Pharmacology of Adenosine Receptors

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Abstract

Adenosine is an endogenous nucleoside molecule, regulating a myriad of physiological and pathological effects in almost all the organs systems including central nervous system (CNS), cardiovascular system (CVS), respiratory system, renal system, and immune system. Biological functions of adenosine are mediated by its interactions with four subtypes of G-protein-coupled receptors (GPCRs), namely A_1, A_{2A}, A_{2B}, and A_3 adenosine receptors (ARs) which are ubiquitously present throughout the body. However, ubiquitous distribution of ARs in both healthy and diseased tissues imposed a great challenge to the researchers in the discovery and development of ligands targeting a particular AR subtype in a specific tissue, devoid of undesirable side effects. This chapter

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provides an overview of the synthesis, metabolism, and cellular transport of adenosine, with particular emphasis on the distribution and signaling mechanisms of ARs, including specific examples of agonists/partial agonists, antagonists, and allosteric modulators of ARs as potential therapeutic agents.

Keywords

Adenosine · A_1, A_{2A}, A_{2B} and A_3 adenosine receptors · G-protein-coupled receptors (GPCRs) · Adenosine receptors signaling

Abbreviations

AC	Adenylyl cyclase
ADA	Adenosine deaminase
AK	Adenosine kinase
AMP	Adenosine monophosphate
AR	Adenosine receptor
ARNO	ADP ribosylation factor nucleotide site opener
ATP	Adenosine triphosphate
BBB	Blood-brain barrier
CADD	Computer-aided drug design
cAMP	Cyclic adenosine monophosphate
CNT	Concentrative nucleoside transporter
COPD	Chronic obstructive pulmonary disease
CREB	c-AMP-responsive element binding protein
DAG	Diacylglycerol
ENT	Equilibrative nucleoside transporter
ERK	Extracellular signal-regulated kinase
GPCR	G-protein-coupled receptor
GSK-3β	Glycogen synthase kinase-3β
HFpEF	Heart failure with preserved ejection fraction
iNKT cells	Invariant natural killer T cells
iNOS	Inducible nitric oxide synthase
IP_3	Inositol 1,4,5-triphosphate
IR	Ischemia-reperfusion
JNK	c-Jun N-terminal kinase
LBDD	Ligand-based drug design
MAPK	Mitogen-activated protein kinase
MPI	Myocardial perfusion imaging
OHT	Orthotopic heart transplantation
PAM	Positive allosteric modulator
PD	Parkinson's disease
PDEs	Phosphodiesterases
PKA	Protein kinase A
PKC	Protein kinase C

PLC	Phospholipase C
PLD	Phospholipase D
SAHH	*S*-adenosyl-homocysteine hydrolase
SAMe	*S*-adenosylmethionine
SBDD	Structure-based drug design
SPECT	Single photon emission computed tomography
TNFα	Tumor necrosis factor-alpha
TRAX	Translin-associated protein X
US FDA	United States Food and Drug Administration
USP4	Ubiquitin-specific protease

10.1 Introduction

Adenosine is an endogenous nucleoside molecule, regulating various physiopathological functions by interacting with four subtypes of G-protein-coupled receptors (GPCRs): A_1, A_{2A}, A_{2B}, and A_3 adenosine receptors (ARs). The primary mechanism of signal transduction of A_1 and A_3 ARs involves the inhibition of adenylyl cyclase (AC), thereby reducing the cyclic adenosine monophosphate (cAMP), whereas the activation of A_{2A} and A_{2B} ARs results in the stimulation of AC and consequent increase in cAMP levels (Fredholm et al. 2001, 2011). However, adenosine shows varying affinity for ARs. In particular, A_1, A_{2A}, and A_3 ARs show moderate to high affinities towards adenosine, requiring only 10 nM to 1 μM concentration for their activation, whereas A_{2B} AR is comparatively a low affinity receptor which requires a higher concentration of adenosine (10 μM) for its activation (Borea et al. 2018a, b; Fredholm 2014). Table 10.1 provides the molecular characteristics and mechanism of action of adenosine receptors. All the ARs are ubiquitously present throughout the body, influencing various physiological and pathological processes of almost all the

Table 10.1 Molecular characteristics and mechanism of action of adenosine receptors

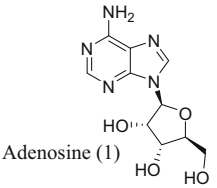
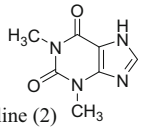
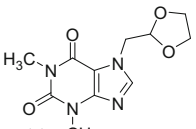
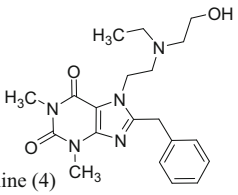
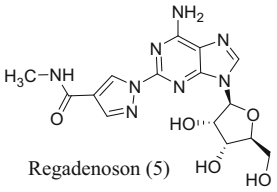
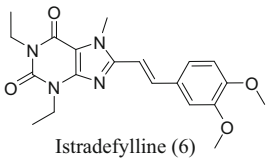
	A_1 AR	A_{2A} AR	A_{2B} AR	A_3 AR
Amino acid residues	326	410	328	318
Amino acid sequence similarity (%) vs hA_1AR		38.3	44.0	46.5
Amino acid sequence similarity (%) vs $hA_{2A}AR$			46.6	31
Amino acid sequence similarity (%) vs $hA_{2B}AR$				35.7
Affinity for adenosine (nM)	1–10	30	1000	100
G-protein coupling	$G_{i/o}$	G_s	$G_sG_{q/11}$	$G_sG_{q/11}$
Signaling system	↓AC, ↑PLC ↑PI3 kinase ↑MAPK, ↑K^+, Ca^{2+}	↓AC, ↑MAPK	↓AC, ↑PLC, ↑MAPK	↓AC, ↑PLC, ↑PI3 kinase, ↑MAPK

organ systems including central nervous system (CNS), cardiovascular system (CVS), respiratory system, renal system, and immune system among others. Thus, ARs represent potential drug targets for various therapeutic interventions (Borea et al. 2018a, b, 2016). Various agonists/partial agonists, antagonists, and allosteric modulators of A_1, A_{2A}, A_{2B}, and A_3 ARs have been discovered, patented, and are currently being investigated in clinical trials (Al-attraqchi et al. 2019; Borah et al. 2019; Chandrasekaran et al. 2019; Deb 2019a, b; Deb et al. 2019a, b; Mailavaram et al. 2019). But only few molecules could successfully reach the market either due to their poor pharmacokinetic profiles or because of the ubiquitous distribution of the ARs both in normal and diseased tissues imposing nonspecific actions or undesirable side effects of the drugs (Borea et al. 2018a, b; Chandrasekaran et al. 2019; Shaik et al. 2019). Istradefylline, the selective A_{2A} AR antagonist, was initially marketed in Japan (2013) for the treatment of Parkinson's disease (PD), but recently (2019) it has got approval from the US FDA as an add-on treatment to levodopa/carbidopa for PD (Hoffman 2019; Voelker 2019). Table 10.2 provides a list of clinically approved drugs and their therapeutic applications targeting ARs. Furthermore, growing advancement in the computer-aided drug design (CADD) software tools and algorithms has been significantly facilitating both the ligand-based and structure-based drug design (LBDD and SBDD) strategies for the discovery and development of novel drugs targeting ARs (Agrawal et al. 2019; Al-Shar'i Nizar and Al-Balas 2019; Deb 2019c; Deb et al. 2018a, b; Deb et al. 2019a, b; Kishore et al. 2011; N et al. 2019; Samanta et al. 2019). In particular, the recent discovery of the 3D crystal structure of A_1 AR (Cheng et al. 2017; Glukhova et al. 2017) along with the previously identified 3D structure of A_{2A} AR (Jaakola et al. 2008) has augmented the understanding of the molecular structures of ARs as well as physicochemical requirements of ligands for selective binding with ARs. This chapter highlights the synthesis, metabolism, and cellular transport of adenosine, with particular emphasis on the body distribution and signaling mechanisms of ARs in various physiological and pathological conditions. Important examples of agonists/partial agonists, antagonists, and allosteric modulators of ARs and their pathophysiological roles are also briefly discussed.

