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## REVIEW

# Adenosine and its receptors as therapeutic targets: An overview



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### KEYWORDS

Purine ribonucleosides;  
Adenosine;  
A<sub>1</sub>, A<sub>2A</sub>, A<sub>2B</sub>, A<sub>3</sub> receptors

**Abstract** The main goal of the authors is to present an overview of adenosine and its receptors, which are G-protein coupled receptors. The four known adenosine receptor subtypes are discussed along with the therapeutic potential indicating that these receptors can serve as targets for various dreadful diseases.

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## 1. Introduction

Adenosine (Fig. 1) is an endogenous nucleoside composed of adenine attached to a ribose. It is an essential compound of life distributed in several mammalian tissues (Cacciari et al., 2005). Adenosine was first recognized as a physiologic regulator of coronary vascular tone by Drury and Szent-György (1929), however it was until 1970 that Sattin and Rall showed that adenosine regulates cell function via occupancy of specific receptors on the cell surface (Haskó et al., 2007; Sattin and Rall, 1970). Adenosine may either leave the intracellular space by exocytosis, or may generate by the enzymatic breakdown of extracellular ATP. ATP may also release from injured neurons and glial cells by passing the damaged plasma membrane (Tautenhahn et al., 2012).

The adenosine directly affects a variety of synaptic processes, signaling pathways and plays an important role in the regulation of several neurotransmitters in the central nervous system (CNS). Unlike a classical neurotransmitter, adenosine is neither stored in synaptic vesicles nor it acts exclusively on synapses. Its release and uptake are mediated by bidirectional nucleoside transporters whereby the direction of transport solely depends on the concentration gradient between the cytoplasm and the extracellular space. Adenosine is therefore considered as a neuromodulator affecting neural activity through multiple mechanisms presynaptically by controlling neurotransmitter release, postsynaptically by hyper or depolarizing neurons, and nonsynaptically mainly via regulatory effects on glial cells (Boison et al., 2012).

Moreover, it also has some characteristics of neurotransmitter as adenosine-producing enzymes are present in synapses. It exerts its actions through the interaction with receptors and its actions can be blocked by specific antagonists. Its actions are terminated by an efficient reuptake system and a metabolizing system (Cacciari et al., 2005).

Adenosine plays a vital role in various physiological functions. It is involved in the synthesis of nucleic acids, when linked to three phosphate groups; it forms ATP, the integral

component of the cellular energy system. It produces various pharmacological effects, both in periphery and in the central nervous system, through an action on specific receptors localized on cell membranes (Matsumoto et al., 2012).

Adenosine produced in hypoxic, ischemic, or inflamed environments reduces tissue injury and promotes repair. The intracellular production of adenosine is increased during hypoxia or ischemia (Linden, 2005). During cellular stress, local intracellular concentrations of adenosine increase followed by the active transport of adenosine into the extracellular space and subsequent activation of adenosine receptor (P<sub>1</sub>) subtypes (Shukla and Mishra, 1995).

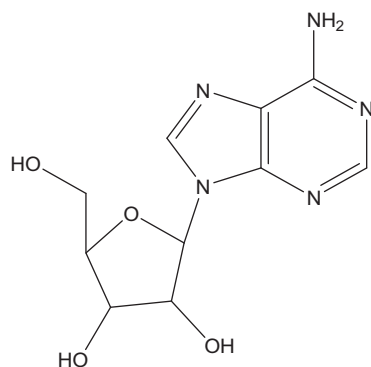
### 1.1. Adenosine formation and metabolism

Adenosine is an endogenous purine nucleoside constitutively present at low concentrations in the extracellular space, which is known to increase dramatically under metabolically stressful conditions. The reason for the increase is related to the activation of an auto regulatory loop, the function of which is to protect organs from injury following the initiating stressful stimuli (Poolsa and Holgate, 2006). Adenosine is formed at both intracellular and extracellular sites by two distinct pathways that involve two different substrates, namely AMP and S-adenosyl homocysteine and transported across cell membranes by nucleoside transporters (Zhou et al., 2009; Poulsen and Quinn 1998; Livingston et al., 2004).

After intracellular reuptake, adenosine undergoes rapid phosphorylation to AMP by adenosine kinase, or deamination to inosine by adenosine deaminase (Fig. 2). These pathways ensure the maintenance of intracellular adenosine concentrations through a strict enzymatic control. So, it is clear that there are essentially three systems that can account for inactivation and/or removal of adenosine in tissues: adenosine deaminase, kinase, and the uptake system (Fig. 2). Strategies to increase local concentrations of adenosine have included inhibition of enzymes responsible for the metabolic transformation of adenosine. Specifically, inhibitors of adenosine deaminase (ADA) and adenosine kinase (AK) have received considerable attention in an attempt to increase concentrations of endogenous adenosine (Fig. 3). Inhibition of adenosine kinase displays neuroprotective potential in areas as pain and inflammation (Mark et al., 2007).

