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Review Article

Adenosine receptor subtype modulators: Insight into molecular mechanisms and their therapeutic application

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Abstract: There are four different subtypes of adenosine receptors (ARs): A1, A2A, A2B, and A3. These receptors play a role in controlling healthy and unhealthy processes related to protecting neurons, inflammation, heart health, and the growth of cancer. The A1 receptors protect neurons and the heart, while the A2A receptors play a role in treating Parkinson's disease and cancer immunotherapy. Although much less abundant than A2A receptors, they are linked to asthma and diabetes, while the A3 receptors are promising targets for autoimmune diseases and cancer. Recent research has shown that agonists and antagonists that are specific to AR can be used as medicines by changing important biological pathways. A2A antagonists, A3 agonists, and other related compounds are being tested in people with heart failure, ischemia, neurodegenerative diseases, and inflammatory disorders. However, the main problem with this is the side effects, which include heart damage, low receptor selectivity, and drug responses that are specific to certain species. In the future, scientists need to find ways to make receptor-specific ligands that work better as medicines and have fewer side effects. Current advances include selective drugs for glaucoma, asthma, and oncology, as well as new approaches for neurodegenerative diseases and chronic inflammation. With these challenges addressed, AR therapies can transform the treatment landscape of complex conditions. This review covers the molecular mechanisms, tissue-specific roles, and translational progress of AR subtypes and further advocates for ongoing innovation to optimally tailor the clinical outcome of such interventions. Therefore, unlocking the full therapeutic potential of changing the AR could lead to new ways of treating a wide range of short-term and long-term illnesses.

Keywords: Adenosine receptors, G-protein coupling, inflammation, cancer, neurodegeneration, preclinical, clinical study

Introduction

Adenosine receptors (A1, A2A, A2B, A3) regulate neuroprotection, inflammation, heart health, and cancer. A1 protects neurons and the heart, A2A aids Parkinson's and cancer therapy, A2B links to asthma and diabetes, and A3 targets autoimmune diseases and cancer. In this section, typical substances are discussed. Often, antagonists and agonists using varied specificity are employed in combination with AR knockout (KO) mice to confirm findings *in vivo* [1]. Moreover, ARs belong to the heterogenic GPCR (guanine nucleotide-binding proteins) and GPCR family A [2]. Adenosine receptors (ARs) have a unique seven-pass transmembrane α-helical form with intracellular carboxyl termini and external amino termini. The N-terminal domain's N-glycosylation locations have a major effect on how receptors are transported to the plasma membrane.

A crucial part of the signaling process in cells is played by receptors linked to G proteins

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(GPCRs), the main category of receptors on the cell surface, which includes ARs. GPCRs react to a wide variety of ligands such as hormones, neurotransmitters, ions, and odorants, as well as light photons. They then couple to different signaling compounds and effector systems [3]. G protein-linked receptors bound to the membrane allow adenosine to have a variety of pathologic and physiologic consequences.

cAMP signaling pathways in drug discovery revolve around four types of adenosine receptors, known as A1AR, A2AAR, A2BAR, and A3AR [4]. The relationships between A1 and A3 receptors as well as Gi/o, in addition to A2A with A2B receptors and Gs, have been extensively understood. Research using chimeric A1/A2A subtypes of ADRs shows that structural components within both the carboxyl terminus and the intracellular looping process affect how well the receptors for A1 bind to Gi, while structural components within the third intracellular looping (in contrast to the carboxyl terminal) affect how well A2A the receptors bind to Gs [5]. However, novel therapeutic drugs are being produced from these types of receptors as various allosteric compounds and agonists, partial agonists, or antagonists that are triggered by both endogenous and exogenous adenosine [4].

The action of adenosine affects cells. The site of adenosine development is determined by multiple metabolic aspects [6]. The presence of an adenine molecule capable of slowing the heart's beat and pulse rate was detected in cardiac tissue extracts in 1927 [7], and this was the first proof of adenosine's role in cellular physiology [8]. This discovery resulted in the detection and cure of paroxysmal supraventricular tachycardia with adenosine fifty years later [7, 9]. Since then, scientists from a variety of fields, including etiology, biological chemistry, pharmaceutical, immunology, as well as chemistry, have already been emphasizing adenosine and its various functions in both fitness and illness, resulting in the creation of novel studies.

Adenosines are a ubiquitous endogenous synthetic compound [10-12]. Their metabolism in the frontal lobe was confirmed, as in the case of the inhibition of AR-driven cyclic adenosine monophosphate buildup generated through the methylxanthines in coffee and theophylline [13]. Methylxanthines are used for the stimulation of behavior. Caffeine is the most abused psychoactive chemical on the planet [14]. However, adenosine exerts its effects primarily through interactions with the seven-transmembrane receptor, which is found among different cells, and many tissues throughout the anatomy possess types of adenosine receptors [15, 16].

Figure 1 depicts the G-protein coupling of adenosine receptor subtypes (A1, A2A, A2B, and A3) and their associated signaling pathways, including their effects on adenylyl cyclase, phospholipase C, PI3 kinase, and MAP kinase. It also highlights receptor-specific affinities (e.g., A1 and A2A: 100 nM, A3: 1000 nM) and their effector system modulation.

Importance of adenosine receptors in humans

Adenosine receptors are found in almost all tissues and organs, including the heart, liver, brain, eye, skin, kidney, lungs, blood vessels, and joints, implying that all these proteins can disrupt nearly every physiologic function [17].

The A1 receptors are responsible for the effects from interacting with AC blocking by Gig/Go proteins. This triggers phospholipase C (PLC) B as well as more specifically K channel activation in neurons and deactivation of P/Q and N kinds of Ca^{2+} channels. They also have a significant role in mitogen-activated protein kinases (MAPK) [18].

Normally, the A2A receptors bind to Gs molecules to increase the cAMP level; nevertheless, in the nervous system, this additionally boosts the activity of Golf, a particular Gs protein in neurons that is further related to AC and is believed to be a crucial mediator of the locomotor response to psychostimulant drugs [20].

Although A2b receptors can be found in neurons, microglia, and astrocytes, their significance in the CNS is less well understood than that of the other AR subtypes [19]. They trigger the phosphorylation of Gs proteins/cAMP/PKA within the sensory system. This type of receptor raises the amounts of Gq protein, PLC, and Ca^{2+} while modifying ion channels through subunits. It is also claimed that there is a connection to MAPK [20].

