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PHARMACOLOGY OF ADENOSINE RECEPTORS: THE STATE OF THE ART

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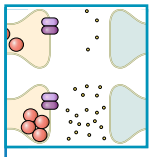

Borea PA, Gessi S, Merighi S, Vincenzi F, Varani K. Pharmacology of Adenosine Receptors: The State of the Art. *Physiol Rev* 98: 1591–1625, 2018. Published May 30, 2018; doi:10.1152/physrev.00049.2017.—Adenosine is a ubiquitous endogenous autacoid whose effects are triggered through the enrollment of four G protein-coupled receptors: A_1, A_{2A}, A_{2B}, and A_3. Due to the rapid generation of adenosine from cellular metabolism, and the widespread distribution of its receptor subtypes in almost all organs and tissues, this nucleoside induces a multitude of physiopathological effects, regulating central nervous, cardiovascular, peripheral, and immune systems. It is becoming clear that the expression patterns of adenosine receptors vary among cell types, lending weight to the idea that they may be both markers of pathologies and useful targets for novel drugs. This review offers an overview of current knowledge on adenosine receptors, including their characteristic structural features, molecular interactions and cellular functions, as well as their essential roles in pain, cancer, and neurodegenerative, inflammatory, and autoimmune diseases. Finally, we highlight the latest findings on molecules capable of targeting adenosine receptors and report which stage of drug development they have reached.

I. INTRODUCTION

The first evidence of a role for adenosine in cellular physiology dates back to 1927, when the presence of an adenine compound able to slow the heart rhythm and rate was discovered in extracts from cardiac tissues (90). Fifty years later, this finding led to the introduction of adenosine in the diagnosis and treatment of supraventricular tachycardia (31, 81). Since then, scientists from different areas—spanning physiology, biochemistry, pharmacology, chemistry and immunology—have been focusing their efforts on investigating adenosine's many roles in health and disease, thereby generating a new field of research.

Thanks to these studies, we now know that adenosine is an ubiquitous endogenous molecule that affects almost all aspects of cellular physiology, including neuronal activity, vascular function, platelet aggregation, and blood cell regulation. To early investigators, adenosine behavior appeared to resemble that of hormones or second messengers, but its particular mechanism of generation during conditions of stress suggested that it was in fact a novel kind of cell regulator, which was accordingly granted a new term: "retaliatory metabolite" (288).

Adenosine mediates its effects mainly through its interaction with four G protein-coupled receptors (GPCR); these, named A_1, A_{2A}, A_{2B}, and A_3 adenosine receptors (ARs), are expressed in several cells and tissues throughout the body (37). Their presence was demonstrated in the cerebral cortex, for example, by observing the specific antagonism of adenosine-induced cAMP accumulation induced by methylxanthines caffeine and theophylline (348). Interestingly, caffeine is the most widely misused psychoactive substance worldwide (22).

The understanding that ARs are implicated in numerous pathological functions crucial in severe human diseases prompted researchers to search for novel potential drugs exploiting ARs (117). These efforts have led to the identification of several useful ligands—from agonists/partial agonists, to antagonists, allosteric enhancers, and enzyme modulators—which now offer a wide spectrum of activity (310). Nevertheless, there is still only a limited number of adenosinergic drugs on the market **(TABLE 1)**. This is due to the complexity of AR signaling; indeed, AR receptors are widely distributed throughout the body, which may lead to redundancy of effect. Among the commercially available AR-mediated drugs, in addition to adenosine itself, an A_{2A}AR agonist is used for coronary artery imaging, and there is an A_{2A}AR antagonist for the treatment of Parkinson's disease (PD), but this is only used in Japan. Great efforts are being concentrated on the clinical development of A_3AR agonists, which show potential in the treatment of various high-impact pathologies, including autoimmune diseases and cancer (37).

Table 1. *List of clinically approved adenosine receptors drugs*

Name	Mechanism of Action	Therapeutic Use
Adenosine	A_1AR agonist	Paroxysmal supraventricular tachycardia (PSVT)
Adenosine	A_{2A}AR agonist	Myocardial perfusion imaging
Regadenoson		
Theophylline	A_1AR antagonist	Asthma
Doxofylline		
Bamifylline		
Istradefylline	A_{2A}AR antagonist	Parkinson's disease

With the intention of ultimately advancing the field of adenosine research, this review is designed to shed light on the pharmacological role of adenosine and ARs, and their relevance in the onset of human diseases. We describe the origin and metabolism of adenosine, and the classification, structure, distribution, and function of ARs, focusing on their physiological aspects in major organ systems (nervous, cardiovascular, immune) as well as their pathological effects in inflammation, pain, and cancer. We then discuss the therapeutic applications of AR ligands, addressing the state of the art in clinical trials, highlighting gaps in our knowledge and points of controversy throughout **(TABLE 2)**.

