severe metabolic stress by stimulating A_3 receptors with high concentrations of adenosine might isolate the worst-affected tissue by physically excising cells from sites of irreversible injury. This might help to shift energetic resources to less severely injured tissue (the penumbra) and increase the chance of survival for the penumbra.

In addition to regulating the proliferation and survival of astrocytes, adenosine has potent effects on the secretory functions of these cells (Figure 2). Stimulation of A_1 receptors causes the release of nerve growth factor (NGF) [38] and, thus, appears to have an important role in supporting neuronal survival and growth. A_{2A} receptor stimulation inhibits the expression of inducible nitric oxide synthase (iNOS), and thus the production of nitric oxide (NO), by astrocytes following stimulation with a combination of either lipopolysaccharide and interferon γ or TNF-α and IL-1β [39]. The production of NO by iNOS in the brain seems to contribute to the pathophysiology of many CNS diseases [40], so the inhibition of NO formation by adenosine might be an important protective mechanism during inflammatory conditions in the brain.

Stimulation of A_{2B} receptors elicits the release of IL-6 from astrocytes [41–43] and this increase in the production of IL-6 occurs by a transcriptional mechanism involving the transcription factors nuclear factor-IL6 (NF-IL6) and NF-κB [42]. Because IL-6 is neuroprotective against hypoxia and glutamate neurotoxicity [44], stimulation of A_{2B} receptors provides a damage-control mechanism during CNS injury. Another target of A_{2B} receptor-mediated activation of NF-IL6 is the gene that encodes protein targeting to glycogen (PTG) [45]. PTG is a glycogen-targeting subunit of the protein phosphatase 1 that is implicated in controlling glycogen concentrations in several tissues. The increase in PTG following A_{2B} receptor stimulation results in delayed synthesis of glycogen, which might replete the early loss in glycogen levels following ischemia [45]. Finally, A_3 receptor stimulation induces the synthesis of a neuroprotective chemokine called chemokine (C-C motif) ligand 2 (CCL2; known formerly as monocyte chemoattractant protein 1) by astrocytes [46]. Taken collectively, adenosine appears to alter astrocyte function in ways that are consistent with a neuroprotective role. Nevertheless, adenosine might also aggravate tissue injury by inducing excessive astrogliosis.

Regulation of the function of resident microglia by adenosine

Resident microglia constitute ∼ 10% of the cells in the CNS [47]. These cells are the intrinsic macrophages of the CNS and, although microglia and infiltrating macrophages have similar functions, they can be distinguished immunohistochemically [48]. Microglia respond rapidly and relatively uniformly to several kinds of injury with characteristic morphological changes, proliferation, upregulation of cell-surface molecules and production of soluble mediators. Most neurological disorders involve activation and, possibly, dysregulation of microglia.

Microglia express A_1 receptors, A_{2A} receptors and A_3 receptors, but there is no evidence that they contain A_{2B} receptors (Table 1). Adenosine stimulates the proliferation of naïve microglial cells through a mechanism that involves the simultaneous stimulation of A_1 receptors and A_2 receptors [49]. By contrast, adenosine also inhibits the proliferation of microglial cells: phorbol 12-myristate 13-acetate-stimulated microglial proliferation is reduced following treatment with an A_1 receptor agonist [50]. Similar to astrocytes, adenosine receptor stimulation causes microglial apoptosis [51]. Because the nonselective adenosine receptor agonist 2-chloroadenosine, but not selective A_1, A_2 and A_3 receptor agonists that were available, evoke apoptosis, it was suggested that this effect is mediated by an atypical adenosine receptor. Together, these observations indicate that adenosine receptor activation affects microglial proliferation and/or apoptosis in different ways, and that the outcome is likely to depend on factors such as the receptor subtype and the environment.

Although the proliferation and/or apoptosis of microglia are regulated by several adenosine receptors, the secretory activity of these cells appears to be stimulated by A_{2A} receptors. For example, A_{2A} receptor stimulation upregulates cyclooxygenase 2 (COX-2) and the release of prostaglandin E_2 (PGE_2), which might indicate a pro-inflammatory role of A_{2A} receptor stimulation [52]. By contrast, based on recent evidence that other products of COX-2, such as PGD_2 and 15-deoxy-PGJ_2, are essential for the resolution of inflammation [53], the induction of COX-2 activity by adenosine in microglial cells might be a beneficial, neuroprotective feature. Furthermore, A_{2A} receptor activation induces the synthesis and release of NGF [54]. Although microglia contain A_3 receptors, the stimulation of which results in increased phosphorylation of extracellular signal-regulated kinase 1,2 (ERK1,2) [55], the role of A_3 receptor stimulation in regulating microglial function is unclear. In summary, adenosine appears to have both pro-inflammatory and anti-inflammatory effects, and it is difficult to provide a clear picture of how adenosine affects microglial functions.