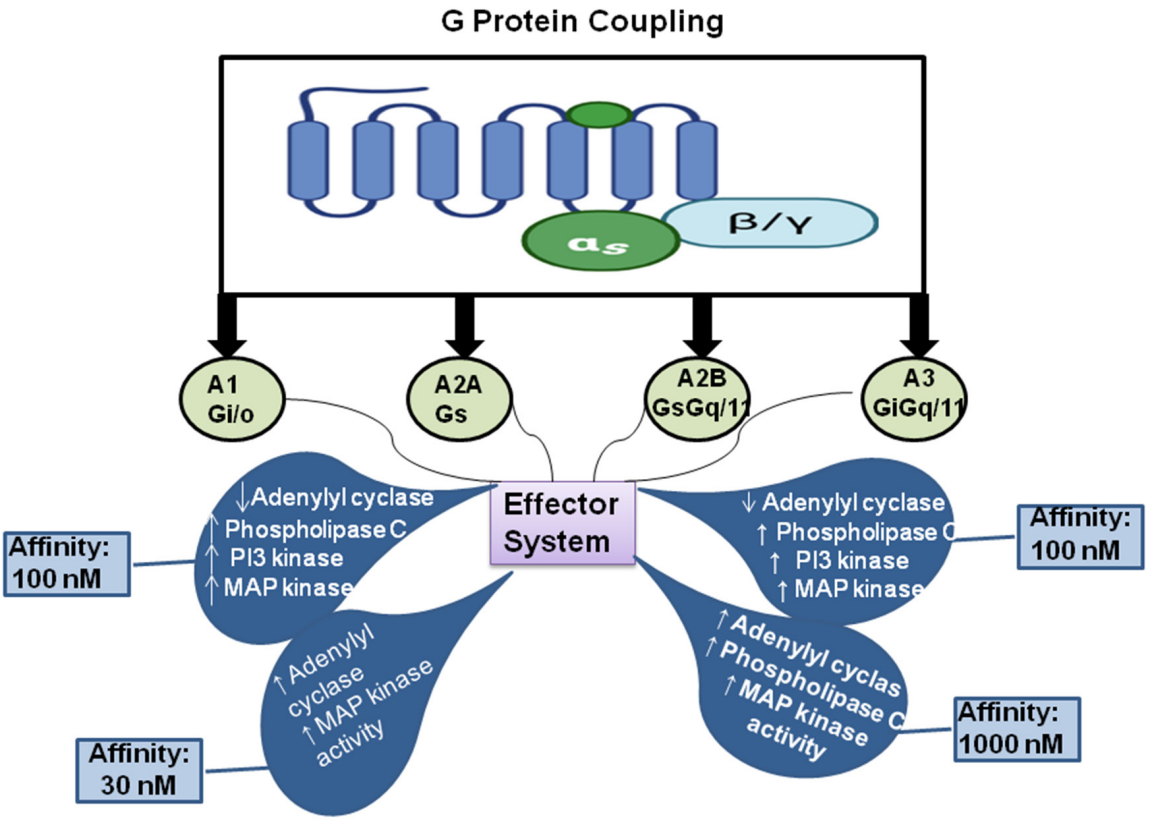

Figure 1. Mechanism of Adenosine receptors [7].

A3 receptors have been found in the neurological areas of the l cortex, hypothalamus, sensory nerve endings, intracerebral, and in the thalamus, pial arteries, and glia. The A3 receptor interacts with the Gi group, decreasing cAMP, while triggering PLC, and increasing Ca^{2+} levels through Gq proteins or G subunits [21].

Classification

A1AR: The most common receptor is the A1 receptor, widely expressed in adenosines, with several varieties [24]. It is abundant in the entire body and is mostly found in the brain, particularly at nerve endings [17]. When it comes to the brain and spinal cord, A1AR subtypes are mostly found in the cerebellum, the vagus nerve endings, the spinal column, and glial cells in general [25]. A1 receptors control the release of neurotransmitters [8]. Activating the A1 receptor makes adenyl cyclase work harder and opens potassium channels like kATP in nerve cells and the heart's middle muscle to protect them. By turning on phospholipase [21], it stops the opening of transient channels that hold calcium and inositol-1,4,5-triphosphate.

The A1 subtype shows an affinity of about 1-10 nM [7]. When the pertussis toxin [24] hit, A1AR could selectively stop the adenylyl cyclase from doing its job in biological processes. This demonstrates its direct connection to the Gi and possibly even G0 protein molecules. A1AR activates phospholipase C, which raises intracellular sodium, potassium, and inositol 1, 4, and 5-trisphosphate (IP3) concentrations. These increases activate calcium-dependent kinases of protein (PKC) or various calcium-binding proteins. There are fewer Q-, P-, and N-type channels that carry calcium when A1AR is present. In neurons and heart tissue, there are more KATP channels and potassium (K) whooping toxin-sensitive channels. Moreover, the intracellular phosphorylative cascades of the extracellular signal-regulated kinase (ERK), Jun NH2-terminal kinase (JNK), and p38 are members of the mitogen-activated protein kinase (MAPK) family [26]. A1 receptors have adverse effects on the heart's ionotropic and

chronotropic systems. They also have major effects on many other cells and organs that are physiologically important [27] (**Table 1**).

A2AR: The brain's striatum, spleen immune cells, leukocytes, thymus, and blood platelets contain increased levels of the A2A receptor compared to the heart, lungs, and blood vessels [28]. The PKA-cyclic AMP pathway is stimulated by the Gs protein and Golf protein-mediated A2A receptor activation in the peripheral tissues and brain, correspondingly [29]. By binding to Gs proteins and activating cAMP-dependent proteins, the A2A AR increases the adenylyl cyclase activity [30]. In the brain, the motor activity, sleep-wake cycle, psychiatric behaviors, and cell death of neurons are regulated by various neurotransmitters while the association with A2A receptors [8, 31]. In addition, it stands for 30 nM of affinity [7]. In the peripheral tissue, these receptors have an essential part in controlling the myocardium's oxygen consumption, the blood flow of coronaries, inflammation, and cancer pathogenesis control [32].

A2BAR: Although A2B receptors regulate subtypes, they have identical potential for mitogen-activated protein kinase (MAPK)/ERK activation since A2A receptors in cultured cells are the prominent adenosine receptors of all four of the ARs [33]. A2BAR signaling processes require activation of AC through Gs proteins, which phosphorylate PKA and recruit various cAMP-dependent effectors, such as exchange proteins, which are activated instantaneously by cAMP [34]. In addition, it has 30 nM of affinity [7]. However, under physiologic conditions, requirements such as the concentration of micromolar adenosine are rarely obtained [29]. In pharmacological studies, A2B has been used as a signaling pathway in some conditions such as hypoxia, ischemia, or inflammation [41]. These are thought to be tissue adaptations to hypoxia, greater ischemia tolerance, or acute inflammation alleviation, and play a crucial role in renal disease, diabetes, and some types of cancer; also, it is important for the vascular and lung disease control [8, 24, 35].