10.2 Synthesis, Metabolism, and Cellular Transport of Adenosine

Adenosine metabolism plays an important role in regulating various pathophysiological functions of the body. In physiological conditions, adenosine is available in low concentration (20–300 nM). However, under metabolic stressful conditions including pain, inflammation, and various disease states, extracellular adenosine concentration increases up to 30 μM due to ATP catabolism, where adenosine exhibits a helper/protective role by restoring the imbalance between energy demand and availability of working cells like neurons and cardiomyocytes by adapting some of their activities such as reducing heart inotropic effect, increasing oxygen and nutrition supply through vasodilation, thereby reducing the ATP requirement (Borea

Table 10.2 Therapeutic applications of clinically approved drugs targeting ARs

Name and structure of drugs	Mechanism of actions	Therapeutic applications
 Adenosine (1)	A_1 AR agonist	Paroxysmal supraventricular tachycardia (PSVT)
	A_{2A} AR agonist	Myocardial perfusion imaging
 Theophylline (2)	A_1 AR antagonist	Treatment of asthma
 Doxofylline (3)	A_1 AR antagonist	Treatment of asthma
 Bamifylline (4)	A_1 AR antagonist	Treatment of asthma
 Regadenoson (5)	A_{2A} AR agonist	Myocardial perfusion imaging
 Istradefylline (6)	A_{2A} AR antagonist	Adjuvant therapy of Parkinson's disease

et al. 2016, a, 2018b). Because of these protective roles, adenosine is considered as a "retaliatory metabolite" rather than a secondary metabolite of cAMP pathway (Newby 1984). Adenosine facilitates tissue protection from ischemic damage via preconditioning cell as well as exerting anti-inflammatory response and promoting angiogenesis (Linden 2005).

In physiological conditions, adenosine is synthesized intracellularly from AMP and *S*-adenosyl-homocysteine (SAH) hydrolysis by endo-5′-nucleotidase and *S*-adenosyl-homocysteine hydrolase (SAHH), respectively (Chen et al. 2013). It should be noted that the SAH hydrolysis leading to the formation of adenosine and homocysteine is a reversible process. The formation of SAH from adenosine and homocysteine is mainly favored under thermodynamic equilibrium conditions, consequently inhibiting the *S*-adenosylmethionine (SAMe) transmethylation due to increased levels of SAH. Thus, an effective decrease in adenosine levels mainly by adenosine kinase (AK) triggers the transmethylation process. Therefore, SAHH can facilitate both the synthesis and removal of adenosine (Bjursell et al. 2011; Finkelstein 1998; Moffatt et al. 2002). Extracellularly, adenosine is mainly produced under stressful conditions in high concentrations from the ATP, ADP, and AMP dephosphorylation with the help of two hydrolyzing enzymes, namely ectonucleosidase triphosphate diphosphohydrolase (CD39) and ecto-5′-nucleotidase (CD73), respectively (Zimmermann 2000). Additionally, extracellular conversion of cAMP to AMP with the help of ecto-phosphodiesterase (ecto-PDE) can further trigger the formation of adenosine via CD73 (Godinho et al. 2015; Pleli et al. 2018; Sassi et al. 2014).

Adenosine, once generated, travels across the cell membrane with the help of concentrative nucleoside transporters (CNTs) and equilibrative nucleoside transporters (ENTs). There are three isoforms of energy-dependent cation-linked (Na^+) CNTs (1–4) facilitating adenosine influx and four energy-independent isoforms of ENTs (1–3) which can assist in influx or efflux based on the concentration of adenosine. In general, adenosine influx takes place from extracellular to intracellular region, whereas the reverse condition is evident in hypoxia (Bading et al. 1993; Deussen 2000; Deussen et al. 1999).

Biotransformation of adenosine inside the cell takes place by hydrolysis to SAH, phosphorylation to AMP, and deamination to inosine with the help of SAHH, adenosine kinase (AK), and adenosine deaminase (ADA), respectively. Under physiological conditions, AK is mainly responsible for adenosine metabolism, whereas under pathological conditions, ADA preferentially facilitates adenosine clearance. Extracellular adenosine clearance occurs through ecto-ADA and influx through ENTs (Boison 2018; Boison et al. 2013; Gracia et al. 2012; Pacheco et al. 2005). Figure 10.1 represents the synthesis, metabolism, and cellular transportation of adenosine.

10.3 Molecular Structure of Adenosine Receptors (ARs)

All the four subtypes of ARs present common molecular structure arrangement, composed of seven transmembrane helices (TMs 1–7) which are connected to each other through three intracellular loops (ILs 1–3) and three extracellular loops (ELs 1–3) of varying lengths and functions. These three ELs play important roles in mediating receptor functions, where cysteine residues connect these ELs by forming disulfide bonds. The N-terminal containing glycosylation site is present on the

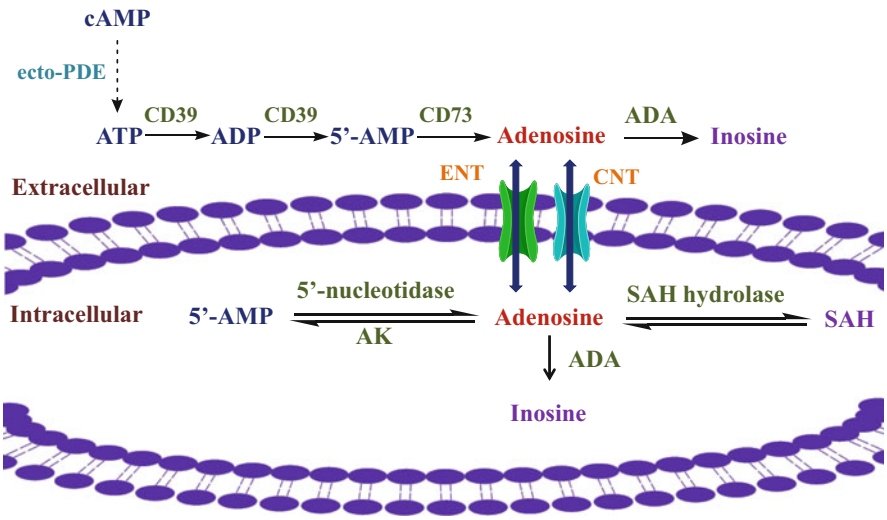


Fig. 10.1 Synthesis, biotransformation, and cellular transportation of adenosine

extracellular region, while the intracellular C-terminal possesses phosphorylation and palmitoylation sites that are responsible for desensitization and internalization of the receptor. The A_{2A} AR possesses longer C-terminal (122 amino acid residues) as compared to A_1, A_{2B}, and A_3 ARs (30–40 amino acid residues). Adenosine receptors present 41–58% amino acid sequence similarity among human species (Table 10.1) (Fredholm et al. 2001, 2011, 2000). Among all the subtypes, only the crystal structures of A_1 AR (Cheng et al. 2017; Glukhova et al. 2017) and A_{2A} AR (Jaakola et al. 2008) have been resolved, based on which several homology models of A_{2B} and A_3 ARs have been constructed to gain insight into their binding interactions with both agonists and antagonists ligands as well as to facilitate the structure-based drug design (Deb et al. 2018a, 2018b; Gutiérrez-de-Terán et al. 2017). ARs also exist in the form of homomer, heteromer, and oligomers, such as A_1 AR-A_{2A} AR, A_1 AR-A_3 AR, A_{2A} AR-D_2 dopamine receptor. In particular, A_{2A} AR-D_2 dopamine receptor complex that is present in striatum is considered as a significant therapeutic target for the treatment of Parkinson's disease (Brugarolas et al. 2014; Ferre et al. 2010; Navarro et al. 2016).

10.4 Distribution of Adenosine Receptors

Adenosine receptors are distributed throughout the cardiovascular, nervous, gastrointestinal, respiratory, urogenital, as well as immune systems. ARs were also detected in bones, eyes, joints, and skin (Peleli et al. 2017). Each subtype has a distinctive cell and tissue distribution, signaling transductors, and hence unique physiological effects (Fredholm et al. 2001).