Under hypoxic conditions, the adenosine reaches high concentrations inside the cell through a cascade of enzymatic actions and leads to the release of adenosine into the extracellular space through nucleoside transporters (Antonioli et al., 2008).

The other major pathway that contributes to high extracellular adenosine concentrations during metabolic stress is release and degradation of precursor adenine nucleotides (ATP, ADP and AMP) by a cascade of ectonucleotidases, which include CD39 (nucleoside triphosphate diphosphohydrolase) and CD73 (5'-ectonucleotidase). Adenosine accumu-



**Figure 1** Structure of adenosine.

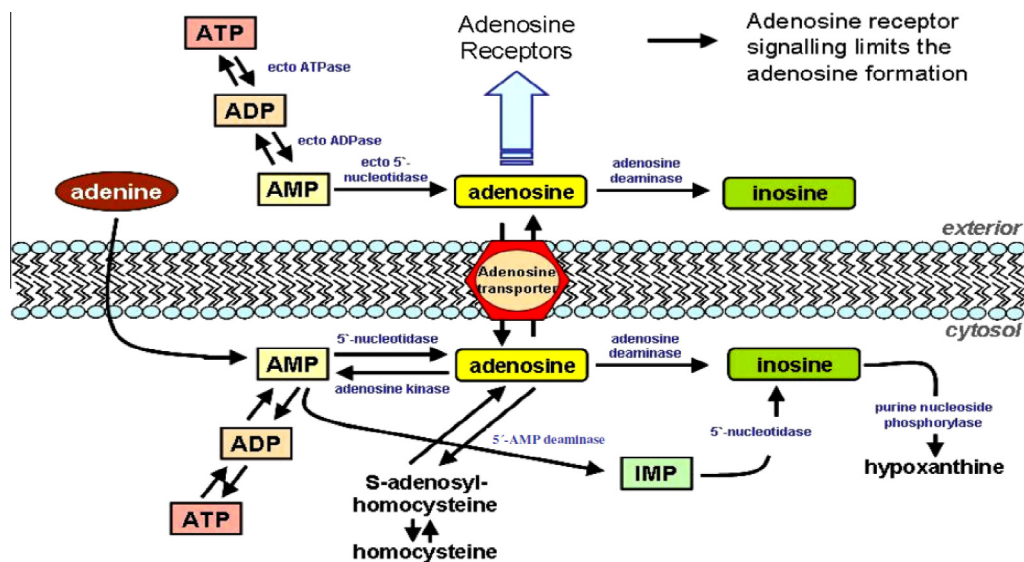


Figure 2 Adenosine formation and catabolism.

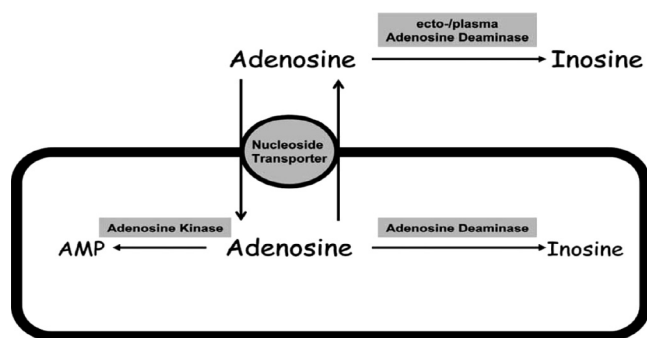


Figure 3 Intracellular and extracellular balancing system of adenosine.

lation is limited by its catabolism to inosine by adenosine deaminase.

