

Adenosine receptor signaling in the brain immune system

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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 (A₁, A_{2A}, A_{2B} and A₃ 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 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 A₁ 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 Ca²⁺ influx, which prevents the generation and propagation of excitatory action potentials, another A₁ 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

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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 1 β (IL-1 β) [22]. Although the release

of ATP and adenosine in response to IL-1 β 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 μ M 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 A₁ receptors to reduce astrocyte proliferation [31].

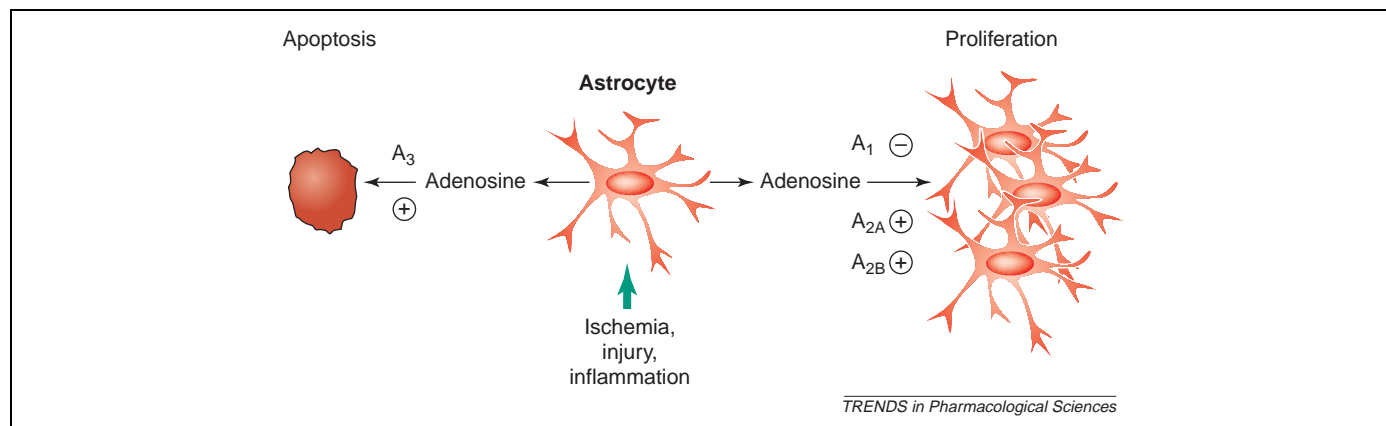


Figure 1. Regulation of astrocyte proliferation and apoptosis by adenosine receptors. Astrocytes are a major source of adenosine during episodes of ischemia, injury and inflammation. Activation of A₁ receptors decreases astrocyte proliferation whereas A_{2A} and A_{2B} receptor stimulation enhance the proliferation of astrocytes. A₃ receptor stimulation induces astrocyte apoptosis.

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-1 β [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- κ B [42]. Because IL-6 is neuroprotective against hypoxia and glutamate neurotoxicity [44],

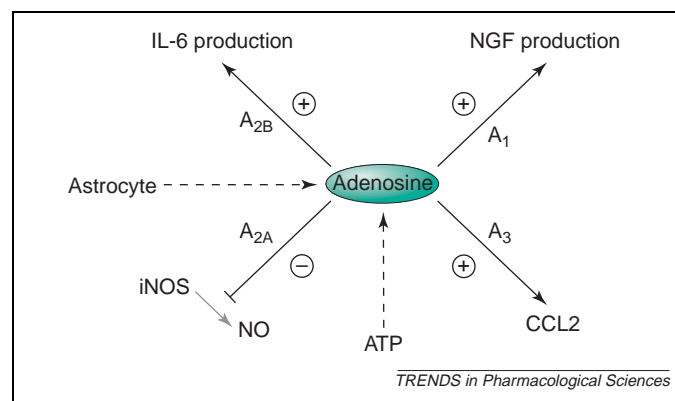


Figure 2. The secretory functions of astrocytes are regulated by all four adenosine receptors. Adenosine that is either released from astrocytes or produced by the extracellular metabolism of ATP exerts neuroprotective effects by augmenting the production of the neuroprotective mediators interleukin 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).