10.4.1 Distribution of A_1 AR

A_1AR has shown a high abundance in the brain as well as other organs and tissues. This receptor subtype has been demonstrated by radioligand-receptor binding studies and imaging (Elmenhorst et al. 2012; Hayashi et al. 2017), along with RNA expression, Western blot, as well as functional characterization. Therefore, the wide distribution of this receptor has suggested its important physiological roles including spanning neurotransmitter release, neuronal excitability dampening, sleep/wakefulness control, reduction of pain, along with the sedative, anxiolytic, anticonvulsant, as well as locomotor depressant effects (Gessi et al. 2011; Sawynok 2016). In the central nervous system (CNS), A_1AR is mainly expressed in the brain cortex, hippocampus, cerebellum, spinal cord, autonomic nerve terminals, and glial cells (Ballesteros-yáñez et al. 2018; Chen et al. 2013). In the heart, the expression of A_1AR has been shown to be higher in atria and much less in the ventricular myocardium (Stenberg et al. 2003; Varani et al. 2017). At the vascular level, A_1ARs are found on the coronary smooth muscle arteries as well as endothelial cells (Headrick et al. 2013). Moreover, A_1ARs have been detected in the endothelial cells of the lung, in the airway's smooth muscles, in the alveolar epithelial cells, and in immune cells such as macrophages, neutrophils, eosinophils, and monocytes (Boros et al. 2016; Sachdeva and Gupta 2013; Sun et al. 2005), where they essentially promote some proinflammatory effects (Ponnoth et al. 2010). A_1AR is also found in the kidney, adipose tissue, and pancreas, where it causes induction of negative chronotropic, inotropic, as well as dromotropic effects, reduction in the renal blood flow and renin release, and inhibition of lipolysis and insulin secretion, respectively (Dhalla et al. 2009; Prystowsky et al. 2003; Rabadi and Lee 2015; Sun et al. 2001; Vallon and Mu 2006; Vincenzi et al. 2012). In the kidney, A_1ARs mostly present in the papilla's collecting ducts, inner medulla, in addition to the cells of the juxtaglomerular apparatus. A_1ARs have been also detected in the retina, skeletal muscle, intestine, and vascular cells of skeletal muscle (Soni et al. 2017; Varani et al. 2017).

10.4.2 Distribution of A_{2A} and A_{2B} ARs

The A_{2A} AR is present centrally and peripherally, where it serves a number of functions that are related to excitotoxicity, the release of spanning neuronal glutamate, glial reactivity, the permeability of the blood-brain barrier (BBB), as well as the migration of the peripheral immune cells (Koupenova et al. 2012; Merighi et al. 2015; Pedata et al. 2016), and greatly expressed in the striatum, the olfactory tubercle, as well as the immune system. However, lower levels are present in the cerebral cortex, heart, hippocampus, lung, and blood vessels. In the peripheral immune system, A_{2A} AR has been shown to have a great expression particularly in leukocytes, platelets, as well as the vasculature, in which it mediates numerous anti-inflammatory, antiaggregatory, as well as vasodilatory effects, respectively (Ruiz et al. 2014). A_{2A} ARs are found in the bowel, lung, bladder, vas deferens, as

well as in other different cell types such as fibroblasts, smooth muscles, alveolar epithelial, chromaffin, and taste cells, platelets, myocardial cells, and retinal, intestinal, endothelial and pulmonary epithelial cells (Aherne et al. 2011).

It has been shown in recent development of A_{2B}AR-knockout/lacZ-knocking mice (Yang et al. 2006) that A_{2B} AR has a wide distribution in numerous tissues and organs, and this includes the aortic vascular smooth muscle, vasculature, cecum, brain, large intestine, and urinary bladder (Wang and Huxley 2006; Yaar et al. 2005). Moreover, A_{2B} AR was found to be highly expressed in various cell types, including several immune cells such as mast cells (Hua et al. 2007; Yang et al. 2006), neutrophils (Ryzhov et al. 2008), dendritic cells (Addi et al. 2008), macrophages (Novitskiy et al. 2008), as well as lymphocytes (Yang et al. 2006), in addition to other cell types that include the type II alveolar epithelial cells (Eckle et al. 2008), endothelial cells (Cagnina et al. 2009), chromaffin cells (Yang et al. 2006), astrocytes (Peakman and Hill 1994), neurons (Christofi et al. 2001), and taste cells (Stein et al. 2001).

10.4.3 Distribution of A_3 AR

The identification of the A_3 AR distribution has been made possible after the generation of cDNA for this receptor (Nishida et al. 2014). The A_3 AR subtype was found to have wide expression in various primary cells, tissues, as well as cell lines. In the brain, A_3AR has been reported in low levels, where it is expressed particularly in the hypothalamus, thalamus, hippocampus, cortex, as well as retinal ganglion cells, and motor nerve terminals, in addition to the pial and intercerebral arteries (Burnett et al. 2010; Janes et al. 2014). Studies have also shown that the expression of A_3 ARs is also reported in microglia and astrocytes; thus inhibiting the neuro-inflammatory response in these particular cells was shown to be associated with the analgesic effect they induce (Borea et al. 2016). Despite the cardioprotective effects that have been related to the A_3 AR, as well as the great expression of this receptor subtype in the coronary and carotid artery, its precise location in the heart is not yet reported. At the periphery, A_3 AR was found to be expressed in enteric neurons, epithelial cells, lung parenchyma, colonic mucosa, and bronchi. Moreover, a broad distribution of A_3 AR subtype has been reported in inflammatory cells (Janes et al. 2014) including mast cells, eosinophils, monocytes, neutrophils, macrophages, dendritic cells, foam cells, lymphocytes, bone marrow cells, splenocytes, lymph nodes, chondrocytes, synoviocytes, as well as osteoblasts, where it is responsible for mediating various anti-inflammatory effects (Borea et al. 2015). It is worth mentioning that A_3 AR subtype is overexpressed in some cancer cells and tissues, which therefore shows the important antitumoral role of this receptor subtype (Borea et al. 2016). At cellular level, A_3 ARs have shown wide expression in motor nerve terminals, astrocytes, microglia, cortex, as well as retinal ganglion cells (Borea et al. 2015; Gessi et al. 2013).

10.5 Signal Transduction Pathways of Adenosine Receptors

Numerous signal transduction pathways are triggered by all the four G-protein-coupled ARs based on the activation of a particular type of cell (Fredholm et al. 2001, 2011).

10.5.1 Molecular Signaling of A_1 AR

The activation of the Gi-protein-coupled A_1 AR causes inhibition of adenylyl cyclase (AC), leading to the reduction of cyclic adenosine monophosphate (cAMP) production (Fredholm et al. 2000), resulting in the reduction of cAMP-dependent protein kinase A (PKA) and cAMP-responsive element-binding protein 1 (CREB-1) phosphorylation (Ellis et al. 1995). A_1 AR can stimulate the phospholipase C (PLC)-β, increasing diacylglycerol (DAG) and inositol 1,4,5-triphosphate (IP3) levels, thus enhancing calcium (Ca^{2+}) concentrations inside the cell, stimulating the activation of Ca^{2+}-dependent protein kinase C (PKC) and/or other binding proteins (Basheer et al. 2002; Biber et al. 1997; Borea et al. 2018a, b; Nalli et al. 2014). Activation of A_1 AR also results in the opening of potassium (K^+) channels in neurons and cardiac tissue, while inhibiting Q, P, and N-type Ca^{2+} channels (Kirsch et al. 1990; Kunduri et al. 2013; Schulte and Fredholm 2003, 2000). Additionally, A_1 AR activation is also linked to the phosphorylation of mitogen-activated protein kinases (MAPK) like p38, ERK1/2, and JNK (Schulte and Fredholm 2003, 2000). The signal transduction pathway of A_1 AR is depicted in Fig. 10.2.