## 2. Adenosine receptors and their classification

The extracellular purines e.g., adenosine, adenosine 5'-diphosphate (ADP) and adenosine 5'-triphosphate (ATP)] and pyrimidines [e.g., uridine 5'-diphosphate (UDP) and uridine 5'-triphosphate (UTP)] mediate diverse biological effects via cell-surface receptors termed as purinergic receptors. These receptors were first formally recognized by Burnstock et al. in 1978. He classified purinoceptors into two subtypes:  $P_1$  and  $P_2$  receptors, based on their pharmacological properties and molecular cloning (Ralevic and Burnstock, 1991).  $P_1$  purinoceptors recognize adenosine as principal natural ligand and  $P_2$  receptors have broad natural ligand specificity, recognizing ATP, ADP, UTP, UDP and some dinucleotides. The  $P_1$  and  $P_2$  receptor families are both further subdivided according to convergent molecular, biochemical, and pharmacological evidences (Matsumoto et al., 2012). These purinoceptors are present in most organ systems in the body, and they play an important role in contractile tone of various arteries including

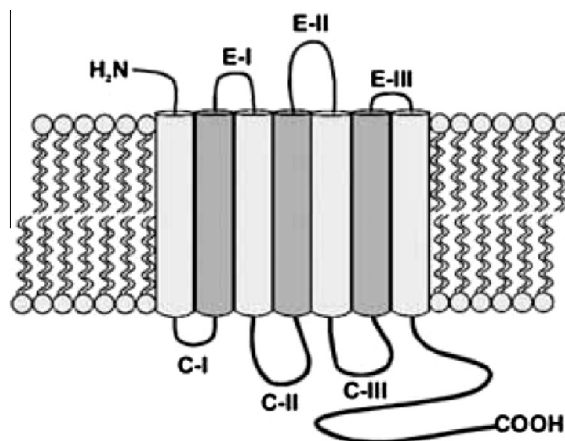


Figure 4 Adenosine receptor model (Figure adapted from Hitchinson et al., 2006).

cerebral arteries, thoracic aorta, mesenteric and femoral arteries. All these receptors belong to class A family of G-protein coupled receptor (GPCR) super-family (Fig. 4) (Göblyös and IJzerman, 2009).

Fig. 4 represents adenosine receptor model. The extracellular domains of the receptor protein comprise the N-terminus and three extracellular loops while the intracellular domains of the receptor protein comprise the C-terminus and three intracellular loops (Hutchinson and Scammells, 2006). Based on IUPHAR nomenclature and classification rules  $P_1$  receptors are also named adenosine receptors (after the endogenous ligand), while the subtypes are named the  $A_1$ ,  $A_{2A}$ ,  $A_{2B}$  and  $A_3$  subtypes, the subscripts (1, 2A, 2B and 3) representing classification neutral labels. Each of the subtypes has been characterized by molecular cloning, agonist activity profile, antagonist activity profile, G protein-coupling and effector systems. The adenosine receptors have been characterized completely allowing determination of actual receptor protein primary sequences, which is fundamental to study receptor structure,

**Table 1** Distribution and expression of adenosine receptors.

Expression level	A <sub>1</sub> receptors	A <sub>2A</sub> receptors	A <sub>2B</sub> receptors	A <sub>3</sub> receptors
High expression	Brain (cortex, hippocampus, cerebellum), spinal cord, eye, adrenal gland, atria (Poulsen and Quinn, 1998)	Blood platelets, olfactory bulb Spleen, thymus, leukocytes (Fredholm et al., 2002)	Cecum, colon, bladder (Cacciari et al., 2005)	Testis (rat), mast cells (rat) (Poulsen and Quinn, 1998)
Intermediate expression	Other brain regions, skeletal muscles, liver, kidney, adipose tissue (Poulsen and Quinn, 1998)	Heart, lung, blood vessels, peripheral nerves (Fredholm et al., 2002)	Lung, blood vessels, eye, mast cells (Cacciari et al., 2005)	Cerebellum, hippocampus (Poulsen and Quinn, 1998)
Low expression	Lungs (but probably higher in bronchi), pancreas (Poulsen and Quinn, 1998)	Other brain regions (Fredholm et al., 2002)	Adipose tissue, adrenal gland, brain, kidney (Cacciari et al., 2005)	Thyroid, most of brain adrenal gland, spleen, liver, kidney, heart (Poulsen and Quinn, 1998)

function and regulation at the molecular level (Poulsen and Quinn, 1998). Experimental evidence has been reported for the existence of two different histidine residues at the active site of the adenosine receptor, one of which is involved in binding with agonists while the other binds with antagonists of adenosine (Shukla and Mishra, 1995).

At present there are four established adenosine receptors in humans that have been cloned consisting of the A<sub>1</sub>, A<sub>2A</sub>, A<sub>2B</sub> and A<sub>3</sub> receptors. Adenosine and its agonists act via these receptors and are able to modulate the activity of adenylate cyclase, the enzyme responsible for increasing cyclic AMP (cAMP). The different receptors have differential stimulatory and inhibitory effects on this enzyme. Increased intracellular concentrations of cAMP can suppress the activity of immune and inflammatory cells (Livingston et al., 2004).