II. ADENOSINE: ORIGIN AND METABOLISM

From a phylogenetic point of view, the earliest evidence of adenosine's role as life-preserving molecule was published in 1981, when excreted adenosine was identified as a cell-density signal able to induce the formation of fruiting bodies, following starvation, in the bacterium *Myxococcus xanthus* (359). Subsequently, its production was linked to energy metabolism, thanks to physiological evidence of an increase in adenosine generation in leukocytes and heart cells during ATP catabolism. Indeed, adenosine has been observed to play a "helper" role in the protection of working cells, like neurons and cardiomyocytes, against stressful conditions by enabling them to adjust their energy intake and adapt their activity to reduce ATP requirement. This effect is mainly brought about by reducing energy-consuming activities, such as the heart inotropic effect, and by increasing nutrients/oxygen support through vasodilation **(FIGURE 1)**. This disproved the existing hypothesis of its origin as a second messenger from the cAMP pathway, and later prompted the introduction of the term "retaliatory metabolite" to describe this useful nucleoside. Under normal physiological conditions, extracellular adenosine levels are between 20 and 300 nM, rising to a low micromolar range under extreme physiological situations—like intensive exercise or low atmospheric oxygen levels (e.g., at high altitude)—and high micromolar levels (30 μM) in pathological conditions such as ischemia (288).

The principal mechanism responsible for the extracellular generation of adenosine is dephosphorylation of its precursor entities: ATP, ADP, and AMP. These are released by several cell types under stressful conditions through specific hydrolyzing enzymes termed ectonucleoside triphosphate diphosphohydrolase (CD39) and ecto-5′-nucleotidase (CD73), without which nucleotide concentrations would be relatively stable (117, 455). However, under physiological conditions, adenosine is principally originated intracellularly, from hydrolysis of AMP and *S*-adenosylhomocysteine (SAH) through the endo-5′-nucleotidase, and SAH hydrolase, respectively (56). Once generated, extracellular adenosine is captured at the intracellular level via the SLC28 family of cation-linked concentrative nucleoside transporters (CNTs) and the SLC29 family of energy-independent, equilibrative nucleoside transporters (ENTs), which allow free passage of adenosine across the cell membrane. The direction of adenosine uptake or release from cells is determined by the concentration difference across the membrane. The role of ENTs in this transfer is more critical than that of CNTs. Indeed, the four isoforms of ENT (1–4) transport nucleosides into or out of cell membranes on the basis of adenosine concentrations, while the three isoforms of CNT (1–3) facilitate adenosine influx against a concentration gradient, using the sodium ion gradient as a source of energy. Normally the flux is from extracellular to intracellular milieu, while during hypoxia, it is reversed, as nicely reported (83–85).

After intracellular uptake, adenosine undergoes deamination to inosine by adenosine deaminase (ADA) or phosphorylation to AMP through adenosine kinase (AK), giving adenosine a physiological half-life of $<$1 s. The respective Michaelis constant (K_m) values of these enzymes are 2 μM (AK) and 17–45 μM (ADA), which suggests that AK is the principal means of adenosine clearance in the physiological milieu, while deamination occurs preferentially under pathological conditions featuring raised adenosine levels. In such situations, deamination through ecto-ADA or influx through ENTs may occur to reduce the extracellular adenosine concentration **(FIGURE 2)**. In addition to its enzymatic activity, ecto-ADA is also able to modulate the ligand binding to ARs. Specifically, A_1ARs, A_{2A}ARs, and A_{2B}ARs rep-