10.5.2 Molecular Signaling of A_{2A} AR

The activation of Gs-protein-coupled A_{2A} AR triggers AC activity and increases the cAMP levels, thereby stimulating PKA which causes phosphorylation and further activation of several proteins including receptors, PDEs, CREB, and dopamine- and c-AMP-regulated phosphoprotein (DARPP-32) (Preti et al. 2015). Additionally, A_{2A} ARs inside the brain can stimulate neuron-specific Gs-protein called G_{olf} that is also connected to c-AMP (Kull et al. 2000). Moreover, in the brain, adenosine level increases following ischemia-reperfusion injury leading to the stimulation of A_{2A} AR resulting in the potentiation of neuronal damage by increasing ERK and consequent stimulation of microglial activation, glial TNFα, glutamate, iNOS, and apoptosis (Mohamed et al. 2016). In the artery of rat tail, it has been observed that A_{2A} AR can also regulate the release of norepinephrine through the stimulation of both PKC and PKA (Fresco et al., 2004). A_{2A} AR is also found to bind with the help of its C-terminus with various other proteins such as dopamine D_2 receptor, α-actinin, ARNO, USP4, and TRAX (Baraldi et al. 2008). Importantly, A_{2A} AR can also modulate the signaling of MAPK (Baraldi et al. 2008; Chen et al. 2013). A_{2A} AR activation also plays an important role in cancer cells by stimulating

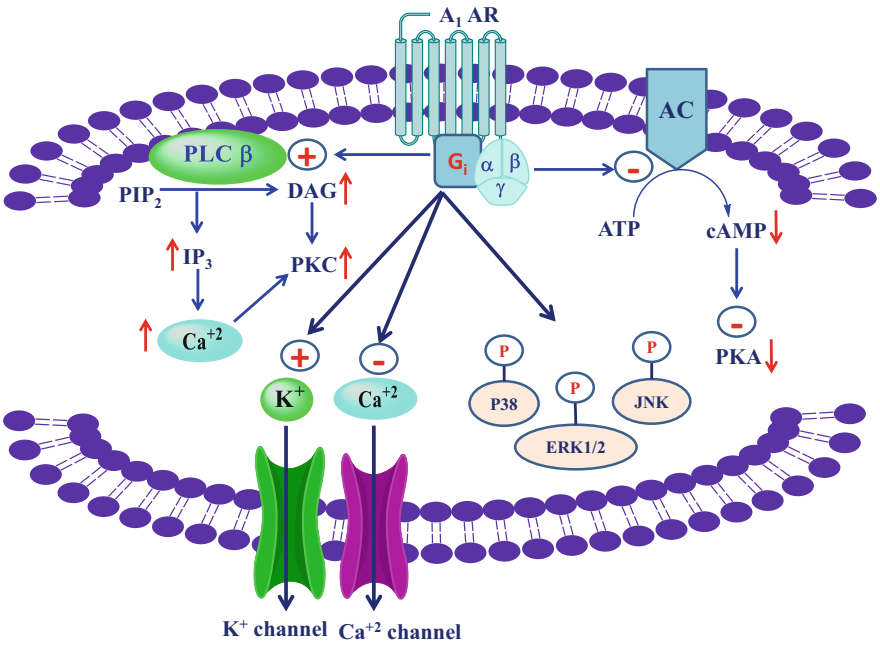


Fig. 10.2 Molecular signal transduction pathways of A_1 AR

proliferation PLC, PKC-δ, ERK, JNK, and AKT (Gessi et al. 2017). Signal transduction pathway of A_{2A} AR is depicted in Fig. 10.3.

10.5.3 Molecular Signaling of A_{2B} AR

Similar to the A_{2A} AR subtype, the A_{2B} AR is also coupled to Gs protein, triggering the AC activity and thereby increasing the cAMP levels, PKA phosphorylation, and cAMP-dependent recruitment of different effectors like exchange proteins (Epac) (Fredholm et al. 2011). A_{2B} AR-stimulated activation of Epac was also found to affect the proliferation of umbilical vascular endothelial cells and induce early gene expression reducing the proliferation of smooth muscle cells of coronary artery in humans (Fang and Olah 2007; Mayer et al. 2011). Unlike A_{2A} AR, the A_{2B} AR is also coupled to Gq protein, stimulating PLC leading to Ca^{2+} mobilization, while regulating the ion channels through the recruitment of γ subunits. A_{2B} AR can regulate various pathophysiological functions in the central and peripheral system through the activation of MAPK and AKT (Sun and Huang 2016). Additionally, A_{2B} AR responses can be influenced by its various binding partners like netrin-1, E3KARP-EZRIN-PKA, SNARE, NF-κB1/P105, and α-actinin-1. In particular, the neuronal guidance protein netrin-1 can bind and activate A_{2B} AR during hypoxia, reducing the migration of neutrophils and consequent inflammation (Rosenberger

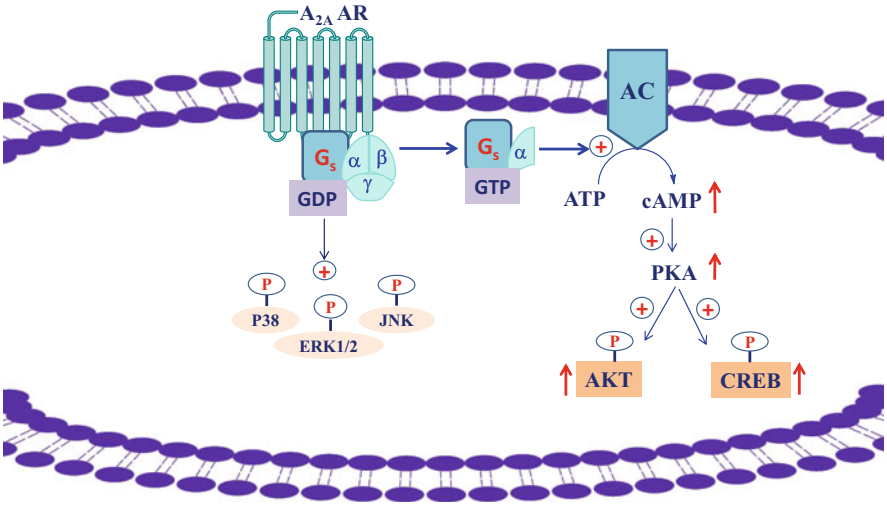


Fig. 10.3 Molecular signal transduction pathways of A_{2A} AR

et al. 2009). SNARE protein can bind and translocate the A_{2B} AR from the cytoplasm to the plasma membrane following agonist binding (Wang et al. 2004) and consequently, a multiprotein complex with E3KARP (NHERF2) and ezrin enables the fixation/stabilization of the A_{2B} AR at the cell surface (Sitaraman et al. 2002). Interestingly, α-actinin-1 can promote the dimerization of A_{2A} and A_{2B} ARs, inducing the cell surface expression of the later (Moriyama and Sitkovsky 2010). Furthermore, interaction of P105 with A_{2B} AR has shown to reduce the inflammatory effects of NF-κB (Sun et al. 2012). Recently, it has been reported that the stimulation of A_{2B} AR reduces ERK1/2, p38, and NF-κB induced by RANKL, thereby reducing osteoclastogenesis in bone (Kim et al. 2017). Several reports also indicate the role of A_{2B} AR signaling in neuroinflammation (Koscsó et al. 2012; Merighi et al. 2017), inflammatory bowel disease (Chin et al. 2012; Dammen et al. 2013), cardiac ischemic preconditioning (Yang et al. 2011), atherosclerosis development (Gessi et al. 2010a), and reduction of cardiac fibrosis (Phosri et al. 2018, 2017). The signal transduction pathway of A_{2B} AR is depicted in Fig. 10.4.

10.5.4 Molecular Signaling of A_3 AR

The A_3 AR subtype is coupled to Gi protein and inhibits AC with consequent reduction of the cAMP levels, while at high concentrations of agonist, A_3 AR couples to Gq protein, thereby stimulating PLC and increasing the Ca^{2+} release from the intracellular storage (Borea et al. 2018a, b). A decrease in cAMP level further causes inhibition of PKA leading to increase in glycogen synthase kinase-3β (GSK-3β); decrease in β-catenin, cyclin D1, and c-Myc; and reduction of NF-kB