Adenosine receptors on infiltrating immune cells regulate inflammatory processes in the brain

Focal ischemia in the CNS is associated with the infiltration of several types of hematogenous cells, including granulocytes, macrophages and T cells [56]. Bacterial meningitis is characterized by pleocytosis of neutrophils into the cerebrospinal fluid [57]. Infiltration of monocytes and/or macrophages into the CNS is also an early feature of HIV-1 infection, and later recruitment of macrophages might be a key step in the development of HIV-1-associated dementia [58]. Although these infiltrating hematopoietic cells protect the CNS from invasion by microorganisms and eliminate debris at sites of tissue injury, they are also responsible for significant tissue damage because uncontrolled inflammation and immune activation can inflict further damage on the affected tissues. These cells, once activated, release many potentially neurotoxic mediators including pro-inflammatory cytokines, free radicals and pro-inflammatory lipid derivatives. All four types of adenosine receptor have been found on infiltrating hematopoietic cells, but the exact function of these receptors in regulating immune/inflammatory events in the CNS is understood poorly (Table 1).

A_1 receptor knockout mice are affected more severely than normal mice by experimental allergic encephalomyelitis, an animal model of multiple sclerosis. The increased demyelination and clinical course observed in A_1 receptor knockout mice is associated with increased activation of macrophages in the brain parenchyma [59]. Expression of the genes that encode the pro-inflammatory factors IL-1β and matrix metalloproteinase-12 is increased in macrophages from A_1 receptor knockout mice compared with wild-type controls, which indicates that A_1 receptors on macrophages initiate crucial anti-inflammatory signals [59]. In agreement with these observations, there is reduced expression of A_1 receptors in macrophages from the brains of patients with multiple sclerosis, which is proposed to be a potential contributing factor to the excessive inflammatory response in these patients [60].

Recently, A_{2A} receptors on bone-marrow-derived cells have been shown to contribute to ischemic brain injury. Selective inactivation of these receptors in chimeric mice protects against ischemic brain injury following occlusion of the middle cerebral artery [61]. This protection is accompanied by reduced concentrations of mRNAs of macrophage-derived pro-inflammatory mediators such as IL-1, IL-6 and IL-12 in the brain, which demonstrates that A_{2A} receptor stimulation has a pro-inflammatory effect in this model. However, the protective, anti-inflammatory effect of selectively inactivating A_{2A} receptors on bone marrow cells appears to be specific for the ischemic brain, because ischemic liver injury is exacerbated in these mice. Similar to the anti-inflammatory role of A_{2A} receptor activation in the liver, A_{2A} receptor stimulation prevents pleocytosis and breakdown of the blood–brain barrier in a rat model of endotoxin-induced meningitis [62]. Furthermore, A_{2A} receptor stimulation inhibits HIV-1 Tat-induced production of TNF-α by macrophages [63]. These latter observations confirm the generally held view that A_{2A} receptor stimulation is anti-inflammatory because it deactivates macrophages and neutrophils [64–66]. By contrast, the finding that selective inactivation of A_{2A} receptors on bone marrow cells prevents injury following middle cerebral arterial occlusion [61] indicates that the mechanisms that lead to and protect from injury might be different in ischemic brain parenchyma than other tissues.

Future perspectives and therapeutic implications

A large body of evidence supports the view that adenosine receptors might be targets for drug development in several disease states that affect the CNS [1–3,5–7]. However, with a few exceptions, there is no direct evidence that the beneficial effects are caused by interfering with the immune system of the brain. Based on the fact that A_1 receptor deficiency aggravates experimental allergic encephalomyelitis [59], A_1 receptor agonists might be worthy of

evaluation for the therapy of multiple sclerosis. Although A_1 receptor agonists have potent anti-ischemic effects in animal models, their therapeutic potential in ischemia might be hampered by desensitization and unwanted side-effects [5]. The study by Yu *et al.* [61] illustrates that A_{2a} receptors on immune cells might be responsible, in part at least, for the neuroprotective effects of A_{2A} receptor antagonists in stroke. Schwarzschild and coworkers [67] have proposed that the mechanism by which A_{2A} receptor antagonists reduce neuronal cell death during Parkinson's disease might involve a glial component, and that modulation of glial-cell function by A_{2A} receptor antagonists might indirectly maintain neuronal survival. By contrast, A_{2A} receptor agonists might be a potential treatment for infectious meningitis because they downregulate the injurious sequelae of brain inflammation [62].

Propentofylline has been developed for therapeutic purposes in dementia; it readily crosses the blood–brain barrier and acts by blocking the uptake of adenosine and inhibiting the phosphodiesterase enzyme [24]. The mechanism of action of propentofylline appears to be twofold both *in vitro* and *in vivo*; it inhibits the production of pro-inflammatory mediators by microglial cells, and it enhances the production of NGF by astrocytes [24,68,69]. Increasing the extracellular concentration of adenosine by inhibiting adenosine kinase and adenosine deaminase is useful in controlling seizures in animal models [70]. It remains to be determined whether the beneficial effects of any of these agents occur as a result of their immunomodulatory effects.