### 2.1. A<sub>1</sub> adenosine receptors

A<sub>1</sub>R is the most abundant adenosine receptor and is densely expressed throughout the CNS with high abundance in the neocortex, cerebellum, hippocampus and the dorsal horn of the spinal cord and are also found in adipose tissue, heart muscle, inflammatory cells such as neutrophils (Table 1) (Townsend-Nicholson et al., 1995; Olah and Stiles, 1995). Adenosine is the main agonist at this receptor class and these receptors have a high affinity for adenosine analogs substituted at the N<sub>6</sub> position e.g., L-N<sub>6</sub>-phenylisopropyladenosine (L-PIA) (Livingston et al., 2004). A<sub>1</sub> receptors mediate the inhibition of adenylate cyclase. A<sub>1</sub> receptor activation can also inhibit G-protein-coupled activation of voltage dependent Ca<sup>2+</sup> channels and is reported to induce phospholipase C activation (Yuzlenko and Kononowicz, 2006).

### 2.2. A<sub>2</sub> adenosine receptors

In contrast to the A<sub>1</sub> receptor, A<sub>2</sub> receptor stimulation leads to the activation of adenylate cyclase resulting in the elevation of intracellular cAMP. A<sub>2</sub> receptors are more widely distributed than A<sub>1</sub> receptors, being found in pre and postsynaptic nerve terminals, mast cells, airway smooth muscle and circulating

leukocytes (Table 1). They bind adenosine with less affinity than A<sub>1</sub> receptors and are preferentially stimulated by adenosine analogs substituted at the 5'-N position e.g., 5'-N-ethylcarboxamideadenosine (NECA). A<sub>2</sub> receptors are subdivided into the A<sub>2A</sub> and A<sub>2B</sub> receptors, based on high and low affinity for adenosine, respectively (Livingston et al., 2004). A<sub>2A</sub>Rs are highly enriched in striatal neurons but lower levels are also expressed in neurons outside of the striatum and in glial cells (Boison et al., 2012). Adenosine A<sub>2A</sub> receptors are abundant in the caudate putamen, nucleus accumbens, and olfactory tubercle in several species. In the caudate putamen, adenosine A<sub>2A</sub> receptors are localized in several neurons and have been shown to modulate the neurotransmission of  $\gamma$ -aminobutyric acid (GABA), acetylcholine, and glutamate. These actions of the A<sub>2A</sub> adenosine receptor could contribute to motor behavior. (Matasi et al., 2005). The A<sub>2A</sub> adenosine receptor signals in the periphery and the CNS, with agonists explored as anti-inflammatory drugs and antagonists explored for neurodegenerative diseases (Carlsson et al., 2010). In most cell types the A<sub>2A</sub> subtype inhibits intracellular calcium levels whereas the A<sub>2B</sub> potentiates them. The A<sub>2A</sub> receptor is therapeutic target for coronary vasodilation (adenosine agonist); and Parkinson's disease (adenosine antagonist) (Yuzlenko and Kononowicz, 2006; Fredholm et al., 2002). The A<sub>2A</sub> receptor generally appears to inhibit mediator release from these immune cells (Borrmann et al., 2009).

A<sub>2B</sub> receptors are highly expressed in gastrointestinal tract, bladder, lung and on mast cells (Table 1). The A<sub>2B</sub> receptor, although structurally closely related to the A<sub>2A</sub> receptor and able to activate adenylate cyclase is functionally very different. It has been postulated that this subtype may utilize signal transduction systems other than adenylate cyclase because of these functional differences (Livingston et al., 2004). Among all the adenosine receptors, the A<sub>2B</sub> adenosine receptor is a low affinity receptor that is thought to remain silent under physiological conditions and to be activated in consequence of increased extracellular adenosine levels (Ryzhov et al., 2008). Activation of A<sub>2B</sub> adenosine receptor can stimulate adenylate cyclase and phospholipase C through activation of G<sub>s</sub> and G<sub>q</sub> proteins, respectively. Coupling to mitogen acti-



vated protein kinases has also been described (Borrmann et al., 2009).

It has been proposed that adenosine contributes to the pathogenesis of inflammatory airways disease by acting on the mast cell  $A_{2B}$  receptor to enhance the release of pro-inflammatory mediators (Livingston et al., 2004).