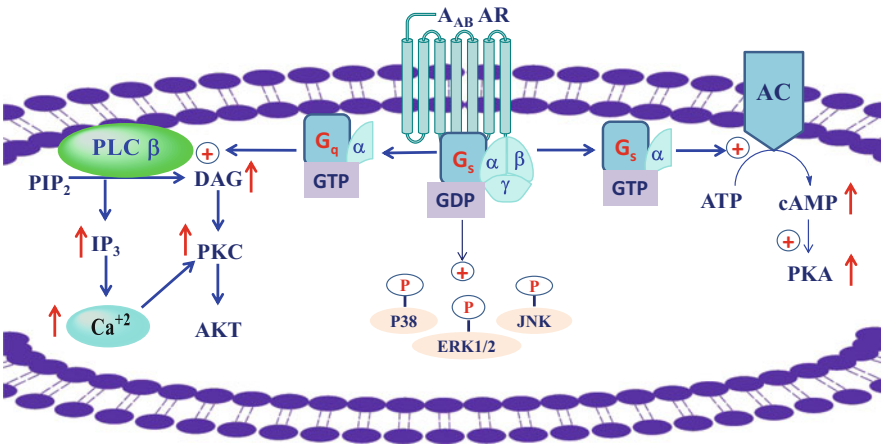


Fig. 10.4 Molecular signal transduction pathways of A_{2B} AR

DNA binding capability (Fishman et al. 2012, 2004, 2002; Stemmer et al. 2008). A_3 AR facilitated neuro- and cardio-protection is regulated via different signaling pathways including G-protein RhoA and phospholipase D (PLD) (Borea et al. 2018a, b). A_3 AR-mediated anti-inflammatory effects are regulated through MAPK, PI3/Akt, and NF-kB transduction pathways (Ochaion et al. 2008). A_3 AR is also found to induce ERK1/2 and proliferation of cells in human fetal astrocytes, microglia, glioblastoma, and melanoma among others (Hammarberg et al. 2003; Merighi et al. 2007; Neary et al. 1998; Soares et al. 2014). Interestingly, reduced ERK activation was also evident in melanoma, prostate cancer, and glioma cells, decreasing the proliferation of cells and release of TNF-α (Hyun et al. 2012; Martin et al. 2006). Activation of A_3 AR also modulates p38 and JNK in various cell types including cancer cells like colon carcinoma (Gessi et al. 2010b). The signal transduction pathway of A_3 AR is depicted in Fig. 10.5.

Readers are also encouraged to read the valuable chapter written by Merigi et al., highlighting various research findings showcasing the involvement of AR signaling in diverse pathophysiological conditions (Merighi et al. 2018).

10.6 Agonists, Partial Agonists, Antagonists, and Allosteric Modulators of Adenosine Receptors

10.6.1 Agonists of Adenosine Receptors

Important agonists of adenosine receptors are presented in Fig. 10.6.

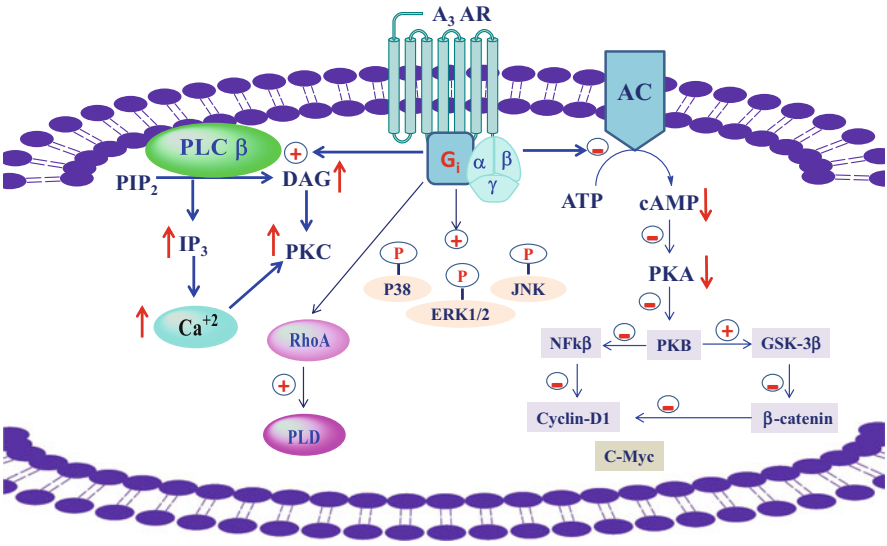


Fig. 10.5 Molecular signal transduction pathways of A_3 AR

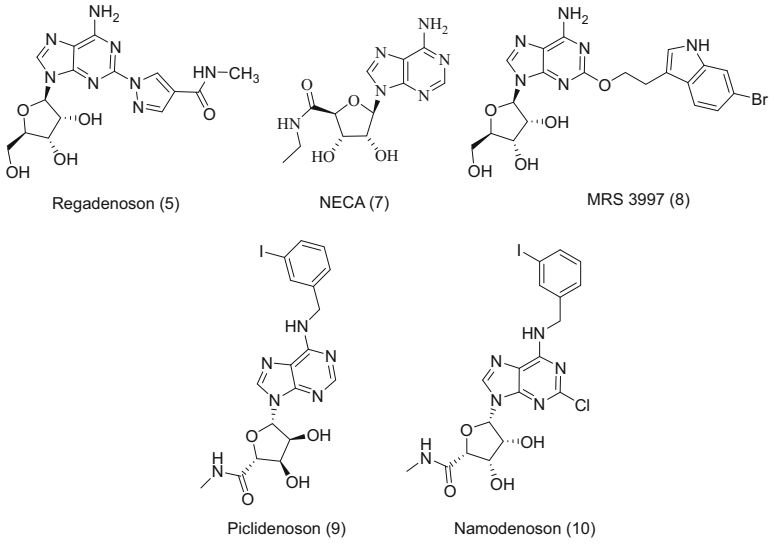


Fig. 10.6 Important agonists of ARs

10.6.1.1 Regadenoson

Regadenoson (5), a selective A_{2A} adenosine receptor agonist, was approved by the FDA (Food and Drug Administration) in 2008 in the injection form as a pharmacologic stress agent for patients unable to perform adequate exercise in order to increase blood flow in coronary arteries for myocardial perfusion imaging (MPI)

test (Thompson 2008). Regadenoson produces coronary arteries vasodilation by selectively activating A_{2A} AR; however it shows a very weak agonist activity on A_1 receptors and a negligible affinity for A_3 and A_{2B} adenosine receptors. Regadenoson has longer half-life than adenosine (Vij et al. 2018).

Following the approval of the FDA for regadenoson, many diverse clinical trials have been performed for the diagnosis and treatment of cardiovascular conditions. For instance, a phase IIIb study (NCT01618669) sponsored by Astellas Pharma Inc. on 1147 participants was conducted to compare between administration of regadenoson after inadequate exercise and administration of regadenoson without exercise for MPI by using single photon emission computed tomography (SPECT). Results have shown that the administration of regadenoson after 3 min of inadequate exercise is well tolerated with careful monitoring in patients without signs and symptoms of ischemia during exercise or after (Thomas et al. 2017). A study on 123 patients to determine the safety of regadenoson stress testing after orthotopic heart transplantation (OHT) has shown that dyspnea was the most common side effect with 66.7% of patients. However, there were no serious adverse effects such as hemodynamic changes and life-threatening arrhythmias which supports its safety and tolerability in OHT patients (Lazarus et al. 2018). Several studies have shown that dyspnea (the most common side effect) is not caused by bronchoconstriction, which makes regadenoson administration safe for patients with mild to moderate COPD and mild to moderate asthma (Golzar and Doukky 2014; Raines et al. 2019).

Agonists of A_{2A} AR have shown to decrease hypoxia/reoxygenation-induced tissue inflammation in mice with SCD (sickle cell disease). A_{2A} agonists reduced invariant natural killer T (iNKT) cells activation, which is higher than normal in patients with SCD. A phase II randomized trial (NCT01788631) on patients with SCD was conducted to test whether regadenoson can reduce iNKT cells activation and vaso-occlusive crises. After 48-h infusion of regadenoson (1.4 mg/kg/h) during vaso-occlusive crises the patients did not show significant decrease in iNKT cells activation as compared to placebo patients which indicates that regadenoson infusion in low doses is not sufficient to induce a significant reduction in iNKT cells activity (Field et al. 2019). The iNKT cells are also activated after lung transplantation due to activation of NOX2 (NADPH oxidase 2) causing ischemia-reperfusion (IR) injury following lung transplantation, and the activation of iNKT cells and NOX2 increases the production of interleukin-17 (IL-17). An *in vivo* study showed that A_{2A} receptor agonists attenuate the production of IL-17 and reduce IR injury in murine and human iNKT cells which indicates that A_{2A} AR agonists offer a possible therapeutic strategy to prevent IR injury and graft dysfunction (Sharma et al. 2016).