Table 2. *Examples of ongoing clinical studies of adenosine receptor ligands*

Ligands	Receptor Selectivity	Indication	Phase	C.T. Identifier Code	Company
Agonists					
8-Chloro-adenosine	$A_1/A_{2A}/A_{2B}/A_3$	Recurrent adult acute myeloid leukemia, relapsed adult acute myeloid leukemia, acute myeloid leukemia arising from previous myelodysplastic syndrome, acute myeloid leukemia arising from previous myeloproliferative disorder	I/II	NCT02509546	City of Hope Medical Center
Neladenoson	A_1	Heart failure	II	NCT03098979	Bayer
		Heart failure	II	NCT02992288	Bayer
Regadenoson	A_{2A}	Sickle cell anemia	II	NCT01788631	Dana-Farber Cancer Institute
		Coronary artery disease	IV	NCT01446094	Dipan Shah
		Coronary artery disease	IV	NCT02115308	Timothy M. Bateman
		Ischemia	IV	NCT02130453	M.D. Anderson Cancer Center
		Cardiovascular diseases, coronary artery disease	II	NCT03103061	Medical University of South Carolina
		Heart failure, diastolic heart failure, hypertension	IV	NCT02589977	Marvin W. Kronenberg, M.D.
		Retinal artery occlusion	II	NCT03090087	University of Aarhus
		Hypertrophic cardiomyopathy, nonischemic dilated cardiomyopathy, microvascular ischemia of myocardium	IV	NCT03249272	Duke University
		Heart disease	I	NCT01433705	University of Michigan
		Microvascular coronary artery disease	II	NCT03236311	Sanofi
		Coronary microvascular disease	I II	NCT02045459	University of Virginia
		Coronary artery disease	I II	NCT03331380	National Heart, Lung, and Blood Institute (NHLBI)
CF-101	A_3	Rheumatoid arthritis	III	*	Can-Fite BioPharma
		Moderate-to-severe plaque psoriasis	III	*	Can-Fite BioPharma
CF-102	A_3	Hepatocellular carcinoma	II	NCT02128958	Can-Fite BioPharma
		Nonalcoholic fatty liver disease, nonalcoholic steatohepatitis	II	*	
Antagonists					
Theophylline	A_1 $A_{2A}/A_{2B}/A_3$	Asthma	IV	NCT03269318	Brighton and Sussex University Hospitals NHS Trust
		Chronic obstructive pulmonary disease	IV	NCT02261727	The George Institute
		End-stage renal disease, olfactory disorders	II	NCT02479451	Massachusetts General Hospital
		Noncardiac chest pain	II/III	NCT03319121	University of Science Malaysia
		Asthma	IV	NCT01696214	University of California, San Diego
Istradefylline	A_{2A}	Idiopathic Parkinson's disease	III	NCT02610231	Kyowa Hakko Kirin Pharma, Inc.
Preladenant	A_{2A}	Neoplasm	I	NCT03099161	Merck Sharp & Dohme Corp.
PBF-509	A_{2A}	Nonsmall cell lung cancer	I/II	NCT02403193	Palobiofarma SL
CPI-444	A_{2A}	Nonsmall cell lung cancer, malignant melanoma, renal cell cancer, triple negative breast cancer, colorectal cancer, bladder cancer, metastatic castration-resistant prostate cancer	I	NCT02655822	Corvus Pharmaceuticals, Inc.

*The C.T. Identifier Code for these trials is not yet available; information derived from Can-Fite BioPharma website at www.canfite.com.

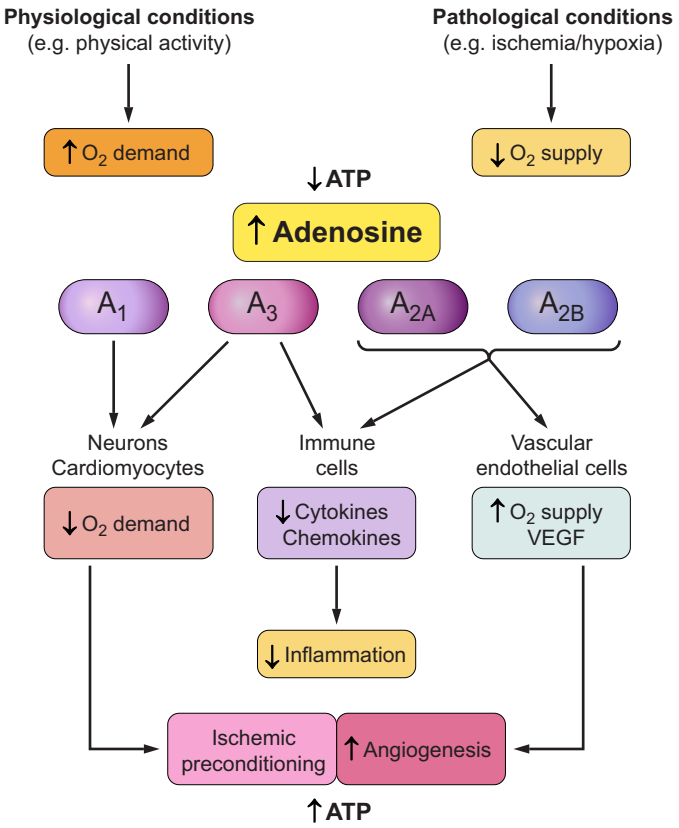

FIGURE 1. Physiological role of adenosine through interaction with A_1, A_{2A}, A_{2B}, and A_3 adenosine receptors (ARs). Adenosine is an endogenous ubiquitous mediator, highly increased following hypoxia, ischemia, or physical activity due to ATP consumption. It exerts body surveillance and protection by different mechanisms triggered by ARs activation, resulting in decreased oxygen demand and inflammation, increased oxygen supply and angiogenesis, as well as ischemic preconditioning.

resent binding sites for ecto-ADA, and its interaction with them has been reported to increase receptor affinity and signaling (143, 301). The relation of ADA with ARs has an important role in immune cells. In particular, the intercellular interaction made by ARs on dendritic cells, ADA, and CD26 on CD4-T cells, increases immune responses, suggesting the role of ADA as a bridge between cells expressing ARs and cells expressing CD26.