A3AR: The pharmacology of A3A receptors varies greatly between cells and tissues [17]. Although A3 receptor signaling binds to the mast cell degranulation in mice, its effects may vary in humans [36]. Adenylate cyclase (AC) action is decreased and cAMP generation is triggered by A3AR activation [7]. When the concentration of A3AR agonists is high, they predominantly bind to Gq proteins or Gβγ subunits, increasing both PLC and cAMP levels [37]. These couplings to Gi proteins initiate a wide range of intracellular signaling processes. Despite the low number of A3 receptors in almost all cells and tissues, they are overexpressed in blood cells in humans with Crohn's disease, rheumatoid conditions, and some cancers including colonic, compared to healthy tissues. This is orchestrated by two pathways: NF-κB signaling, and PI3K-PKB-AKT signaling [38]. Preclinical research has shown that A3 receptor agonists have anti-inflammatory, cytoprotective, and cancer-fighting properties [24].

Therapeutic potential of agonist and antagonist of adenosine receptors

AR agonists and antagonists with specificity are being developed, and therapeutic applications to benefit the peripheral and central nervous systems [39] are being explored. The four subtypes of GPCR are A1, A2A, A2B, and A3. This makes it possible to create selective agonists and antagonists. Many new drug concepts have been introduced using these ligands as pharmacologic probes [40].

Synthetic AR agonists that are both selective and powerful have a long-lasting effect on the body as compared to adenosine; for example, regadenoson is an A2A agonist used for diagnostic purposes. Agonists have effects based on anti-inflammation (A2A and A3), cerebroprotection (A1 and A3), as well as antinociceptive (A1) characteristics [22].

The specific and potent synthetic AR antagonists have therapeutic potential as kidney-protecting (A1), antifibrotic (A2A), antiasthmatic (A2B), and antiglaucoma (A3) medicines [22].

*Agonists and antagonists of AR in preclinical and clinical trials (**Tables 2** and **3**)*

All four AR subtypes have had selective and potent agonists and antagonists synthesized, along with selective A2BAR agonists. A single AR subtype is selective for several ligands [46]. As a result, several pharmacologic requirements have been established for understand-

Table 1. Adenosine receptor classification with their distribution in human body

Name of Adenosine receptor	G-proteins/transduction mechanism	Human gene	Chromosome	Distribution	Ref.
A1AR	Gi, Go ↓cAMP	ADORA1	1q32.1	Highly delivery; Hyperpolarization inside the neuron, sedative, cardio, renal, and body fat	[7]
A2AAR	Gs ↑cAMP	ADORA2A	22q11.23	Highly delivery; in the basal ganglia; extremely high in nerve cells, blood arteries, and immune system cells	[22]
A2BAR	Gs [Gq/11; G12/13] ↑cAMP	ADORA2B	17p12-p11.2	Highly delivery, but generally low abundance	[16]
A3AR	Gi/o ↓cAMP	ADORA3	1p13.2	Less delivery; varies according to species: greatest in the mast cells	[23]

Table 2. Adenosine receptor agonist literature in preclinical and clinical studies

No.	Agonist	Animal/Humans/Dose	Objectives/Mechanism	Outcomes	Reference
1.	Adenosine	[Rat] Verapamil Diltiazem B-blockers	Paroxysmal supraventricular tachycardia Treated by vagal maneuvers	Releases transient atrioventricular nodal blocks, when injected as an IV bolus.	[4, 42]
2. A1	Capadenoson (BAY684986)	[Mice] In vivo- 0.03-1 mg/kg	Stimulates additional AR subtypes [particular the A2BAR]	Promote cardiac protection and modulate cardiac fibrosis. Chronic treatment fibrillation (phase-2)	[43]
3.	GW493838	All [18 to 80 years - humans]	Females of non-child-bearing potential Glial activation Role of immunocompetent cell Role of skin cells	Pain intensity Peripheral neuropathic pain (Phase-2) (discontinued)	[44]
4.	Selodenoson	All [18 to 85 years - humans]	Primary purpose; treatment Combine treatment with Capadenoson.	A1AR agonist to reduce heart rate in patients with Atrial Fibrillation (Phase-2)	[45]
5.	Tecadenoson	Humans [0.3-15 micro/kg]	Examine the protection and efficacy of converting PSVT to a sinus rhythm. Restored normal sinus rhythm after terminating remained PSVT by lowering AV nodal conduction.	Adenosine is the initial therapy for a person with paroxysmal atrial tachycardia. (Phase-2)	[46]
2. A2A-SELECTIVE AGONIST					
6.	Apadenoson	Humans - 18 years and older	Primary purpose -diagnostic Coronary artery disease The use of BMS068645 stimulates A2aAR responsible for coronary vasodilation. Reduce or eliminate side effects.	Safety and efficacy for identifying Myocardial perfusion (Phase-3)	[47]
7.	Regadenoson	Rat/Humans-[18-100 years old]	Diagnostic purpose Selective low-affinity agonist that mimics the effects of adenosine in causing coronary vasodilation and raising blood flow of the myocardium.	Stress MRI for detection of coronary artery disease (Sensitivity, specificity, accuracy). (Phase-2)	[48]

8.	Sanderson [MRE0094]	Humans	Pathophysiology and progression of diabetic foot ulcer. Treatment and management for wound healing and diabetic ulcers. Treatment with antibiotics.	Treatment for diabetes complications wound healing and diabetic foot ulcer. (Phase-1)	[35]
9.	Binodenosone [MRE0470, SHA-174, WRC-0470]	Humans [30 years/older]	Highly selective Increased cardiac blood flow, using a single injection, requires a 15-20-minute infusion.	Efficacy and safety in assessing cardiac ischemia.	[49]
3. Adenosine receptor Agonist					
10.	BAY 60-6583	Humans/Rabbits/Mice	Activating the adenosine A2b receptor has anti-inflammatory properties that include promoting cancer growth, and metastasis, and generating immunosuppressive cells.	Ophthalmic disease (Phase-3) Protect from ischemia in the heart and kidney. (Preclinical)	[50]
11.	Piclidenoson IB-MECA [CF101] (A3 adenosine receptor agonist)	Humans [oral dose] 18 years/older	Reflecting on its role in the remote inflammatory process. Activation of A3AR activation with a specific agonist degranulates the NF-kappaB signaling pathway in inflammation and initiates immunomodulatory effects.	Nature and frequency of adverse effects. Psoriasis, dry eye, autoimmune inflammatory disease, glaucoma (Phase-2)	[51]
12.	Cl-IB-MECA [CF102] (A3 adenosine receptor agonist)	Humans [18-80 years old]	Primary treatment Regulate the proliferation signaling pathway by three critical pathways' levels of protein expression in pancreatic and HCC cell lines.	Liver cancer: Hepatocellular Carcinoma (Phase-1&2)	[52]