Regadenoson has also shown to cause BBB disruption in healthy rodents, which presents a potential solution for the limitations caused by the BBB in preventing many therapeutic agents including chemotherapy to reach the brain in higher concentrations. In a study on healthy rodents, regadenoson increased the concentration of temozolomide (a chemotherapeutic agent used in the treatment of glioblastoma) (Jackson et al. 2016). However, a clinical trial (NCT02389738) by Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins included six patients with

recurrent glioblastoma that received regadenoson with temozolomide. Results showed no increase in temozolomide concentration in brain unlike previous studies on rodents indicating that further studies and trials with different doses are needed for determining the optimum regadenoson dose to induce the desired BBB disruption and increase chemotherapeutic agent concentration in CNS. Another phase I trial (NCT03971734) is estimated to start in March 2020 by the same cancer center to determine regadenoson dose that can alter BBB integrity in patients with high-grade gliomas (Jackson et al. 2018).

Approximately 2–8% of patients experienced gastrointestinal side effects including abdominal discomfort, diarrhea, and nausea after receiving regadenoson with higher side effects frequency in patients with advanced renal disease. However, in 2017, there has been 11 cases of partial seizures and seizure-like adverse effects and 55 cases of convolutions reported to the FDA, which resulted in The American Society of Nuclear Cardiology (ASNC) guidelines to consider seizure disorders a relative contraindication with regadenoson administration (Andrikopoulou and Hage 2018; Henzlova et al. 2016).

10.6.1.2 NECA

In recent years, adenosine receptors have shown to be possible pharmacological targets to alter BBB integrity. A study included intravenous administration of NECA (5′-N-ethylcarboxamide adenosine) (6), a nonselective ARs agonist, has resulted in increasing brain concentration of dextrans (both low molecular weight and high molecular weight). However, NECA pharmacological effect was dose-specific, producing highest effect at 0.08 mg/kg; lower or higher doses showed less effect. It was interpreted that doses higher than 0.08 mg/kg of NECA showed less effect due to adenosine receptors desensitization. The fact that adenosine receptor agonists can be found in the market and are clinically approved makes these findings even more valuable presenting a possible less invasive method for BBB disruption (Carman et al. 2011; Cheng et al. 2016; Malpass 2011).

NECA intraperitoneal administration has shown to increase fasting serum glucose level. Further investigation showed that NECA administration has elevated glucose 6-phosphatase (G6Pase) enzyme mRNA leading to an increase in the liver G6Pase enzyme and gluconeogenesis, which is thought to be the cause for serum glucose elevation (Matsuda et al. 2014). NECA has also been studied for reducing intestinal IR injury in rats. Results showed that NECA reduced leukocyte activation and caused a significant improvement in capillary perfusion, thus reducing intestinal IR injury (Zhou et al. 2015).

10.6.1.3 MRS 3997

MRS 3997 (7) is a potent adenosine receptor agonist that activates mainly A_{2A} and A_{2B} AR and acts as a weak agonist for A_1 and A_3 ARs (Adachi et al. 2007; Gao et al. 2014).

10.6.1.4 Piclidenoson, CF101

Piclidenoson or CF101 (8) is a highly specific A_3 AR agonist that has proven to have an anti-inflammatory effect in many preclinical studies for conditions such as uveitis, rheumatoid arthritis, colitis, and osteoarthritis. Piclidenoson mechanism of action is mainly through the downregulation of NF-κB signaling pathway which causes an inhibition in TNF-α. Phase II clinical studies of piclidenoson on patients with plaque psoriasis have shown its efficacy in reducing signs and symptoms (Cohen et al. 2018).

A phase IIb clinical study (NCT01034306) utilizing piclidenoson as a monotherapy drug was conducted on 79 patients with rheumatoid arthritis sponsored by Can-Fite BioPharma. After 12 weeks of twice daily administration of 1 mg of piclidenoson or placebo, the patients treated with piclidenoson showed a significant improvement compared to placebo and reduction in rheumatoid arthritis symptoms, supporting previous clinical studies (Fishman and Cohen 2016; Stoilov et al. 2014). The same company is currently developing piclidenoson in an oral form as a first-line treatment for patients with moderate to severe plaque psoriasis (Fellner 2016).

10.6.1.5 Namodenoson, CF102

Namodenoson (CF102) (9) is a potent and selective A_3 AR agonist that is considered safe and tolerable after phase I and II (NCT00790218) clinical trials for hepatocellular carcinoma in combination with sorafenib. In those trials namodenoson has caused an increase in the median overall survival by approximately 7 months (Stemmer et al. 2013). Namodenoson has been tested in a phase II trial (NCT02128958) as a second-line treatment of Child-Pugh B (CPB) advanced hepatocellular carcinoma (HCC). Despite the fact that the primary end point has not been met in this trial, the median overall survival of CPB patients increased. Namodenoson was well tolerated by patients and considered safe for further phase III trials. Adverse effects that were observed in almost $>10\%$ of the patients were nausea, fatigue, anemia, asthenia, peripheral edema, and abdominal pain (Stemmer et al. 2019).

10.6.2 Partial Agonists of Adenosine Receptors

Important partial agonists of adenosine receptors are presented in Fig. 10.7.

10.6.2.1 CVT 2759

CVT-2759 (10) is a partial A_1 AR agonist that has shown to have the ability to selectively inhibit AV conduction in a moderate rate without causing an AV block despite application of high concentrations. It means that CVT-2759 has the ability to cause a predictable moderate inhibition on the AV nodal conduction while avoiding the risk of AV blockage. It has been observed in these studies that CVT-2759 has a minimum effect on the sinoatrial rate or on action potential durations (ventricular and atrial) (Szentmiklósi et al. 2015; Wu et al. 2001). Accordingly, CVT-2759 administration does not induce flutter of atrial fibrillation. Most importantly, A_1

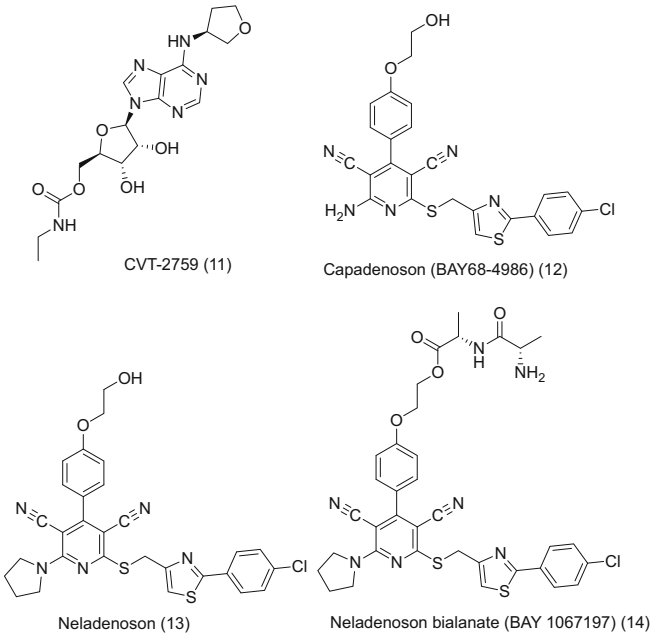


Fig. 10.7 Important partial agonists of ARs

AR partial agonists induce desensitization and downregulation of the receptor much less than full agonists, which makes these compounds a great option in treating certain cardiac arrhythmias while avoiding nonspecific adverse effects that are seen with adenosine administration.

10.6.2.2 Capadenoson (BAY68-4986)

Capadenoson (11) is a non-nucleoside A_1 AR partial agonist that has reached clinical trials, two phase II trials, one for patients with atrial fibrillation and the other for patients with stable angina (Albrecht-küpper et al. 2012; Szentmiklósi et al. 2015). Capadenoson was also investigated for advanced heart failure in animal models and has shown to reduce cardiac remodeling. Neladenoson bialanate is a capadenoson derivative that has entered clinical trials to treat patients with chronic heart failure. Mainly the therapeutic action of capadenoson is due to the partial activation of A_1 adenosine receptors, but it is important to note that capadenoson can also stimulate A_{2B} adenosine receptors. A study was conducted to investigate the effect of capadenoson on A_{2B} AR in cardiomyocytes, cardiac fibroblasts (physiologically relevant cells). Results have shown a significant effect on A_{2B} AR by capadenoson, suggesting that capadenoson should be reclassified from an A_1 AR partial agonist into a dual $A_1AR/A_{2B}AR$ agonist (Baltos et al. 2017). A phase II clinical trial (NCT00518921) of capadenoson was also conducted to evaluate the efficacy and safety in patients with stable angina with 1–4 mg doses; however, the trial was later withdrawn (Jacobson et al. 2019).