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-chloro-adenosine, 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 (PGE₂), 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 PGD₂ and 15-deoxy-PGJ₂, are essential for the resolution of inflammation [53], the induction of COX-2 activity by adenosine in microglial cells might be a

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-1 β 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

^aAbbreviations: COX-2, cyclooxygenase 2; ERK1,2, extracellular signal-regulated kinase 1,2; IL-1 β , interleukin 1 β ; NGF, nerve growth factor.

beneficial, neuroprotective feature. Furthermore, A_{2A} receptor activation induces the synthesis and release of NGF [54]. Although microglia contain A₃ receptors, the stimulation of which results in increased phosphorylation of extracellular signal-regulated kinase 1,2 (ERK1,2) [55], the role of A₃ 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).

A₁ 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 A₁ 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-1 β and matrix metalloproteinase-12 is increased in macrophages from A₁ receptor knockout mice compared

with wild-type controls, which indicates that A₁ receptors on macrophages initiate crucial anti-inflammatory signals [59]. In agreement with these observations, there is reduced expression of A₁ 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 A₁ receptor deficiency aggravates experimental allergic encephalomyelitis [59], A₁ receptor agonists might be worthy of evaluation for the therapy of multiple sclerosis. Although A₁ 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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References

- Ralevic, V. and Burnstock, G. (1998) Receptors for purines and pyrimidines. *Pharmacol. Rev.* 50, 413–492
- Fredholm, B.B. *et al.* (2001) International Union of Pharmacology. XXV. Nomenclature and classification of adenosine receptors. *Pharmacol. Rev.* 53, 527–552
- Ribeiro, J.A. *et al.* (2002) Adenosine receptors in the nervous system: pathophysiological implications. *Prog. Neurobiol.* 68, 377–392
- Huang, Z.L. *et al.* Adenosine A_{2A}, but not A₁, receptors mediate the arousal effect of caffeine. *Nat. Neurosci.* (in press)
- Cunha, R.A. (2005) Neuroprotection by adenosine in the brain: from A₁ receptor activation to A_{2A} receptor blockade. *Purinergic Signaling* 1, 111–134
- Picano, E. and Abbracchio, M.P. (2000) Adenosine, the imperfect endogenous anti-ischemic cardio-neuroprotector. *Brain Res. Bull.* 52, 75–82
- de Mendonca, A. *et al.* (2000) Adenosine: does it have a neuroprotective role after all? *Brain Res. Brain Res. Rev.* 33, 258–274
- Fischer, S. *et al.* (1995) Expression of vascular permeability factor/vascular endothelial growth factor in pig cerebral microvascular endothelial cells and its upregulation by adenosine. *Brain Res. Mol. Brain Res.* 28, 141–148
- Vizi, E.S. (2000) Role of high-affinity receptors and membrane transporters in nonsynaptic communication and drug action in the central nervous system. *Pharmacol. Rev.* 52, 63–89
- Cunha, R.A. (2001) Adenosine as a neuromodulator and as a homeostatic regulator in the nervous system: different roles, different sources and different receptors. *Neurochem. Int.* 38, 107–125
- Dunwiddie, T.V. and Masino, S.A. (2001) The role and regulation of adenosine in the central nervous system. *Annu. Rev. Neurosci.* 24, 31–55
- Stone, T.W. (2002) Purines and neuroprotection. *Adv. Exp. Med. Biol.* 513, 249–280
- Sperlágh, B. and Vizi, E.S. (1996) Neuronal synthesis, storage and release of ATP. *Semin. Neurosci.* 8, 175–186
- Zimmermann, H. (2000) Extracellular metabolism of ATP and other nucleotides. *Naunyn Schmiedeberg's Arch. Pharmacol.* 362, 299–309
- Linden, J. (2001) Molecular approach to adenosine receptors: receptor-mediated mechanisms of tissue protection. *Annu. Rev. Pharmacol. Toxicol.* 41, 775–787
- Mitchell, J.B. *et al.* (1993) Activity-dependent release of endogenous adenosine modulates synaptic responses in the rat hippocampus. *J. Neurosci.* 13, 3439–3447
- Cunha, R.A. *et al.* (1996) Preferential release of ATP and its extracellular catabolism as a source of adenosine upon high- but not low-frequency stimulation of rat hippocampal slices. *J. Neurochem.* 67, 2180–2187