Table 3. Adenosine receptor antagonists literature in preclinical and clinical studies

No.	Antagonist	Animals/Sex/ Dose	Objectives/Mechanism	Outcomes	Reference
1. NON-SELECTIVE ANTAGONIST					
1.	Caffeine	Human Rat	Used as a psychoactive compound Promotes wakefulness by blocking A1ARs in the brain. Blocks opioids by attachment of receptors without their activation.	Depression treatment Apnea (Phase-3)	[53]
2.	Theophylline	Humans/Rats/ Rabbits/Cows	Xanthine is used to regulate the symptoms of Asthma and COPD. Used as a phosphodiester, and adenosine receptor blockers. Inhibitor relaxes the smooth muscle cells of the airway and pulmonary blood vessels. Blocked are classes 3 and 4 PDE, the enzymes in cells of smooth muscle that break down cyclic AMP.	Lung conditions are caused by reversible airflow obstruction. Chronic asthma, Lung diseases like, emphysema and chronic bronchitis. (Approved)	[54, 55]

2. A1-SELECTIVE ANTAGONISTS					
3.	Rolofylline [KW3902, NAX]	Humans [18 years and older]	Change in cardiac output, systemic and pulmonary vascular resistance. To identify the optimal dose range of IV drug combination with IV furosemide, with or without other diuretics in inhibition of renal control in patients with CHF.	Heart failure Regulate the pulmonary capillary wedge pressure. Effects on heart failure's indicators and symptoms The impact on kidney function. (Phase-2)	[56, 57]
4.	Toponafylline [BG-9928]	Humans/Rats/	A1 receptor stimulation in the decrease in GFR in the kidney via tubuloglomerular action and raise sodium reabsorption. It is a xanthine derivative that binds to receptors in different organisms, including humans, with a great deal of affinity and serves as an antagonist of competition at this receptor.	Heart failure, renal insufficiency (Phase-2)	[22]
3. A2a-SELECTIVE ANTAGONIST					
5.	Istradefylline [KW6002] (Others-Vipadenant and preladenant)	Humans [20-40 mg] 30 years and older	Indicated in adjunct to levodopa and carbidopa. The basal ganglia are a brain area that is targeted to produce deregulation in PD and is considered motor activity.	Parkinson's disease treatment Useful for Dyskinesia conditions. (Phase-3)	[58]
4. A2B-SELECTIVE ANTAGONISTS					
6.	CVT-6883 [GS 6201]		Binding with four subtypes of adenosine receptors determined, while using competition radioligand binding assays in membrane isolation by cell lines that over express each of the four types.	Potential treatment of asthma and other inflammation and fibrosis (Phase-1)	[59]
7.	MRE-2029-F20	Humans	A2b subtype-specific radioligand with a high affinity that is utilized for determining endogenous sites and reveals their existence and activity of coupled in lymphocytes and neutrophils that have anti-inflammatory properties.	Anti-inflammatory effects [preclinical]	[60]
5. Adenosine A2A receptor antagonist as Adjuvant therapy					
8.	SYN-115	Humans	Adjunctive therapy with levodopa.	Parkinson's disease (Phase-3) Liver disorders (Phase-1)	[61]
9.	SLV320	Humans	A single i.v. SLV320 dose did not affect BP, RAP, SVR, or CO. When compared to baseline, furosemide therapy resulted in a substantial increase in cystatin c.	Heart failure (Phase-2)	[62]

ing ARs, and in clinical trials, progress has been made with a few compounds. A fundamental fact in the construction of selective agonists and antagonists, of similar subtypes in diverse species, is a variable affinity to provide compounds by intervals of observation [42]. There are numerous examples of remarkable species dependent on the affinity of ligands at the adenosine receptors [16]. Therefore, one must exercise caution when comparing the selectivity of a given drug from one species to another. In general, either AR antagonists or agonists must be therapeutically compatible with species variations [7].

Pharmacological actions of adenosine receptors in various disease conditions

Adenosine-1 receptor

Arrhythmias: Arrhythmia can be caused by various pathophysiologic phases, including both hypoxia and ischemia [8]. Because of its endogenous characteristics, this receptor is regarded as an antiarrhythmic agent of the endogenous group [63]. Its preceding ATP has been used to prevent paroxysmal supraventricular tachycardia (PSVT) for many years [64]. Adenosine's antiarrhythmic effect occurs because of the action of A1AR in the atrioventricular and sinoatrial nodes, resulting in changes in AV nodal reflection, and the A1AR activity causes ATP-sensitive potassium channel opening [65]. In 1995, the first Adenoscan was approved as an infusion of adenosine receptor, which is used in MPI (myocardial perfusion imaging) by dilating the coronary artery through A2AAR short-term action [66].

Recently, adenosine was used in a clinical experiment designed to repair Takotsubo syndrome left ventricle destruction, but this was halted in 2018 [8]. Adenosine has been shown to have an A1AR-dependent beneficial effect in PSVT (e.g., Tecadenoson -13 and Selodenoson -14); however, in 15% of patients, it shortens the atrial refractory period and causes additional side effects linked to the activation of other AR subtypes [89]. Consequently, a great deal of effort has been expended in creating specific A1AR agonists sometimes referred to as inhibitory-arrhythmic drugs [90]. Them A1AR complete agonists, Tecadenoson 13, Selodenoson 14, and Trabodenoson 4 have been produced [91]. Full agonists, on the other hand, have been linked to tachyphylaxis, most likely due to A1AR desensitization. Tecadenoson is now being investigated for the therapy of supraventricular tachycardia in phase 3 trials (SVT) [92].

Epilepsy: As a naturally occurring seizure drug, adenosine stops epileptogenesis and this type of epigenetic action is counteracted by nuclear adenosine [67]. High levels of adenosine stop DNA methyltransferases from working by stopping the end product of the enzymes, and they also start the SAH process [17]. In epileptic brains, astrocytes overexpress adenosine kinase, which reduces adenosine in the cells and in the extracellular space [65]. Since peripheral adenosine prevents flow, and at a high concentration, a drug delivery system is required [68]. Microspheres envelop the adenosine and are submerged in nanofilm-coated silk fibroin scaffolds [69]. The A1AR antagonist 1,3-dipropyl xanthine, also known as 8-cyclopentyl, inhibits this process [70].