III. MOLECULAR STRUCTURE OF ADENOSINE RECEPTORS

Adenosine mediates its physiological effects through the activation of four ARs. These are characterized by different tissue distribution and effector coupling and by either high (A_1, A_{2A}, A_3) or low (A_{2B}) affinity for the parent molecule. All four ARs have been well identified, cloned and pharmacologically studied, and present a common structure: each possesses a core domain which crosses the plasma membrane seven times, in which each helix is 20–27 amino acids long and linked by three intracellular and three extracellular loops (115). The extracellular NH_2 terminus contains one or more glycosylation sites, while the intracellular COOH terminus provides sites for phosphorylation and palmitoylation, thereby playing a role in receptor desensitization and internalization mechanisms. Different AR subtypes present different numbers of amino acids. For instance, a longer COOH terminus, with 122 amino acids, is found on A_{2A}AR, whereas A_1AR, A_{2B}AR, and A_3AR bear COOH-terminal tails consisting of ~30–40 amino acids (116). Details of the structures of human A_1AR and A_{2A}AR have been provided by crystallization studies (51, 95, 139, 170, 213, 433), which will ultimately aid in the structure-based drug design of A_1AR and A_{2A}AR ligands (139, 377).

The generation of selective ligands is particularly desirable, as ARs present a sequence homology of 80–95% (there is 70% homology in their amino acids between human and rat). The exception to this rule is A_3AR, which differs significantly among species, with the A_1AR sequence being the most conserved (323). ARs have been cloned from several species, with A_3AR being the only subtype isolated before its pharmacological characterization (270), and the chromosome location of human and mouse ARs genes is reported in **TABLE 3**. Interestingly, a comparison between human (h) A_1AR/A_3AR and hA_{2A}R/hA_{2B}R shows overall amino acid sequence identities of 46.5% and 46.6%, respectively.

Recent evidences document the presence of several GPCRs including ARs in homomer, oligomer, and heteromer forms (43, 101, 102, 285–287). GPCR heteromers appear as new signaling entities characterized by different functional properties when compared with homomers. In this field, the adenosine A_1AR-A_{2A}AR unit represents the first reliable structure of a macromolecular complex, including two dif-

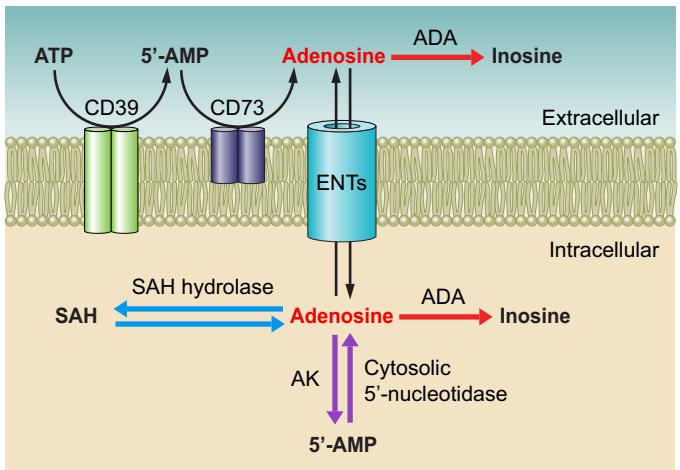

FIGURE 2. Adenosine metabolism and transport in the extra-intracellular milieu. At the intracellular level, adenosine derives from *S*-adenosylhomocysteine (SAH) hydrolase or cytosolic 5′-nucleotidase and is degraded by adenosine deaminase (ADA) and adenosine kinase (AK). Extracellularly, it is generated by CD73 and converted by ADA. Equilibrative nucleoside transporters (ENTs) allow adenosine free flux through cell membrane, following gradient concentration.

Table 3. *Molecular characteristics of adenosine receptors*

	A_1AR	$A_{2A}R$	$A_{2B}R$	A_3AR
Human (h) chromosome gene location	1q32.1	22g11.2	17p11.2–12	1p21-p13
Mouse (m) chromosome gene location	1	10	11	3
Amino acids (h)	326	410	328	318
Amino acids (m)	326	409	332	320
Sequence identity (%) vs. hA_1AR		38.3	44.0	46.5
Sequence identity (%) vs. $hA_{2A}AR$			46.6	31
Sequence identity (%) vs. $hA_{2B}AR$				35.7
Cloning	Human, dog, cow, rabbit	Human, dog, guinea pig	Human	Human, rat, sheep, rabbit