10.6.2.3 Neladenoson

Neladenoson, an A_1 AR partial agonist (12), currently is being tested clinically on patients with chronic heart failure in the form of dipeptide prodrug. Neladenoson shows higher selectivity to A_1 AR as compared to capadenoson. Many promising effects caused by Neladenoson have been observed including improvement in cardiac function without causing undesired effects on blood pressure, atrioventricular blocks, or bradycardia. The preference of using a partial agonist instead of full agonist of A_1 AR is due to the fact that partial agonist can activate the receptors without producing severe adverse effects as compared to full agonists. A multiple dose phase II study (NCT02040233) of Neladenoson has been also conducted to investigate tolerability, pharmacokinetics, and safety in patients with chronic heart failure (ParSiFAL study) (Jacobson et al. 2019; Voors et al. 2017).

10.6.2.4 Neladenoson Bialanate

Neladenoson bialanate (13), also referred to as BAY-1067197, is a prodrug of Neladenoson, an A_1AR partial agonist with high potency and selectivity. The need to develop a partial A_1 AR agonist comes from the fact that a full agonist produces extra-cardiac adverse effects including neurological (e.g., sedation) and anti-diuretic effects due to the vasoconstriction of renal afferent arterioles caused by the activation A_1 AR (Dinh et al. 2017; Greene et al. 2016).

Preclinical studies of Neladenoson bialanate have shown promising results including anti-ischemic cardio-protective properties, improved mitochondrial function, and preventing ventricular remodeling, which further supported this compound for phase II clinical trials such as PANACHE (NCT03098979) and PANTHEON (NCT02992288) trials. PANACHE trial was to evaluate Neladenoson in patients with chronic heart failure with preserved ejection fraction (HFpEF) while PAN THEON trial was for evaluating it on patients with chronic heart failure with reduced ejection fraction (HFrEF). Both trials were conducted to evaluate the safety and efficacy of the compound and both of these trials were sponsored by Bayer (Voors et al. 2018). In PANACHE trial, no significant dose to response relationship has been detected after 20 weeks of neladenoson administration, which indicates the need for further investigation and development required for Neladenoson to treat conditions such as HFpEF (Shah et al. 2019).

10.6.3 Antagonists of Adenosine Receptors

Important antagonists of adenosine receptors are presented in Fig. 10.8.

10.6.3.1 Caffeine and Theophylline

Caffeine (14) (3,7-trimethylpurine-2,6-dione) is a nonselective natural methylamine that acts as an A_{2A} and A_1 AR antagonist. Caffeine can be found in common beverages such as tea, coffee, products containing cocoa, soft drinks, dietary sources, and some medications. In the United States, the daily intake of a caffeine consumer is approximately 280 mg. The main purpose of caffeine consumption is to

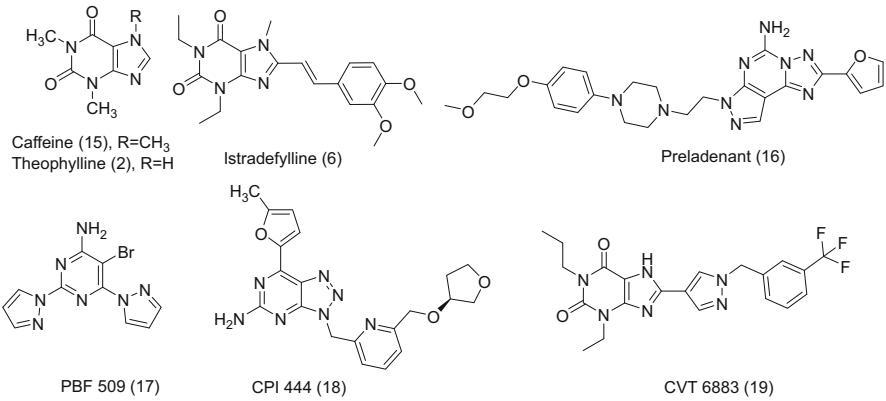


Fig. 10.8 Important antagonists of ARs

increase energy, alertness, and arousal. In normal population, caffeine consumption has been associated with mood and cognitive performance changes with more observed enhancement in performance in fatigued individuals compared to well-rested ones (López-cruz et al. 2018). Caffeine's antagonist effect on A_{2A} adenosine receptors has shown its potentials in treating PD. *In vitro* and *in vivo* studies have both shown that caffeine reduces parkinsonian motor symptoms. Also, drug tolerance associated with current PD drugs has been found to be reduced when co-administered with caffeine (Chen et al. 2010; Roshan et al. 2016). Currently, caffeine is used as an adjuvant treatment for migraine headache. Clinical trials have shown that caffeine can reduce postdural puncture headache (PDPH). In addition, caffeine was reported to produce an effective result in the treatment of hypnic headache; however, further clinical trials are still needed to prove its efficacy as a first-line treatment choice (Baratloo et al. 2016, 2015).

Theophylline (dimethylxanthine) (2) is a nonselective A_1 and A_2 AR antagonist. It has been used for over 80 years to treat airway diseases. Originally it was used as a bronchodilator; however the doses that were required were relatively high, which caused frequent occurrence of adverse effects that lead to the decline of its use and it was more widely used in inhaled form. Recent studies have shown that theophylline possess an anti-inflammatory effect in chronic obstructive pulmonary disease (COPD) and asthma at lower concentrations. Currently, theophylline is used in patients with asthma as an add-on therapy to inhaled corticosteroids. Theophylline is also given to patients with severe COPD when symptoms cannot be controlled by bronchodilators. Side effects of theophylline are related to the plasma concentration of the drug; most common side effects are headaches, vomiting, and nausea that are caused by phosphodiesterase (PDE) isoenzymes inhibition. At high concentrations the inhibition of A_1 receptors caused by theophylline induces seizures and cardiac arrhythmias (Barnes 2013).

10.6.3.2 PBF-680

The PBF-680 is an A_1 AR potent antagonist (structure not disclosed) that is currently in clinical trials for the treatment of asthma. An ongoing phase II trial (NCT02635945) aimed to evaluate the efficacy of PBF-680 in patients with mild to moderate asthma. In this study, 10 mg of PBF-680 was administered orally for 5 days; the efficacy was evaluated by the amount to attenuation of late asthmatic responses that occurs due to allergen broncho-provocation. Previous studies have shown that the activation of adenosine A_1 receptors has a pro-inflammatory role in certain immune cells and also broncho-constrictory effect in pulmonary tissue. Adenosine on the other hand has shown to provoke bronchoconstriction in asthmatic patients, while an adenosine receptor antagonist such as theophylline is an effective drug for asthma treatment. Selective A_1 receptor antagonists may offer a promising therapeutic option for asthmatic patients in the future (Gao and Jacobson 2017).

10.6.3.3 Istradefylline

Istradefylline (15) was the first selective A_{2A} AR antagonist; initially it was available only in Japan for treating the wearing-off phenomenon in Parkinson's disease patients receiving levodopa-containing treatment (Saki et al. 2013).

A recent clinical trial of Istradefylline on 31 patients with Parkinson's disease has proven its effect in decreasing gait disorders including slow walking speed, short steps, forward-bent posture, toe dragging, and reduced arm swing which improved the quality of life of those patients without a serious adverse effect detected (Iijima et al. 2019). Istradefylline has also been investigated in clinical trials for improving mood disorders in PD patients. Doses between 20 and 40 mg of Istradefylline were administered for 12 weeks. Results have shown an improvement in overall mood disorders. However, further trials are needed to confirm the effectiveness of istradefylline due to the fact that this trial recruited only 30 patients with dropout rate of 17% and it was an open-label trial which indicates the possibility of placebo effect in patients (Nagayama et al. 2019). Recently, it has got the US FDA approval (2019) and available in the market as an add-on to levodopa/carbidopa for the treatment of PD (Hoffman 2019; Voelker 2019).