Inflammation: Regarding allergic conditions, the expression of this receptor causes either pro- or anti-inflammatory reactions. Reports have indicated that A1 is not expressed in human lung mast cell populations [71] and is only weakly present in the lungs [4]. It could nevertheless play a role in the pathophysiology of inflammation-related airway illnesses, as demonstrated by studies. The bronchial epithelium and smooth muscle of people with asthma have been shown to have elevated levels of A1. Furthermore, bronchoconstriction was shown to result from its activation [72]. Animal model research shows adenosine as well as exposure to allergens cause breathing problems and this provides evidence in favor of this conclusion [73]. However, by decreasing neutrophil chemotaxis as well as edema in a lung ischemic reperfusion model, A1 activity demonstrated an anti-inflammatory effect [74]. According to research, damage to the lungs caused by LPS (lipopolysaccharide) additionally revealed a decrease in polymorphonuclear cell traffic as well as microvascular permeation [4].

Asthma: A naturally occurring 5'-phosphodiester of adenosine 5'-phosphate produces the adenosine *in situ*. The testing of inhalation employs adenosine 5'-monophosphate (AMP) as a diagnostic marker. Because AMP forms adenosine *in situ*, most activation is mediated

by ARs. However, not all actions have *in vivo* outcomes mediated by AR activity. The endogenous and exogenous adenosine is present in asthma [8, 75].

Glaucoma: Glaucoma is an optic neuropathy that is related to elevated intraocular pressure and leads to blindness [76]. Glaucoma treatments aim to reduce intraocular pressure (IOP) and preserve retinal ganglion cells [77]. Recently, it was discovered that adenosine plays an important role in intraocular pressure (IOP) neuroprotection due to its neuromodulatory activity [78]. IOP is increased or decreased by adenosine derivatives through the A2AAR [79]. Activation of A1AR decreases the resistance of egress and thus IOP. The Cl (-) channel activation, mediated by adenosine can be easily prevented by A3 receptor antagonists in non-pigmented epithelial cells. This is because A1 agonists lower vascular resistance and increase blood flow to the retina and optic nerve. In addition, after an ischemia attack, A1 agonists such as Tecadenoson enhance the function of the retina [77, 80].

Hypothermia and pain: MRS7469 is a highly selective agonist, like CL-ENBA 7, that is frequently injected peripherally; the central A1AR becomes activated resulting in A1AR-mediated hypothermia and psychomotor dysfunction [81]. When administered intracerebroventricularly (icv) at a dose of 52 g/kg, this causes severe hypothermia, because it crosses the blood-brain barrier (BBB) enough to turn on the A1AR. Furthermore, MRS7469, which has a non-chiral N6 category, is a purified diastereoisomer that can be used for *in vivo* studies [8].

Neuroprotection: NNC-21-013615 is a selective A1AR agonist with neuroprotective properties. It has fewer hemodynamic effects, such as a neuroprotective effect in stroke models, but it was never tested in humans [82]. The agonists are classified based on their *in vitro* state, as well as their *in vivo* activity in comparable animal models [83]. The neuroprotective capabilities of agonists in serious transient forebrain ischemia paradigms in Mongolian gerbils, using hippocampus CA1 injury terminals, and their effect on A1 activity assays, indicate similar strategies to several noted adenosine receptor agonists [84, 85].

Diabetes: A1ARs (GR79236 11, ARA 12, and CVT-3619 (GS-9667) 10) seem to have an essential function in the regulation of insulin and glucose homeostasis, particularly for active metabolic organs including the liver, muscles of the skeleton, and adipose tissue - all of which are associated with diabetes type 2 [86]. A1AR has been shown to be crucial for the proper function of lipid homeostasis. As a result, type 2 diabetes, also known as T2D, and overweight are treated with an A1AR agonist [87]. The A1AR on white adipocytes regulates lipolysis. Mammalian PET imaging indicated that A2AAR-activated thermogenic brown adipose tissue (BAT) is functional, suggesting that A2AAR agonists may be beneficial in metabolic disorders [88].

Figure 2 shows how the A1 adenosine receptor (A1AR) regulates cardiac protection, neuroprotection, and broncho-inflammation, aiding in conditions like myocardial infarction, pain management, and COPD.

A2A adenosine receptors

Sickle cell disease: A2AAR agonists (REGADENOSON 21) are being utilized to alleviate inflammation in sickle cell anemia patients. In animal studies with SCD transgenic, A2AAR activation in indigenous killer T (iNKT) cells has an anti-inflammatory effect [93] A2BAR activation in erythrocytes, on the other hand, is thought to be harmful in SCD. A clinical trial was conducted to assess the efficacy of regadenoson 21 as an A2AAR agonist in patients of SCD; however, no statistically important properties were found [8, 94].

Glioblastoma: A2AAR agonists temporarily raise BBB permeability; they are being studied for a unique pharmacologic strategy for brain-based administration [95]. Regadenoson was clinically tested in glioblastoma patients and shown to raise the amount of chemotherapy medications like Temozolomide in the brain's interstitium, as measured by microdialysis [26].

Hypoxia and multiple myeloma: Apadenoson 25 was studied in multiple clinical studies for MPI SCD, all of which include hypoxia [96]. To shorten the time that it acts, it has a labile ester moiety that is broken down *in vivo*. Evodenoson (ATL-313)26, a more stable urethane-consisting congener, has been accepted as a possible treatment and used for multiple myeloma [97].