- Parkinson, F.E. and Xiong, W. (2004) Stimulus- and cell-type-specific release of purines in cultured rat forebrain astrocytes and neurons. *J. Neurochem.* 88, 1305–1312
- Parkinson, F.E. *et al.* (2005) Astrocytes and neurons: different roles in regulating adenosine levels. *Neurol. Res.* 27, 153–160
- Lynch, J.J., 3rd. *et al.* (1998) Inhibition of adenosine kinase during oxygen-glucose deprivation in rat cortical neuronal cultures. *Neurosci. Lett.* 252, 207–210
- Jennings, L.L. *et al.* (2001) Distinct regional distribution of human equilibrative nucleoside transporter proteins 1 and 2 (hENT1 and hENT2) in the central nervous system. *Neuropharmacology* 40, 722–731
- Sperlágh, B. *et al.* (2004) Potent effect of interleukin-1 β to evoke ATP and adenosine release from rat hippocampal slices. *J. Neuroimmunol.* 151, 33–39
- von Lubitz, D.K. (1999) Adenosine and cerebral ischemia: therapeutic future or death of a brave concept? *Eur. J. Pharmacol.* 371, 85–102
- Rudolphi, K.A. and Schubert, P. (1997) Modulation of neuronal and glial cell function by adenosine and neuroprotection in vascular dementia. *Behav. Brain Res.* 83, 123–128
- Hagberg, H. *et al.* (1987) Extracellular adenosine, inosine, hypoxanthine, and xanthine in relation to tissue nucleotides and purines in rat striatum during transient ischemia. *J. Neurochem.* 49, 227–231
- Haskó, G. *et al.* (2000) Inosine inhibits inflammatory cytokine production by a posttranscriptional mechanism and protects against endotoxin-induced shock. *J. Immunol.* 164, 1013–1019
- Haskó, G. *et al.* (2004) Immunomodulatory and neuroprotective effects of inosine. *Trends Pharmacol. Sci.* 25, 152–157
- Spitsin, S. *et al.* (2001) Inactivation of peroxynitrite in multiple sclerosis patients after oral administration of inosine may suggest possible approaches to therapy of the disease. *Mult. Scler.* 7, 313–319
- Liberto, C.M. *et al.* (2004) Pro-regenerative properties of cytokine-activated astrocytes. *J. Neurochem.* 89, 1092–1100
- Dong, Y. and Benveniste, E.N. (2001) Immune function of astrocytes. *Glia* 36, 180–190
- Rathbone, M.P. *et al.* (1991) Extracellular guanosine increases astrocyte cAMP: inhibition by adenosine A₂ antagonists. *Neuroreport* 2, 661–664
- Hindley, S. *et al.* (1994) Stimulation of reactive astrogliosis *in vivo* by extracellular adenosine diphosphate or an adenosine A₂ receptor agonist. *J. Neurosci. Res.* 38, 399–406
- Brambilla, R. *et al.* (2003) Blockade of A_{2A} adenosine receptors prevents basic fibroblast growth factor-induced reactive astrogliosis in rat striatal primary astrocytes. *Glia* 43, 190–194
- Trincavelli, M.L. *et al.* (2004) Regulation of A_{2B} adenosine receptor functioning by tumour necrosis factor α in human astroglial cells. *J. Neurochem.* 91, 1180–1190
- Abbracchio, M.P. *et al.* (1997) Modulation of apoptosis by adenosine in the central nervous system: a possible role for the A₃ receptor. Pathophysiological significance and therapeutic implications for neurodegenerative disorders. *Ann. New York Acad. Sci.* 825, 11–22
- Di Iorio, P. *et al.* (2002) Mechanisms of apoptosis induced by purine nucleosides in astrocytes. *Glia* 38, 179–190
- Appel, E. *et al.* (2001) Roles of BCL-2 and caspase 3 in the adenosine A₃ receptor-induced apoptosis. *J. Mol. Neurosci.* 17, 285–292
- Ciccarelli, R. *et al.* (1999) Activation of A₁ adenosine or mGlu₃ metabotropic glutamate receptors enhances the release of nerve growth factor and S-100 β protein from cultured astrocytes. *Glia* 27, 275–281
- Brodie, C. *et al.* (1998) Activation of the A_{2A} adenosine receptor inhibits nitric oxide production in glial cells. *FEBS Lett.* 429, 139–142
- Licinio, J. *et al.* (1999) Brain iNOS: current understanding and clinical implications. *Mol. Med. Today* 5, 225–232
- Fiebich, B.L. *et al.* (1996) Adenosine A_{2b} receptors mediate an increase in interleukin (IL)-6 mRNA and IL-6 protein synthesis in human astrogloma cells. *J. Neurochem.* 66, 1426–1431
- Schwaninger, M. *et al.* (1997) Stimulation of interleukin-6 secretion and gene transcription in primary astrocytes by adenosine. *J. Neurochem.* 69, 1145–1150
- Fiebich, B.L. *et al.* (2005) IL-6 expression induced by adenosine A_{2b} receptor stimulation in U373 MG cells depends on p38 mitogen activated kinase and protein kinase C. *Neurochem. Int.* 46, 501–512