### 2.3. $A_3$ adenosine receptor

The  $A_3$  receptor is distributed widely, being found in the kidney, testis, lung, mast cells, eosinophils, neutrophils, heart and the brain cortex (Table 1) (Livingston et al., 2004). As with the  $A_1$  receptor, stimulation of the  $A_3$  adenosine receptor leads to inhibition of adenylate cyclase. It has also been shown to stimulate directly phospholipases C and D.  $A_3$  receptor activation also results in the influx of calcium and its release from intracellular stores (Jacobson, 1998). The  $A_3$  receptor usually exhibits large differences in structure, tissue distribution and its functional and pharmacological properties between species (Linden, 1994).  $A_3$  mediated degranulation of mast cells or enhancement of allergen induced mast cell degranulation may be important in animal models of allergic responses. However, the  $A_3$  receptor is not present on human lung mast cells. The presence of  $A_3$  receptors in human eosinophils and macrophages suggests other mechanisms for the involvement of  $A_3$  receptors in inflammatory conditions including asthma (Livingston et al., 2004).

Although a subtype labeled as the adenosine  $A_4$  receptor has been characterized, it seems that this particular subtype may be a binding state of adenosine  $A_{2A}$  receptors. The majority of published data indicates that the direct vascular actions of adenosine are mediated via the adenosine  $A_1$ ,  $A_{2A}$ , or  $A_{2B}$  receptor subtypes (Tabrizchi and Bedi, 2001).

Adenosine  $A_1$  and  $A_{2A}$  receptors are characterized by high affinity for adenosine, while  $A_{2B}$  and  $A_3$  receptors show significantly lower affinity for adenosine. Activation of adenosine  $A_1$  receptors occurs at 0.3–3 nM concentration of adenosine, adenosine  $A_{2A}$  receptors at 1–20 nM, while adenosine  $A_{2B}$  or  $A_3$  receptor activation requires an agonist concentration larger

than 1  $\mu$ M (Cieslak et al., 2008). Adenosine receptors are attractive targets for therapeutic intervention of a wide range of disorders, such as hypoxia, asthma, Parkinson's disease, and many others. Among the four subtypes,  $A_{2B}$  receptor is functionally active on both human airway smooth muscle cells and lung fibroblast cells, which is related to inflammation and asthma (Fredholm et al., 2002).

### 3. Therapeutic target for various adenosine receptors

The therapeutic potential for adenosine was first evaluated in the 1930's (Kaiser and Quinn, 1999). At that time its short plasma half-life (3–6 s) limited any meaningful efficacy measures. Interestingly, the short half-life of adenosine has made it an ideal compound for the treatment of supraventricular tachycardia, for which use it has been approved (Belardinelli et al., 1995). Adenosine receptors are involved in several diseases, for example and most importantly, Parkinson's disease, ischemia and inflammation (Federico and Spalluto, 2012). The stimulation of cell surface adenosine receptors (ARs) is largely responsible for the broad variety of effects produced by adenosine throughout several organ systems. Based on the widespread and frequently beneficial effects, attributed to the accumulation of endogenously released adenosine, it has long been considered that regulation of ARs has substantial therapeutic potential (Moro et al., 2005). Adenosine, marketed by Fujisawa Healthcare Inc. as Adenocard®, is one of the adenosine receptor agonist approved for clinical use. Bolus administration of adenosine has proven to be the therapy of choice for the termination of paroxysmal supraventricular arrhythmias (PSVT). Adenosine is also marketed as Adenoscan® for use in myocardial perfusion imaging. Adenoscan® is a pharmacological stress agent used to increase coronary blood flow for thallium-201 myocardial perfusion scintigraphy with patients who are unable to exercise sufficiently (Hutchinson and Scammells, 2006).

A summary of novel targets for selective adenosine receptor ligands is given in Table 2. The selective agonists are well advanced in clinical trials for the treatment of atrial fibrillation, pain, neuropathy, pulmonary and other inflammatory

**Table 2** Therapeutic potential of adenosine receptor ligands.

Adenosine receptors		Therapeutic role	References
Agonist	$A_1$	Atrioventricular node block and supraventricular tachyarrhythmia	Ellenbogen et al. (2005)
	$A_{2A}$	Respiratory disorders, sepsis, reperfusion injury, thrombosis, hypertension, inflammatory disorders	Scheiff et al. (2010), Haskó et al. (2007), Jordan et al. (1997), Gomez and Sitkovsky (2003), Sullivan et al. (2004)
	$A_{2B}$	Allergic reactions	Yang et al. (2006)
	$A_3$	Cardiac ischemias, arrhythmias	Haskó et al. (2007), Gomez and Sitkovsky (2003)
Antagonists	$A_1$	Bradyarrhythmia associated with inferior myocardial infarction, cardiac arrest, cardiac transplant rejection	Dhalla et al. (2003)
	$A_{2A}$	Parkinson's disease, neurodegeneration	Scheiff et al. (2010), Collins et al. (2012)
	$A_{2B}$	Asthma, pulmonary inflammation	Baraldi et al. (2008)
	$A_3$	Glaucoma, asthma	Jung et al. (2004), Baraldi et al. (2003), Avila et al. (2002)

conditions, as well as cancer whereas the antagonism is useful in the treatment of Parkinson's disease and congestive heart failure for which selective antagonists are already in clinical trials (Brand, 2007).