ferent receptors plus two different G proteins coupled to them **(FIGURE 3)** (43, 285). Indeed A_1AR is coupled to G_i and $A_{2A}AR$ to G_s, thus rendering heteromer able to trigger opposite signals affecting the cAMP-dependent intracellular pathway. Specifically, this unit represents a cell surface sensor of adenosine concentration, able to discriminate between low and high nucleoside level (285). When adenosine levels are low, its interaction occurs preferentially with A_1AR protomer of the heteromer and activates $G_{i/o}$ protein, thus reducing adenylate cyclase (AC), protein kinase A (PKA), and GABA uptake. Instead, when adenosine levels are higher, its binding is favored to $A_{2A}R$ component of the complex, which reduces A_1AR activation and, through G_s protein, associates with the AC/cAMP/PKA cascade, resulting in the increase of GABA uptake (68). Therefore, adenosine depending on its concentration may affect a number of other physiological process, including the release of glutamate (63). Interestingly, the heteromerization phenomenon appears as a general mechanism affecting also A_3ARs, forming homodimers and A_1AR-A_3AR heterodimers (157, 190). This opens up new horizons in drug development (102); in particular, $A_{2A}AR$-D2 dopamine receptor heterodimers have been detected in the striatum and may be a viable therapeutic target in PD (121, 122, 283).

IV. DISTRIBUTION, PHYSIOLOGICAL EFFECTS, AND SIGNAL TRANSDUCTION

ARs are found throughout the nervous, cardiovascular, respiratory, gastrointestinal, urogenital, and immune systems as well as in bone, joints, eyes, and skin (310)—a pattern of distribution that denotes their significant control of neuronal, cardiac, metabolic, and renal activities (3). Each AR is charac-

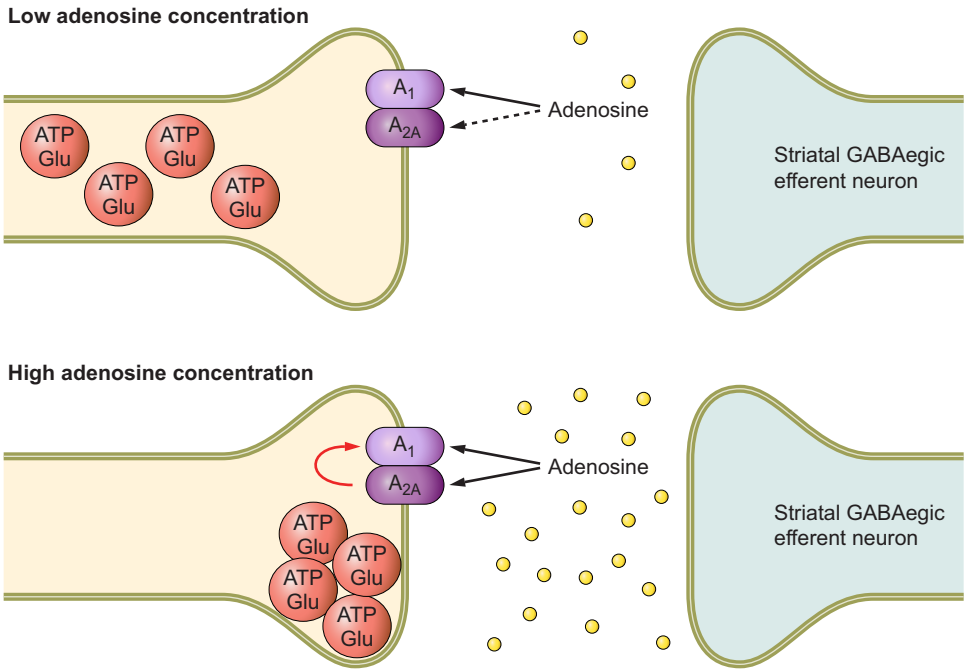

FIGURE 3. Schematic representation of A_1AR–$A_{2A}AR$ heteromer as adenosine sensor. Low adenosine concentration preferentially stimulates the A_1AR protomer of the heteromer, which would inhibit glutamatergic transmission. On the other hand, high adenosine concentration activates adenosine $A_{2A}AR$ that blocks adenosine A_1AR-mediated effects and results in potentiation of glutamate release.

terized by unique cell and tissue distribution, secondary signaling transductors (TABLE 4), and physiological effects (TABLE 5). A_1AR and A_3AR signals are mediated through G_i and G_o members of the G protein family, through which they reduce AC activity and cAMP levels, while A_{2A}ARs and A_{2B}ARs are coupled to G_s proteins, through which they stimulate AC and increase cAMP levels, thereby leading to the activation of a plethora of mediators, depending on the signaling triggered by cAMP in specific cells (116).