10.6.3.4 Preladenant

Preladenant (16) is an A_{2A} AR antagonist; mainly it was developed to treat patients with PD. However, clinical trials have not been successful and got discontinued. The development of preladenant was discontinued in 2013 after two phase III clinical trials to test its efficacy in treating fluctuating motor disturbances in patients. Results indicated that preladenant had no significant effect as compared to placebo (Pinna et al. 2018).

A preladenant phase I study (NCT03099161) in combination with pembrolizumab was conducted to treat neoplasm. Solid tumors that do not respond to conventional therapy were targeted in the trial. The study was to assess the efficacy and safety of preladenant as a treatment and to set the recommended dose for further clinical trials. However, the study was terminated because the data did not support the study end point (Congreve et al. 2018).

10.6.3.5 PBF-509

PBF-509 (17) is a non-xanthine potent A_{2A} AR antagonist that has been tested for the treatment of PD on rodent models. Studies have shown its efficacy in reducing pilocarpine-induced tremulous jaw movements, haloperidol-mediated catalepsy, and L-DOPA-induced dyskinesia, which indicates that PBF-509 is an anti-dyskinetic agent along with reversing parkinsonian motor impairments making it a potential treatment option for PD in the future (Núñez et al. 2018).

10.6.3.6 CPI-444

CPI-444 (18) is a selective and highly potent A_{2A} AR antagonist for oral administration. The adenosine A_{2A} receptors expressed on immune cells have a suppressive effect on antitumor activity. Blockage of this receptor with a compound such as CPI-444 has shown to restore IL2 and IFNγ production and T-cell signaling in *in vitro* studies. Preclinical studies of CPI-444 on mice have proven its efficacy in producing antitumor response when anti–PD-L1 immunotherapy failed to produce the required therapeutic response. The mechanism that explains how blocking of A_{2A} receptors can overcome the resistance of anti–PD-L1 treatment is still under investigation (Willingham et al. 2018).

A clinical phase I trial (NCT02655822) is currently ongoing (by Corvus Pharmaceuticals, Inc.) for dose selection, tolerability, and safety of CPI-444 as a single antitumor agent or in combination with atezolizumab. Adenosine has shown to suppress antitumor activity in immune cells (T-cells) (Mobasher et al. 2019).

10.6.3.7 CVT 6883 (GS-6201)

CVT-6883 (19) is a selective and potent A_{2B} AR antagonist. Preclinical studies have shown that CVT-6883 has an inhibitory effect on pulmonary injury and inflammation in bleomycin-induced fibrosis models and adenosine deaminase-deficient mice. CVT-6883 has also shown to reduce airway reactivity induced by allergen or NECA in sensitized mice. However, CVT-6883 was discontinued from phase I clinical trials (Basu et al. 2016).

CVT-6883 has also shown to significantly reduce lung fibrosis mediators in multi-walled carbon nanotube (MWCNT) treated mice. CVT-6883 has also decreased inflammatory and cytotoxicity in animal models, which indicates that a selective A_{2B} AR antagonist might offer a possible treatment option for MWCNT-induced lung fibrosis in humans and requires further investigation and development (Liu et al. 2019).

10.6.4 Allosteric Modulators of ARs

Important allosteric modulators of adenosine receptors are presented in Fig. 10.9.

10.6.4.1 T-62 and LUF 5484

T62 (20) is a positive allosteric modulator (PAM) of A_1 AR. T62 preclinical studies have shown that oral administration caused a reduction in hypersensitivity

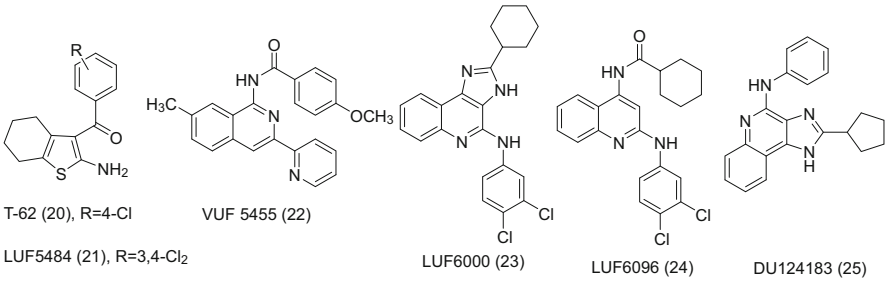


Fig. 10.9 Important allosteric modulators of ARs

neuropathic pain and inflammatory models. It was also noticed to induce sedation after the initial dosing; 5 days after daily administration tolerance has occurred due to downregulation of the A_1 AR. T62 has progressed into clinical trials, a phase II trial (NCT00809679) to evaluate the safety and efficacy of this compound as an analgesic for patients with postherpetic neuralgia. However, some patients experienced transient elevations in liver enzymes (transaminases) which terminated the study (Romagnoli et al. 2015; Sawynok 2016). LUF 5484 (2-amino-4,5,6,7-tetrahydrobenzo[b]thiophen-3-yl)(3,4-dichlorophenyl)methanone (21) is an A_1 adenosine receptor allosteric modulator (Bueters et al. 2002).

10.6.4.2 VUF5455

VUF5455 (22) is a 3-(2-pyridinyl) isoquinoline derivative, the first selective PAM of A_3 AR. VUF5455 enhances the binding of A_3 receptor agonists and increases the dissociation rate of antagonist (Briddon et al. 2018; Soudijn et al. 2006).

10.6.4.3 LUF6000

LUF6000 (2-Cyclohexyl-*N*-(3,4-dichlorophenyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine) (23), an A_3 AR PAM, increases the activity of orthosteric agonists. The maximal effect of the native ligand increases by 45% when an allosteric enhancer binds to the receptor. LUF6000 has been studied on animal models including mice and rats, and results have shown that LUF6000 induces anti-inflammatory effect by slightly stimulating neutrophils and normal white blood cells (Cohen et al. 2014).

10.6.4.4 LUF6096

LUF6096 (*N*-{2-[(3,4-dichlorophenyl)amino]quinolin-4-yl}cyclohexanecarboxamide) (24) is a positive A_3 AR allosteric modulator; it was developed by the scission of the imidazole ring of LUF6000. LUF6096 has been through preclinical studies on animal models and human cell membranes to evaluate its efficacy in reducing myocardial ischemia/reperfusion injury. Results have shown that LUF6096 is well tolerated and effective in deceasing the myocardial ischemia/reperfusion injury on dog models (Du et al. 2018, 2012).

10.6.4.5 DU124183

DU124183 (2-cyclopentyl-4-phenylamino-1*H*-imidazo[4,5-*c*]quinoline) (25) is a selective allosteric modulator that enhances agonist binding and function of A_3 AR (Göblyös and Ijzerman 2009). DU124183 causes a decrease in agonist potency meanwhile enhancing its maximum effect (Emax) (Gao et al. 2008).

10.7 Conclusions

Adenosine and its four receptor subtypes (A_1, A_{2A}, A_{2B}, and A_3 ARs) are widely distributed throughout the body, modulating the physiological and pathological conditions of almost every organs and tissues. The ubiquitous distribution of ARs not only signifies their potential drug targets but also imposed a great challenge in the process of discovery and development of drugs selectively targeting a particular subtype of AR in disease-specific tissues, while culminating in undesirable side effects. In the last three decades, extensive research efforts from academia and pharmaceutical industries resulted in the discovery of various potential ligands targeting ARs, but only few of them could sustain the clinical trials to successfully reach the market. Istradefylline, an A_{2A} selective antagonist, is the most recently US FDA approved (2019) drug available in the market as an add-on to levodopa/carbidopa for the treatment of PD. Moreover, the recent discovery of the 3D crystal structure of A_1 AR and the previously identified 3D structure of A_{2A} AR have not only enhanced the understanding of the binding site topology of these receptors but also facilitated the development of improved homology models of other two AR subtypes as well as computer-aided structure-based strategies to design and discover novel AR-specific ligands. In this regard, the future discovery of the 3D crystal structures of remaining A_{2B} and A_3 ARs would further provide a clear insight into all the four subtypes of ARs, thus boost up the rational drug discovery process and development of novel clinical candidates, selectively targeting a particular AR subtype relevant to the therapeutic intervention of specific pathological disorders.

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