Various adenosine receptor ligands have been developed. Almost all known AR agonists are derivatives of the cognate ligand, whereas antagonists are more diverse (Carlsson et al., 2010).

Animal models, with genes either over-expressed or deleted have now been created in attempts to elucidate the roles of all four adenosine receptors. Various therapeutic targets for all the adenosine receptors are as follows:

### 3.1. Immunomodulatory activity

The fact that the distinct adenosine receptors can selectively regulate discrete macrophage functions make adenosine receptors a promising target for pharmacological interventions in a wide range of disease states that involve macrophage activation e.g., protective effects of adenosine receptor stimulation (mainly A<sub>2A</sub> and A<sub>3</sub>) have been observed in models of ischemia-reperfusion as well as autoimmune diseases such as rheumatoid arthritis, multiple sclerosis, colitis, and hepatitis (Haskó et al., 2007).

Ezeamuzie and Khanin 2007 found that the inhibition of TNF- $\alpha$  release by adenosine is mediated by the A<sub>2A</sub> receptors whereas the enhancement of PGE<sub>2</sub> release appears to be mediated by the A<sub>2B</sub> receptors. In mouse peritoneal cavity they found that both the non-selective agonist NECA and the selective A<sub>2A</sub> receptor agonist CGS 21680 were more potent than the A<sub>1</sub> and the A<sub>3</sub> receptor agonists, CPA and IB-MECA, respectively suggesting that the A<sub>2</sub> receptors are responsible for the inhibitory effect of adenosine on TNF- $\alpha$  release rather than the A<sub>1</sub> and A<sub>3</sub> receptors. This suggests that the A<sub>2A</sub> receptor sub-type is the key receptor mediating the inhibitory effect of adenosine on TNF- $\alpha$  production in this model (Ezeamuzie and Khan, 2007).

### 3.2. Anti-inflammatory activity

A<sub>2A</sub> agonist CGS 21680 inhibits neutrophil accumulation and protects the heart from reperfusion injury (Jordan et al., 1997). Many recent studies indicate that adenosine acting on A<sub>2A</sub> receptors can powerfully inhibit inflammation and protects tissues from injury by reducing inflammation during reperfusion injury. Anti-inflammatory properties of adenosine were shown in many animal models of inflammation.

Yang et al. in 2006 found the prominent role of A<sub>2B</sub> AR in attenuating inflammation, at baseline or in response to endotoxin treatment, by regulating pro inflammatory cytokine production and adhesion properties of the vasculature by using adenosine receptor-null mouse models. These effects were primarily mediated via signals from hematopoietic cells to the vasculature. Contrary to the speculated function of A<sub>2B</sub>AR in vasodilation, the A<sub>2B</sub>AR-null mice have normal BP at baseline or in response to adenosine infusion (Yang et al., 2006).

Gomez and Sitkovsky in 2003 demonstrated that A<sub>2A</sub> and A<sub>3</sub> adenosine receptors are differentially utilized by inosine for the down-regulation of tissue damage under different inflammatory conditions *in vivo*. Inosine, which can interact

and stimulate A<sub>3</sub> and A<sub>2</sub> adenosine receptors, has been shown to be protective in both concanavalin (ConA) induced fulminant hepatitis and lipopolysaccharide (LPS) induced endotoxemia by inhibiting the production of pro inflammatory cytokines (Gomez and Sitkovsky, 2003). A<sub>3</sub>R is essential for protection against ConA-induced fulminant hepatitis since only A<sub>3</sub>R-expressing mice were protected by inosine whereas wild-type and A<sub>2A</sub>R-deficient mice exhibited severe liver damage even after administration of inosine. Studies in knockout mice for either A<sub>2A</sub> receptors, A<sub>3</sub> receptors or both revealed that the A<sub>3</sub>-receptor subtype was necessary for protection in the ConA-induced hepatitis model, whereas the protective effect in the LPS induced endotoxemia model was mediated by both, the A<sub>2A</sub> and the A<sub>3</sub> receptor subtypes (Gomez and Sitkovsky, 2003).