A. A_1AR and A_3AR G_i and G_o-Coupled Receptors

The A_1AR subtype is expressed in the central nervous system (CNS), mainly in the brain cortex, cerebellum, hippocampus, autonomic nerve terminals, spinal cord, and glial cells (56). This broad distribution reflects the wide range of physiological functions regulated by A_1AR, spanning neurotransmitter release, dampening of neuronal excitability, control of sleep/wakefulness, pain reduction, as well as sedative, anticonvulsant, anxiolytic, and locomotor depressant effects (131, 349, 375). This subtype is also present at high levels in the heart atria, kidney, adipose tissue, and pancreas, where it induces negative chronotropic, inotropic, and dromotropic effects, reduces renal blood flow and renin release, and inhibits lipolysis and insulin secretion, respectively (86, 263, 319, 322, 378, 397, 410). It is also located on airway epithelial and smooth muscle cells, where it stimulates a bronchoconstrictory response, and in several immune cells such as neutrophils, eosinophils, macrophages, and monocytes, where it promotes essentially proinflammatory effects (165, 317, 422).

A_1AR also induces phospholipase C (PLC)-β activation, thereby increasing inositol 1,4,5-trisphosphate (IP_3) and intracellular Ca^{2+} levels, which stimulate calcium-dependent protein kinases (PKC) and/or other calcium-binding proteins.

Table 4. *Classification and mechanism of action of adenosine receptors*

Name	A_1	A_{2A}	A_{2B}	A_3
G protein coupling	$G_{i/o}$	G_s	$G_sG_{q/11}$	$G_iG_{q/11}$
Effector system	↓ Adenylyl cyclase	↑ Adenylyl cyclase	↑ Adenylyl cyclase	↓ Adenylyl cyclase
	↑ Phospholipase C	↑ MAP kinase	↑ Phospholipase C	↑ Phospholipase C
	Ion channels:		↑ MAP kinase	↑ PI 3-kinase
	↑ K^+ ØCa^{2+}			↑ MAP kinase
	↑ PI 3-kinase			
	↑ MAP kinase			
Adenosine affinity	1–10 nM	30 nM	1,000 nM	100 nM
Agonists	CCPA, R-PIA, CPA, IB-MECA, NECA	CGS21680, UK-432,097, HE-NECA, NECA, R-PIA	NECA, BAY60–6583, R-PIA, IB-MECA	Cl^-IB-MECA, IB-MECA, MRS5698, NECA, R-PIA, CGS21680
Antagonists	PSB36, KW-3902, DPCPX, caffeine, theophylline	SCH442416, ZM241385, SCH58261, DPCPX, caffeine, theophylline	PSB-603, ZM241385, MRS 1754, DPCPX, caffeine, theophylline	MRE3008F20, MRS1523,DPCPX, ZM241385, caffeine, theophylline
PAM (positive allosteric modulators)	T62, TRR469			LUF6000

BAY60–6583, 2-[[6-amino-3,5-dicyano-4-[4-(cyclo propylmethoxy)phenyl]-2-pyridinyl]thio]-acetamide; CCPA, 2-chloro-*N*-cyclopentyladenosine; CGS21680, 4-[2-[[6-amino-9-(*N*-ethyl-β-D-ribofuranuronamidosyl)-9H-purin-2-yl]amino]ethyl]benzenepropanoic acid hydrochloride; Cl^-IB-MECA, CF102, 2-chloro-*N*6-(3-iodobenzyl)-adenosine-5′-*N*-methyluronamide; DPCPX, 8-cyclopentyl-1,3-dipropylxanthine; MRS5698, (1S,2R,3S,4R,5S)-4-[6-[[(3-chlorophenyl)methyl]amino]-2-[2-(3,4-difluorophenyl)-ethynyl]-9H-purin-9-yl]-2,3-dihydroxy-*N*-methylbicyclo[3.1.0]hexane-1-carboxamide; KW-3902, 8-(hexahydro-2,5-methanopentalen-3a (1H)-yl)-3,7-dihydro-1,3-dipropyl-1H-purine-2,6-di one; LUF6000, *N*-(3,4-dichloro-phenyl)-2-cyclohexyl-1H-imidazo[4,5-c]quinolin-4-amine; MRS 1754, *N*-(4-cyanophenyl)-2-[4-(2,3,6,7-tetrahydro-2,6-dioxo-1,3-dipropyl-1H-purin-8-yl)phenoxy]-acetamide; MRE 3008F20, *N*-[2-(2-furanyl)-8-propyl-8H-pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidin-5-yl]-*N*′-(4-methoxyphenyl)urea; MRS1523, 3-propyl-6-ethyl-5-[(ethylthio)carbonyl]-2 phenyl-4-propyl-3-pyridine carboxylate; PAM, positive allosteric modulators; PSB36, 1-butyl-8-(hexahydro-2,5-methanopentalen-3a(1H)-yl)-3,7-dihydro-3-(3-hydroxypropyl)-1H-purine-2,6-dione; PSB-603, 8-[4-[4-(4-chlorophenzyl)piperazide-1-sulfonyl)phenyl]]-1-propylxanthine; SCH442416, 2-(2-furanyl)-7-[3-(4-methoxyphenyl)propyl]-7H-pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidin-5-amine; SCH 58261, 2-(2-furanyl)-7-(2-phenylethyl)-7H-pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidin-5-amine; T62, 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophen-3-yl)-(4-chlorophenyl)-methanone; TRR469, 2-amino-4-[(4-(phenyl)piperazin-1-yl)methyl]-5-(4-fluorophenyl)thiophen-3-yl)-(4-chlorophenyl)methanone; UK-432,097, 6-[2,2-di(phenyl)ethylamino]-9-[(2R,3R,4S,5S)-5-(ethylcarbamoyl)-3,4-dihydroxyoxolan-2-yl]-*N*-[2-[(1-pyridin-2-ylpiperidin-4-yl)-carbamoylamino]-ethyl]-purine-2-carboxamide; ZM 241385, 4-[2-[7-amino-2-(2-furyl)[1,2,4]triazolo[2,3-a][1,3,5]triazin-5-ylamino]ethyl)phenol.