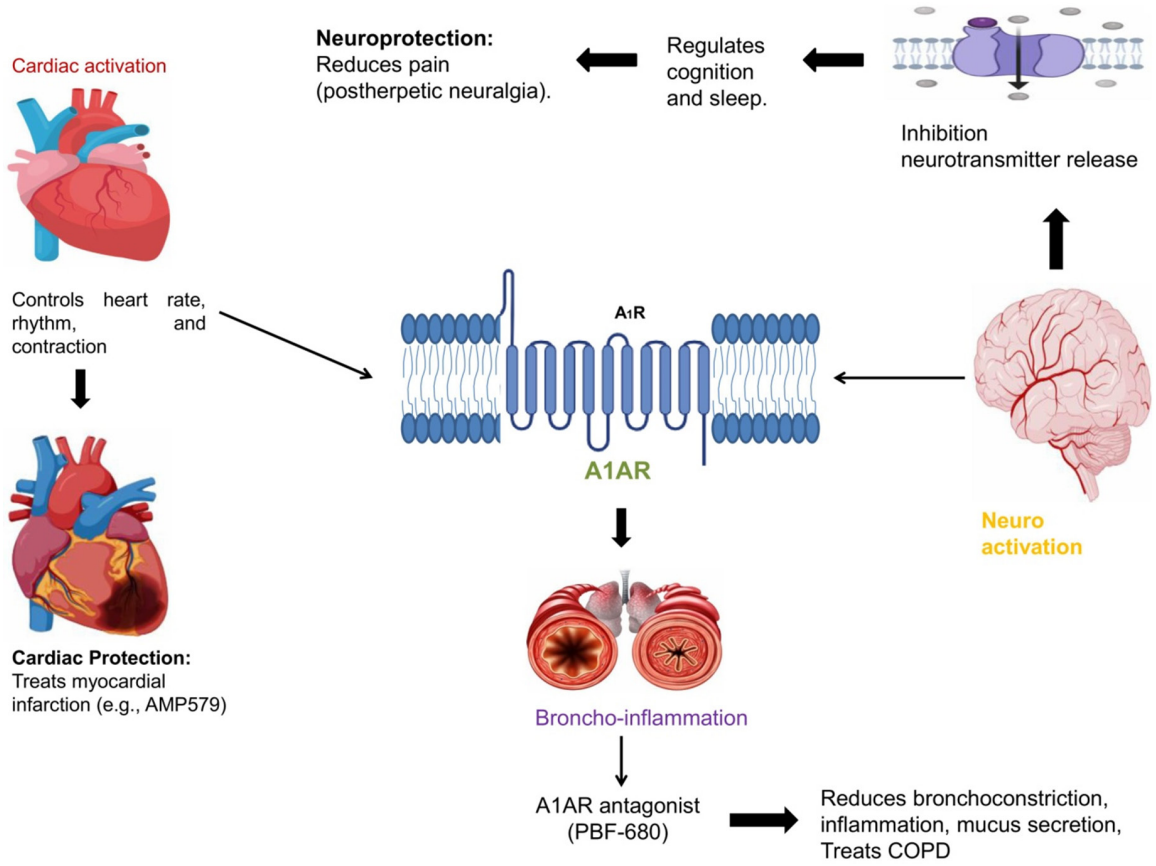

Figure 2. Role of A1AR in different diseases.

A2B adenosine receptors

Asthma: The activation of A2BAR on mast cells may help in the diagnosis of asthma because adenosine in the air causes mast cell regulators to be made in bronchitis fluid, which then makes prostaglandin and histamine [98]. It has an anti-ischemic effect in the intestine and kidneys. Researchers found BAY 60-6583 to be protective against reperfusion injuries to the myocardium. It changes macrophages to an M2 phenotype through A2BAR. This activates the PI3K/Akt pathway, which reduces inflammation [99].

Diabetes and atherosclerosis: A2BAR activation may also be beneficial in the diagnosis of type 2 diabetes as well as atherosclerosis, as well as in the prevention of vascular lesions caused by an important event leading to their formation after angioplasty [100]. Because this receptor is absent in macrophages, A2BAR knockout (KO) mice exhibited increased fatty liver disease, inflammation of liver tissue, and insulin resistance [11]. FFA-induced macrophage and inflammation activation were reduced by A2BAR activation [11].

Ischemia: Even though no A2BAR agonists are currently in clinical trials, animal models suggest that activating them may play a crucial role in acute lung injury and ischemia [101]. The nucleotides such as BAY 60-6583 30 a key 3, 5-dihydropyridine agonist known as *in vivo* as well as *in vitro* pharmacological approach, though its component of species and efficacy affinity could be different [8]. The agent acted as an A2BAR antagonist in some models, such as the release of insulin in MIN6 mouse insulinoma cells. As a result, extremely selective or consistently effective A2BAR agonists remain deficient. Furthermore, signaling mechanisms that the Gs-coupled A2BAR activates or inhibits are complex and may use various G proteins [102].

Novel approaches: **Figure 3** shows the important role of agonists and antagonists in

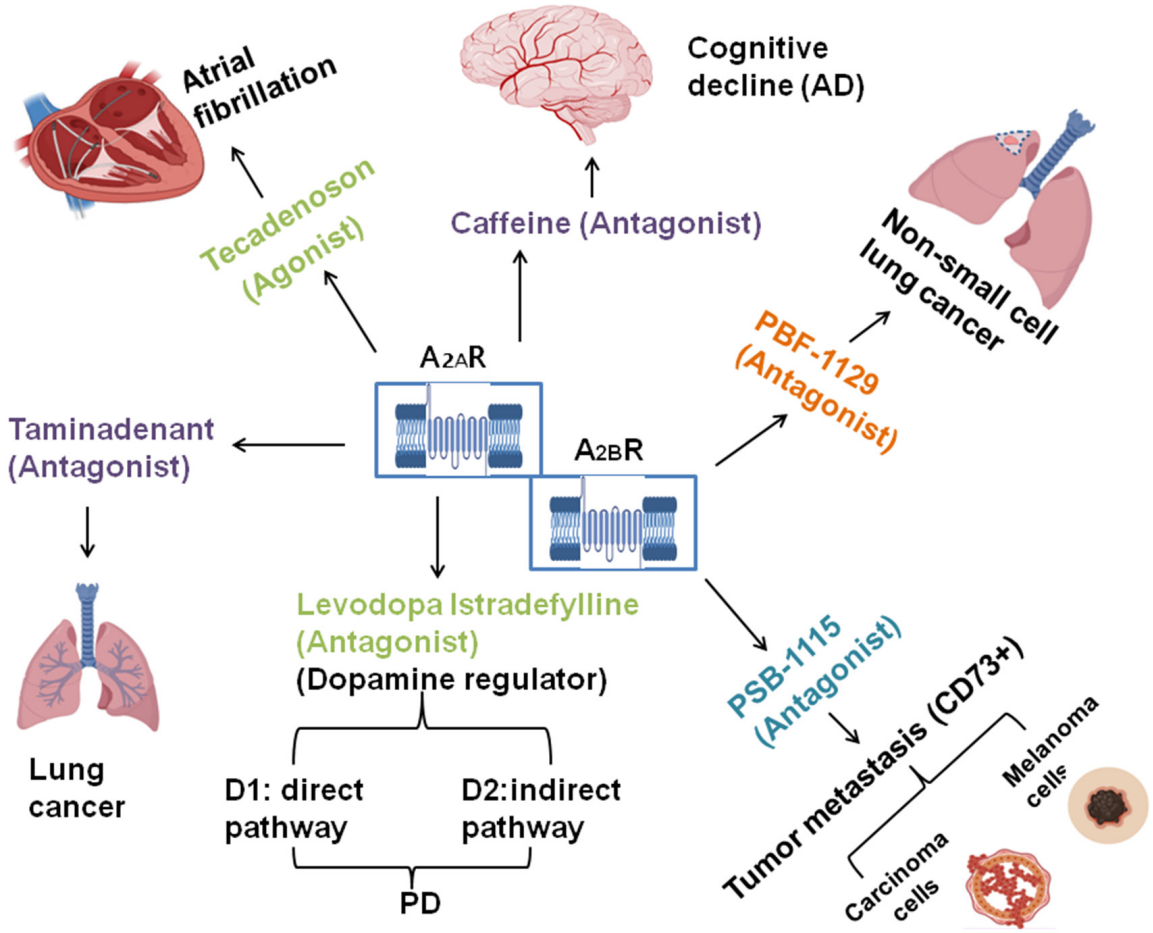

Figure 3. Role of A2AR in different diseases.