The A<sub>2B</sub> receptor antagonist, CVT-6883 had been used in laboratory studies and also showed the inhibition of pulmonary inflammation and injury in adenosine deaminase deficient mice and in a mouse model of bleomycin-induced pulmonary fibrosis (Baraldi et al., 2008).

A<sub>2A</sub>R agonists and antagonists can intervene inflammation by enforcing and blocking A<sub>2A</sub>R dependent immunomodulatory mechanism (Ohta and Sitkovsky, 2009).

### 3.3. Cardiovascular disorders

The A<sub>1</sub> receptor is potential therapeutic target for a number of disorders including atrioventricular (AV) node block and supraventricular tachyarrhythmia (adenosine agonist); AV block of cardiac arrest (adenosine antagonist); bradyarrhythmias in transplanted hearts (adenosine antagonists); diuresis (adenosine antagonists) (Dhalla et al., 2003).

In patients with documented paroxysmal supraventricular tachycardias involving the AV node, 99% are successfully terminated with standard doses of adenosine (Strickberger et al., 1997).

Ellenbogen et al. in 2005 found that tecadenoson is a potent selective A<sub>1</sub>-adenosine receptor agonist with a dose-dependent negative dromotropic effect on the AV node. They evaluated tecadenoson (6-[N-3'-(R)-tetrahydrofuranyl]-amino-purine riboside, formerly CVT-510), a selective A<sub>1</sub>-adenosine agonist, for the acute termination of PSVT. In the atrial-paced guinea pig heart model, tecadenoson caused an A<sub>1</sub>-adenosine receptor-mediated negative dromotropic effect on the AV node and lengthening of the AV nodal refractory period, leading to termination of reentrant PSVT at doses that did not affect blood pressure (BP), sinus cycle length, or the His-ventricular interval. Side effects mediated by the A<sub>2A</sub>-, A<sub>2B</sub>-, and A<sub>3</sub>-adenosine receptors such as flushing, chest pressure, hypotension, and bronchospasm were infrequent, consistent with the A<sub>1</sub>-adenosine receptor selectivity of the drug (Ellenbogen et al., 2005).

### 3.4. Bacterial sepsis

AR agonists increase mouse survival in endotoxemia and sepsis via A<sub>2A</sub> AR-mediated mechanisms and reduce the number of live bacteria in blood. In a bacterial sepsis model (*Escherichia coli*) treatment with an A<sub>2A</sub>-receptor agonist ATL-146e in combination with antibiotic therapy increased survival from 40% to 100%. The protective effects of both ATL146e and

IB-MECA were counteracted by the A<sub>2A</sub> AR selective antagonist 4-(2-[7-amino-2-furyl][1,2,4]triazolo[2,3-a][1,3,5]triazin-5-yl-amino)ethyl-phenol (Sullivan et al., 2004).

### 3.5. Asthma and glaucoma

The potent adenosine A<sub>3</sub> receptor antagonists have been developed for therapeutic treatment of inflammatory diseases such as asthma and glaucoma (Jung et al., 2004). Activation of A<sub>3</sub> receptors has been shown to stimulate phospholipase C and to inhibit adenylate cyclase. A<sub>3</sub> agonists also cause stimulation of phospholipase D and the release of inflammatory mediators, such as histamine from mast cells, which are responsible for inflammation and hypotension. For these reasons, the clinical use of A<sub>3</sub> adenosine receptor antagonists for the treatment of asthma and inflammatory disease has been suggested (Baraldi et al., 2003).

A<sub>3</sub> adenosine receptors also contribute to the regulation of intraocular pressure (IOP). Avila et al. in 2002 found the IOP responses to adenosine, A<sub>3</sub>AR agonists and A<sub>3</sub>AR antagonists using A<sub>3</sub>-knockout (A<sub>3</sub>AR<sup>-/-</sup>) and A<sub>3</sub>AR<sup>+/+</sup> control mice by the servo-null approach. The IOP was significantly lower in A<sub>3</sub>AR<sup>-/-</sup> mice (12.9 ± 0.7 mm Hg) than in A<sub>3</sub>AR<sup>+/+</sup> control animals (17.4 ± 0.6 mm Hg). The nonselective AR agonist adenosine produced a much smaller increase in IOP (2.2 ± 0.8 mm Hg) in the knockout than in A<sub>3</sub>AR<sup>+/+</sup> control mice (14.9 ± 2.4 mm Hg). The A<sub>3</sub>-selective agonist IB-MECA did not affect IOP in A<sub>3</sub>-knockout mice, but raised it in A<sub>3</sub>AR<sup>+/+</sup> mice. The highly selective A<sub>3</sub>AR antagonist MRS 1191 (25 µM) had no effect on baseline IOP in the A<sub>3</sub>AR<sup>-/-</sup> mice. In contrast, MRS 1191 at the same concentration reduced IOP in the A<sub>3</sub>AR<sup>+/+</sup> C57Bl/6 mice by 7.0 ± 0.9 mm Hg (Avila et al., 2002).