Table 5. *Biological effects of adenosine*

Effects	Receptor Subtype
Central nervous system	
Inhibition of neurotransmitter release	A_1
Neuroprotection	A_1/A_3
Anxiolytic activity	A_1
Anticonvulsant activity	A_1
Reduction of pain	A_1/A_3
Excitatory activity	A_{2A}
Stimulation of glutamate and acetylcholine release	A_{2A}
Reduction of locomotor activity	A_{2A}
Trophic effects	A_{2A}/A_{2B}
Cardiovascular system	
Negative inotropic effect	A_1
Negative chronotropic effect	A_1
Negative dromotropic effect	A_1
Ischemic preconditioning	A_1/A_3
Vasodilation	A_{2A}/A_{2B}
Inhibition of platelet aggregation	A_{2A}
Immune system	
Inhibition of reactive oxygen species	A_{2A}/A_3
Neutrophils	A_1/A_3
Increase of chemotaxis	A_1
Decrease of chemotaxis	A_3
Lymphocytes	
Immunosuppression	$A_{2A}/A_3/A_{2B}$
Monocytes/macrophages	
Inhibition of proinflammatory cytokines release	$A_{2A}/A_3/A_{2B}$
Mast cells	
Stimulation of degranulation	A_3/A_{2B}
Respiratory system	
Bronchoconstriction	$A_1/A_3/A_{2B}$
Renal system	
Vasoconstriction	A_1
Vasodilation	A_{2A}
Reduction of the glomerular filtration rate	A_1
Inhibition of diuresis	A_1
Inhibition of renin secretion	A_1
Gastrointestinal system	
Inhibition of acid secretion	A_1
Stimulation of intestinal chloride secretion	A_{2B}/A_3
Cellular metabolism	
Inhibition of lipolysis	A_1
Inhibition of insulin secretion	A_1
Stimulation of gluconeogenesis	A_{2A}
Production of glucose	A_{2B}

At the neuronal and myocardial level, A_1AR stimulates potassium (K) pertussis toxin-sensitive and K_{ATP} channels, while reducing Q-, P-, and N-type Ca^{2+} channels. Furthermore, the involvement of A_1AR in the intracellular phosphorylative cascade of the mitogen-activated protein kinase (MAPK) family—including extracellular signal-regulated kinase (ERK), p38, and Jun NH_2-terminal kinase (JNK)—has been reported (351, 352) **(FIGURE 4)**.

Pharmacological agents that increase the activation of A_1AR in response to adenosine would be useful for the treatment of CNS, cardiovascular, and inflammatory pathologies. A_1AR drawback effects, due to their wide distribution, broad spectrum of physiological effects, and promiscuous signaling pathway transduction, can fortunately be mitigated through allosteric enhancers, which stabilize the ternary complex formed by agonist-A_1AR-G protein molecules. This enhances the agonist action only at the site affected by injury, where adenosine concentrations are increased (330).