- 44 Maeda, Y. *et al.* (1994) Hypoxia/reoxygenation-mediated induction of astrocyte interleukin 6: a paracrine mechanism potentially enhancing neuron survival. *J. Exp. Med.* 180, 2297–2308
- 45 Allaman, I. *et al.* (2003) A2B receptor activation promotes glycogen synthesis in astrocytes through modulation of gene expression. *Am. J. Physiol. Cell Physiol.* 284, C696–C704
- 46 Wittendorp, M.C. *et al.* (2004) Adenosine A3 receptor-induced CCL2 synthesis in cultured mouse astrocytes. *Glia* 46, 410–418
- 47 Minagar, A. *et al.* (2002) The role of macrophage/microglia and astrocytes in the pathogenesis of three neurologic disorders: HIV-associated dementia, Alzheimer disease, and multiple sclerosis. *J. Neurol. Sci.* 202, 13–23
- 48 Stoll, G. and Jander, S. (1999) The role of microglia and macrophages in the pathophysiology of the CNS. *Prog. Neurobiol.* 58, 233–247
- 49 Gebicke-Haerter, P.J. *et al.* (1996) Both adenosine A1- and A2-receptors are required to stimulate microglial proliferation. *Neurochem. Int.* 29, 37–42
- 50 Si, Q.S. *et al.* (1996) Adenosine and propentofylline inhibit the proliferation of cultured microglial cells. *Exp. Neurol.* 137, 345–349
- 51 Ogata, T. and Schubert, P. (1996) Programmed cell death in rat microglia is controlled by extracellular adenosine. *Neurosci. Lett.* 218, 91–94
- 52 Fiebich, B.L. *et al.* (1996) Cyclooxygenase-2 expression in rat microglia is induced by adenosine A2a-receptors. *Glia* 18, 152–160
- 53 Gilroy, D.W. *et al.* (2004) Inflammatory resolution: new opportunities for drug discovery. *Nat. Rev. Drug Discov.* 3, 401–416
- 54 Heese, K. *et al.* (1997) Nerve growth factor (NGF) expression in rat microglia is induced by adenosine A2a-receptors. *Neurosci. Lett.* 231, 83–86
- 55 Hammarberg, C. *et al.* (2003) Evidence for functional adenosine A3 receptors in microglia cells. *J. Neurochem.* 86, 1051–1054
- 56 Stoll, G. *et al.* (1998) Inflammation and glial responses in ischemic brain lesions. *Prog. Neurobiol.* 56, 149–171
- 57 Kim, K.S. (2003) Pathogenesis of bacterial meningitis: from bacteraemia to neuronal injury. *Nat. Rev. Neurosci.* 4, 376–385
- 58 Rappaport, J. *et al.* (1999) Molecular pathway involved in HIV-1-induced CNS pathology: role of viral regulatory protein, Tat. *J. Leukoc. Biol.* 65, 458–465
- 59 Tsutsui, S. *et al.* (2004) A1 adenosine receptor upregulation and activation attenuates neuroinflammation and demyelination in a model of multiple sclerosis. *J. Neurosci.* 24, 1521–1529
- 60 Johnston, J.B. *et al.* (2001) Diminished adenosine A1 receptor expression on macrophages in brain and blood of patients with multiple sclerosis. *Ann. Neurol.* 49, 650–658