### 3.6. CNS disorders

Several pharmacological studies suggest that the A<sub>2A</sub> receptor is involved in motor activity. In particular, adenosine A<sub>2A</sub> receptor antagonists have been demonstrated to restore the deficits caused by degeneration of the striatonigral dopamine system, and therefore offer a possible treatment for Parkinson's disease (Zhang et al., 2008).

Antagonists of the A<sub>2A</sub> subtype of adenosine receptor have emerged as a leading candidate class of nondopaminergic antiparkinsonian agents (Feigin, 2003). The ability of Lu AA47070, adenosine A<sub>2A</sub> antagonist to reverse the effects of D<sub>2</sub> receptor blockade suggests that this compound could have potential utility as a treatment for parkinsonism, and for some of the motivational symptoms of depression. In the adult male Sprague Dawley rats the tremulous jaw movements induced by subchronic administration of the DA D<sub>2</sub> antagonist pimozide were reversed by Lu AA47070. Lu AA47070 was also able to reverse the catalepsy induced by subchronic administration of the D<sub>2</sub> antagonist pimozide and it also reverse the locomotor

suppression induced by subchronic administration of the D<sub>2</sub> antagonist pimozide (Collins et al., 2012).

Currently the main approach used in clinical trials involves the co-administration of A<sub>2A</sub>R antagonists with L-DOPA. The proposed advantage of this strategy is a reduction in the required dose of L-DOPA, with concomitant reductions in the associated side effects, consisting mainly of dyskinesias and progressive cognitive impairment (Armentero et al., 2011).

Adenosine as a contributing element in the pathophysiology of schizophrenia embraces several neurotransmitter systems and brain regions due to its multiple and widespread modulatory actions (Lara et al., 2006).

Adenosine also plays a very important role in the regulation of immune response during pathogenesis of AIDS. Barat et al. in 2008 found that extracellular ATP can act as a factor controlling HIV-1 propagation. They showed that extracellular ATP reduces HIV-1 transfer from immature monocyte-derived DCs (iDCs) to autologous CD4<sup>+</sup> T cells. This observed decrease in viral replication was related to a lower proportion of infected CD4<sup>+</sup> T cells following transfer, and was seen with both X4- and R5-tropic isolates of HIV-1. Extracellular ATP had no effect on direct CD4<sup>+</sup> T cell infection as well as on productive HIV-1 infection of iDCs. These observations indicate that extracellular ATP affects HIV-1 infection of CD4<sup>+</sup> T cells *in trans* with no effect on *de novo* virus production by iDCs.

HIV-1 associated dementia is a major problem in patients suffering from AIDS. This occurs due to the direct toxic effect of viral proteins on neuronal cells and indirectly by the release of proinflammatory mediators and neurotoxins by activated macrophages/microglia and astrocytes, causing apoptosis of neuronal cells (Barat et al., 2008).

## 4. Conclusion

The objective of this article is to highlight the exploration of adenosine receptors and to illustrate their potential as therapeutic agents to treat an impressively wide range of diseases.

From the above discussion, it has been concluded that adenosine is a purine ribonucleoside which has the properties of neuromodulator as well as neurotransmitter and it displays a wide range of biological activities. Effects of adenosine are mediated by membrane bound receptors, which are linked to G-proteins. Adenosine concentrations appear to be low during resting conditions, but can be substantially elevated during hypoxia and ischemia and by increased mechanical and biochemical work.

These receptors are currently investigated as drug targets, for example, for the treatment of cardiovascular disorders, renal diseases, hypertension, Parkinson's disease, Alzheimer's disease, asthma, chronic obstructive pulmonary disease (COPD), inflammatory and allergic disorders and cancer.

Great strides have thus been made over the past few years to exploit the biological properties of adenosine, and we now have in hand an impressive number of promising adenosine based drug candidates for treatment of various dreadful diseases like rheumatoid arthritis, asthma, cancer and various CNS disorders like Parkinson's disease.

There is every reason to believe that new and important therapeutic applications of adenosine ligands are just waiting to be discovered.

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