the treatment of various diseases. Moreover, A2AAR acting through forms of agents as caffeine inhibits the action of Alzheimer's disease. Tecadenoson is used to inhibit atrial fibrillation. Taminadenant and Levodopa may prevent lung cancer and Parkinson's disease respectively. However, A2BAR has PBF-1129 for non-small cell lung cancer and PBS-1115 for melanoma cells and carcinoma cells. Additionally, each agent has a different pathway to inhibit specific sites to reduce the activity of disease (Clinicaltrials.gov reports representative adenosine receptor modulators in clinical trials both presently and in the past).

A3 adenosine receptors

Liver disease: The CI-IB-MECA test is utilized to diagnose liver illnesses such as nonalcoholic steatohepatitis (NASH) and hepatocellular carcinoma (HCC) [103, 104]. Wnt ZZ degranulation causes A3AR agonists to have anticancer and apoptotic nature *in vivo* [104]. Namodenoson drug is useful for liver cancer and it has much less serious adverse effects or dose-related complications. It has been suggested that A3AR be used to reduce releasing syndrome in immunotherapy of cancer [105].

Rheumatoid arthritis: This medication was developed to aid in the diagnosis of autoimmune anti-inflammatory disorders, including a condition known as psoriasis and rheumatoid arthritis (RA) [106]. Moreover, in the phase 2 trial for RA, the intermediate most favorable outcomes were obtained with an oral dose of 1 mg, as contrasted with 0.1 and 4 mg. Peripheral blood mononuclear cells from people with psoriasis expressed A3AR (PBMCS). IB-MECA decreased a human keratinocyte cell line's ability to make cells proliferate and produce IL-17 and IL-23 [107]. In phase 2 clinical trials,

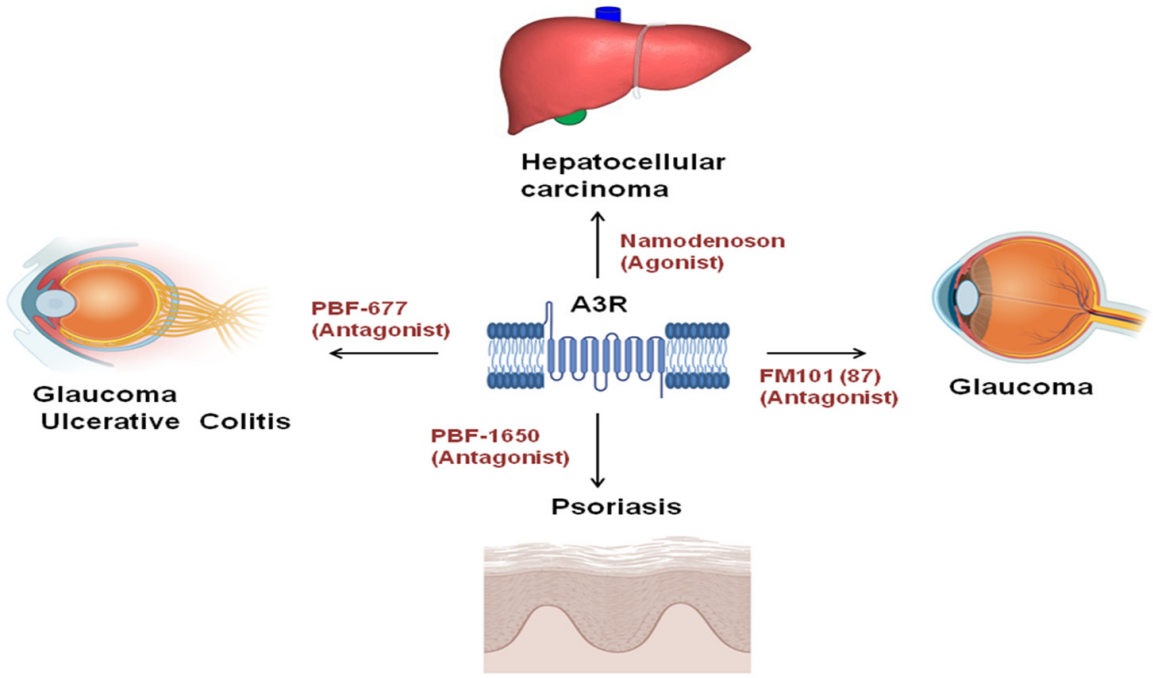

Figure 4. Role of A3AR in different diseases.

IB-MECA has not demonstrated efficacy for glaucoma or dry eye at dosages of 1 mg or 2 mg (oral, twice daily) [108].

Myocardial ischemia: CP-608,039 is soluble in water and is an extremely A3AR-selective agonist that has been explored for the management of perioperative myocardial ischemia. The current study contributes to an expanding body of evidence demonstrating that A3AR amplification through preparation is helpful for ischemic cardiomyocytes [109]. Currently, selective A3AR excision in mouse cardiomyocytes has been used as evidence of the triggering of a cardiac A3AR by the selective agonist CP-532,903(34). Ischemic resistance is based on KATP pathways. By confirming the existence of a beneficial A3AR in adult ventricular cardiomyocytes, our study resolves a long-running controversy [110].

New approaches: **Figure 4** illustrates the effects of A3AR in hepatocellular carcinoma, ulcerative colitis, psoriasis, and glaucoma with namodenoson agonist, PBF-677 antagonist, PBF-1650 antagonist, and FM101 (87) antagonist correspondingly. All agonists and antagonists have inhibiting activity in various diseases (Clinicaltrials.gov reports representative adenosine receptor modulators in clinical trials both presently and in the past).