- 61 Yu, L. *et al.* (2004) Selective inactivation or reconstitution of adenosine A2A receptors in bone marrow cells reveals their significant contribution to the development of ischemic brain injury. *Nat. Med.* 10, 1081–1087
- 62 Sullivan, G.W. *et al.* (1999) Neutrophil A2A adenosine receptor inhibits inflammation in a rat model of meningitis: synergy with the type IV phosphodiesterase inhibitor, rolipram. *J. Infect. Dis.* 180, 1550–1560
- 63 Fotheringham, J. *et al.* (2004) Adenosine receptors control HIV-1 Tat-induced inflammatory responses through protein phosphatase. *Virology* 327, 186–195
- 64 Haskó, G. *et al.* (1996) Adenosine receptor agonists differentially regulate IL-10, TNF- α , and nitric oxide production in RAW 264.7 macrophages and in endotoxemic mice. *J. Immunol.* 157, 4634–4640
- 65 Haskó, G. *et al.* (2000) Adenosine inhibits IL-12 and TNF- α production via adenosine A_{2A} receptor-dependent and independent mechanisms. *FASEB J.* 14, 2065–2074
- 66 Haskó, G. and Cronstein, B.N. (2004) Adenosine: an endogenous regulator of innate immunity. *Trends Immunol.* 25, 33–39
- 67 Schwarzschild, M.A. *et al.* (2003) Neuroprotection by caffeine and more specific A2A receptor antagonists in animal models of Parkinson's disease. *Neurology* 61, S55–S61
- 68 Plaschke, K. *et al.* (2001) Neuromodulatory effect of propentofylline on rat brain under acute and long-term hypoperfusion. *Br. J. Pharmacol.* 133, 107–116
- 69 Chauhan, N.B. *et al.* (2005) Propentofylline attenuates tau hyperphosphorylation in Alzheimer's Swedish mutant model Tg2576. *Neuropharmacology* 48, 93–104
- 70 Boison, D. (2005) Adenosine and epilepsy: from therapeutic rationale to new therapeutic strategies. *Neuroscientist* 11, 25–36

Current Opinion in Pharmacology

The August 2005 issue of *Current Opinion in Pharmacology* focuses on two areas of pharmacology. The first, edited by Simon J. Cook and Michael Wakelam, reviews some of the current therapeutic targets of interest in cancer pharmacology, such as EGFR, BRCA, phosphoinositide 3-kinases, the cell cycle and the Raf-MEK-ERK pathway. The second, edited by Christopher D. Buckley and David Simmons, focuses on anti-inflammatory targets and discusses well-established treatments such as aspirin, plus the identification of new targets, such as siglecs and T-cell receptors. The issue includes:

Phosphoinositide 3-kinases as drug targets in cancer

Len Stephens, Roger Williams and Phillip Hawkins, pp. 357–365

Targeting the DNA repair defect of BRCA tumours

Nicholas Turner, Andrew Tutt and Alan Ashworth, pp. 388–393

Aspirin and steroids: new mechanistic findings and avenues for drug discovery

Derek W. Gilroy and Mauro Perretti, pp. 405–411

mTOR – beyond transplantation

Deborah A. Young and Cheryl L. Nickerson-Nutter, pp. 418–423

Siglecs in innate immunity

Paul R. Crocker, pp. 431–437