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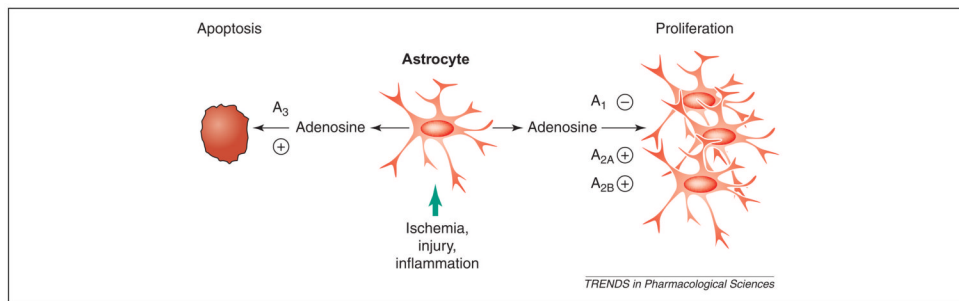
Figure 1.
Regulation of astrocyte proliferation and apoptosis by adenosine receptors. Astrocytes are a major source of adenosine during episodes of ischemia, injury and inflammation. Activation of A_1 receptors decreases astrocyte proliferation whereas A_{2A} and A_{2B} receptor stimulation enhance the proliferation of astrocytes. A_3 receptor stimulation induces astrocyte apoptosis.
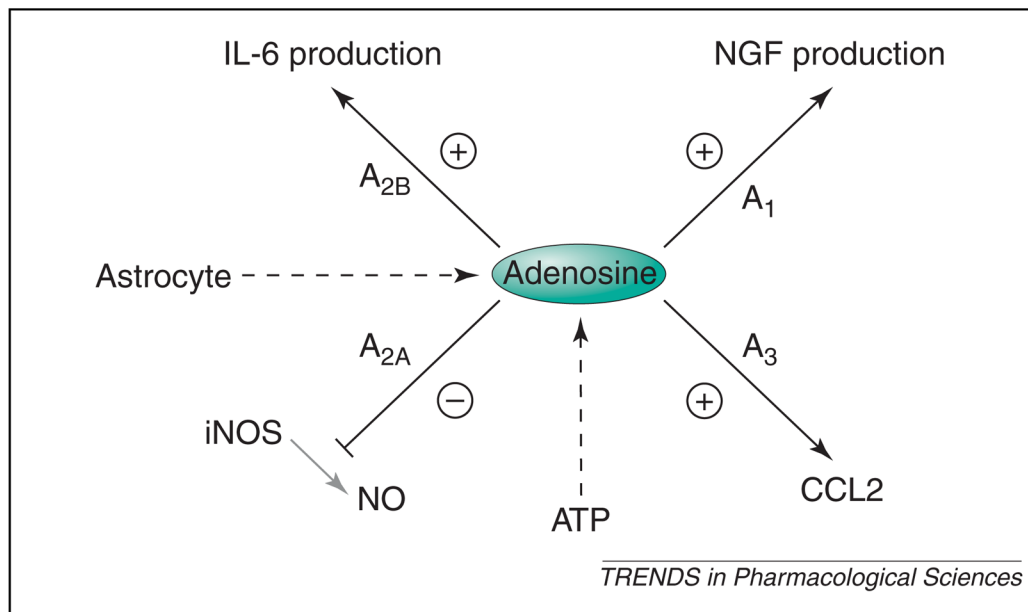
Figure 2.
The secretory functions of astrocytes are regulated by all four adenosine receptors. Adenosine that is either released from astrocytes or produced by the extracellular metabolism of ATP exerts neuroprotective effects by augmenting the production of the neuroprotective mediators interleukin 6 (IL-6), nerve growth factor (NGF) and chemokine (C-C motif) ligand 2 (CCL2), and by reducing the production of nitric oxide (NO) by inducible nitric oxide synthase (iNOS).

Table 1

Regulation of the function of microglia and infiltrating immune cells by adenosine receptors[a]

Receptor	Function
A_1	Promotes proliferation of naïve microglia
	Inhibits proliferation of phorbol myristate acetate- activated microglia
	Inhibits production of IL-1β and matrix metalloproteinase 12 by infiltrating macrophages
A_{2A}	Promotes proliferation of microglia
	Upregulates COX-2 expression and enhances release of prostaglandins in microglia
	Induces NGF release by microglia
	Increases production of IL-1, IL-6 and IL-12 by infiltrating cells
A_{2B}	Unknown
A_3	Increases ERK1,2 phosphorylation in microglia

[a] Abbreviations: COX-2, cyclooxygenase 2; ERK1,2, extracellular signal-regulated kinase 1,2; IL-1β, interleukin 1β; NGF, nerve growth factor.