Drug targeting adenosine receptor for future treatment (Tables 4 and 5)

Adenosine receptors (AR) have been investigated as possible targets for therapy for several disorders affecting the peripheral and central nervous systems, including asthma, Parkinson's illness, arrhythmias of the heart, and newborn apnea [111]. These receptors are also used in diagnostic research, namely in evaluating the coronary circulatory system in patients who are incapable of operating on a treadmill. Over the years, using animals in experiments has been very helpful for testing adenosine receptor drugs in many areas, such as wound healing, sickle cell disease, congestive heart failure, Alzheimer's disease, major depressive disorders, grand mal epilepsy, diabetes, and inflammatory diseases. Studies on humans followed this example, examining these drugs' effectiveness in practical situations. In the past 10 years, intriguing uses for adenosine receptor medicines have been marked by the identification of additional possible disease domains through recent discoveries. However, there remains a knowledge gap, nonetheless, among

Table 4. Adenosine receptor Targeted therapy for Congestive heart failure and Cancer

Title	Congestive Heart Failure and Adenosine A1 Receptors	Cancer and Adenosine A2A Receptors	References
Concepts	Focus on A1 receptors, their role in congestive heart failure, and the impact of A1AR activation.	Emphasis on A2A receptors, their association with cancer, and the immunosuppressive effects of adenosine, including the role of A2AAR in suppressing adaptive immunity and influencing tumor development.	[112, 113]
Findings	Investigated the impact of A1AR activation on renal function, sodium retention, and the potential therapeutic role in congestive heart failure.	Explored the link between adenosine deaminase deficiency, A2AAR, and the immunosuppressive effects of adenosine. Highlighted the rejection of A2AAR mutant mice's melanoma and lymphoma cell types and how A2AAR antagonists respond to anti-PD1 as well as anti-CTLA4 treatment.	[112, 114]
Clinical Trials	Mentioned the testing of rolofylline, a selective A1AR antagonist, in congestive heart failure with no significant benefit.	Explored the potential synergy between anti-PD1 and anti-CTLA4 therapy with a range of A2AAR, A2BAR, and dual antagonists at varying levels of clinical development.	[115, 116]
Experimental Approach	Explored the possibility of using regadenoson, an incomplete A1AR agonist, to prevent the cardiac irregular heartbeats caused by complete A1AR agonists.	Highlighted how A2AAR altered mice completely rejected lymphoma cell and melanoma types, indicating the critical function A2AAR plays in immunity to tumors. Additionally, the possibility of A2AAR antagonists interacting with CAR-T cells to boost their effectiveness against tumors was considered.	[117, 118]
Results and Outcomes	Mentioned that short courses of roofline did not improve exercise tolerance in heart failure patients.	The groundbreaking research that demonstrated how A2AAR mutant mice entirely excluded melanoma and lymphoma cell lines most effectively demonstrates the role of A2AAR in the growth of cancers.	[114, 117]
Further Considerations	Discussed the potential therapeutic impact of A1AR on Ca21-ATPase, cardiac myocyte function, and mitochondrial function.	Explored the broader implications of A2AAR in cancer development, including the potential synergy with immunotherapy A2AAR, A2BAR, and dual antagonists are still in the drug development stage, as is (anti-CTLA4 and anti-PD1 treatment). Additionally, alternative treatment modalities that target CD73's role in adenine nucleotide formation into adenosine were highlighted.	[119-121]

Table 5. Adenosine Targeted therapy for Neurodegenerative disease

Aspects	Investigation of neurodegenerative diseases, with a particular emphasis on motor and Parkinson's diseases	Investigation of neurodegenerative diseases, with a particular emphasis on cognitive dysfunction and Alzheimer's diseases	References
Concepts	Highlights the function of dopamine D2 receptor-interacting A2A adenosine receptors (A2AARs) in the basal ganglia, as well as the possibility of using A2AAR antagonists to lessen dopamine deficiency in the condition Parkinson's (PD).	Explains the genetic or pharmacological blockage of A2AARs and their preventive effect on memory deficits across various animal models, extending to conditions beyond Alzheimer's disease, including convulsions, diabetes, hypoxia, and others.	[122, 123]
Experimental Approach	Highlights the antagonistic interaction between A2AARs and dopamine D2 receptors, forming A2AAR-D2 receptor heteromers.	Mentions the pharmacological or genetic strategies used to block A2AARs and prevent memory deficits in different animal models.	[123, 124]
Targeted treatment	Proposes targeting A2AARs to alleviate dopaminergic depletion, especially in the context of Parkinson's disease.	Proposes the potential of A2AAR antagonists in preventing memory dysfunction associated with various conditions, broadening the scope beyond Alzheimer's disease, including convulsions, diabetes, hypoxia, and others.	[123, 124]
Experimental outcomes	Highlights the antagonistic interaction between A2AARs and dopamine D2 receptors, forming A2AAR-D2 receptor heteromers.	Proposes the potential of A2AAR antagonists in preventing memory dysfunction associated with various conditions, broadening the scope beyond Alzheimer's disease, including convulsions, diabetes, hypoxia, and others.	[123, 125]

the few publications on native human tissues and cells and the highly developed research on animals. It is believed that closing this gap is necessary for translational research to successfully move into clinical use [7].

Conclusion and future direction

Selective agonists and antagonists exist for the treatment of several diseases. First, clinical trials are currently testing selective agonists for a variety of diseases such as pain, pulmonary inflammation, atrial fibrillation, and neuropathy. Secondly, doctors primarily use selective antagonists for treating Parkinson's disease, cognitive heart failure, and various other diseases. For tissue and organs of the human body, adenosine is used as a cytoprotective agent and responds to stress conditions. Moreover, ADRs play a significant role in therapeutic research on adenosine receptors in the peripheral and central nervous systems. A2BAR signaling is also needed for tumor growth, blood vessel development, metastasis, and stopping the immune system from attacking cancer cells.

A2BAR antagonists inhibit the immune response in cancer cells. A2BAR antagonists present a promising avenue for novel anticancer therapies, currently undergoing clinical trials for various cancer types. However, different mechanisms and pathways use adenosine receptor subtypes for specific disease conditions. Moreover, these subtypes are essential for the activities of various systems and the treatment of disease. Consistent research on adenosine receptors demonstrates that it has the potential for revealing new activity in humans. Recently, researchers found that adenosine and its subtypes can provide benefits in the future. To create ADR receptor-modulating drugs that can either amplify or decrease the adenosinergic responses when exposed to various medical conditions, agonist and antagonist drugs are also being tested in both preclinical and clinical settings. These drugs could help with both short-term and long-term illnesses, such as neuro- disorders, immunomodulators, inflammatory diseases, cardiovascular disease and cancer.

Disclosure of conflict of interest

None.

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