The A_3AR subtype is widely expressed in a variety of primary cells, tissues, and cell lines. Low levels have been reported in the brain, where it is located in the thalamus, hypothalamus, hippocampus, cortex, and retinal ganglion cells, as well as at motor nerve terminals and the pial and intercerebral arteries. A_3ARs are also expressed in microglia and astrocytes, and the inhibition of a neuroinflammatory response in these cells has been associated with their induction of an analgesic effect (175). Although A_3AR is also known to have cardioprotective effects, and to be greatly expressed in the coronary and carotid artery, its precise location in the heart has not yet been reported. At the peripheral level, however, A_3AR has been found in enteric neurons, as well as epithelial cells, colonic mucosa, lung parenchyma, and bronchi. Furthermore, A_3AR has a broad distribution in inflammatory cells like mast cells, eosinophils, neutrophils, monocytes, macrophages, foam cells, dendritic cells, lymphocytes, splenocytes, bone marrow cells, lymph nodes, synoviocytes, chondrocytes, and osteoblasts, where it mediates anti-inflammatory effects (37). Interestingly, A_3AR is overexpressed in several cancer cells and tissues and is therefore likely to have an important antitumoral role (39).

A_3ARs trigger a variety of intracellular signaling by preferentially coupling to G_i proteins, by which they reduce cAMP levels, and, at high concentrations of A_3AR agonists, to G_q proteins or $G\beta\gamma$ subunits, thereby inducing an increase in both PLC and calcium. A reduction in cAMP results in PKA inhibition, which leads to an increase in glycogen synthase kinase-3β (GSK-3β); downregulation of beta-catenin, cyclin D1, and c-Myc; and reduction of nuclear factor (NF)-κB DNA-binding ability (108). A different pathway from GPCR signaling—involving monomeric G protein RhoA and phospholipase D—is important for A_3AR-mediated neuro- and cardioprotection. A_3ARs are also known to regulate MAPK, PI3K/Akt, and NF-κB signaling pathways, by which

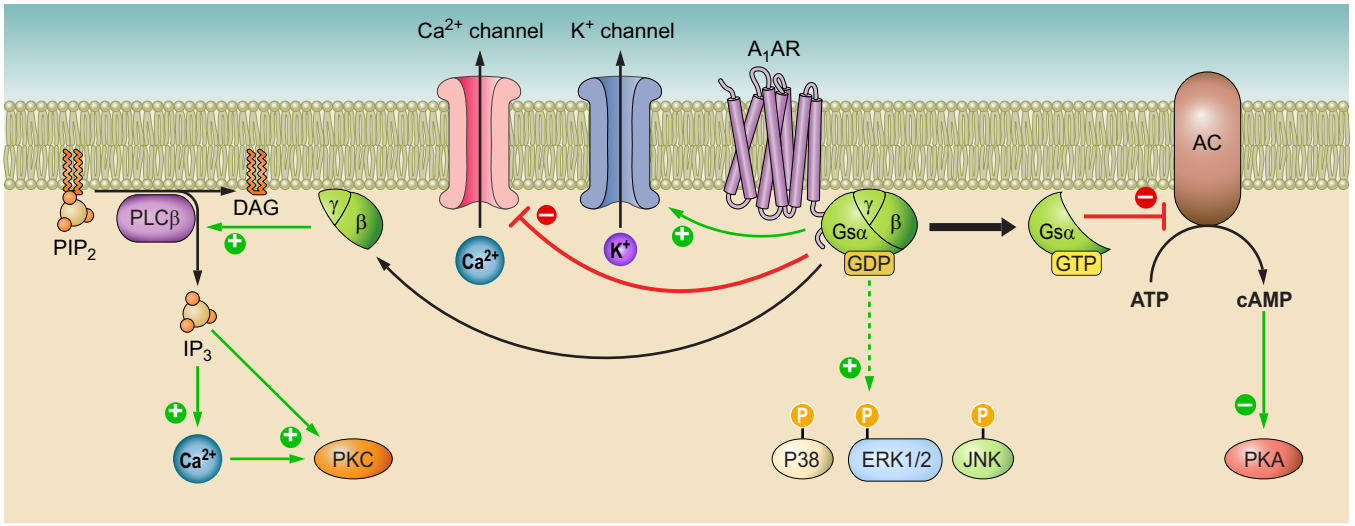

FIGURE 4. Overview of A_1AR intracellular signaling pathways. A_1AR stimulation decreases adenylate cyclase (AC) activity and cAMP production, thus inhibiting protein kinase A (PKA), while activated phospholipase C (PLC)-β and Ca^{2+}. K^+ and Ca^{2+}channels are opened and closed, respectively, by A_1AR enrollement. Mitogen-activated protein kinases p38, ERK1/2, and JNK1/2 phosphorylation are induced by A_1AR activation.

they exert anti-inflammatory effects. Stimulation or inhibition of HIF-1 has been also demonstrated to have protumoral and neuromodulatory effects in cancer cells and astrocytes, respectively (39) **(FIGURE 5)**.

B. A_{2A}AR and A_{2B}AR G_s-Coupled Receptors

The A_{2A}AR subtype occurs both centrally and peripherally, but its greatest expression is in the striatum, the olfactory tubercle, and the immune system, while lower levels are

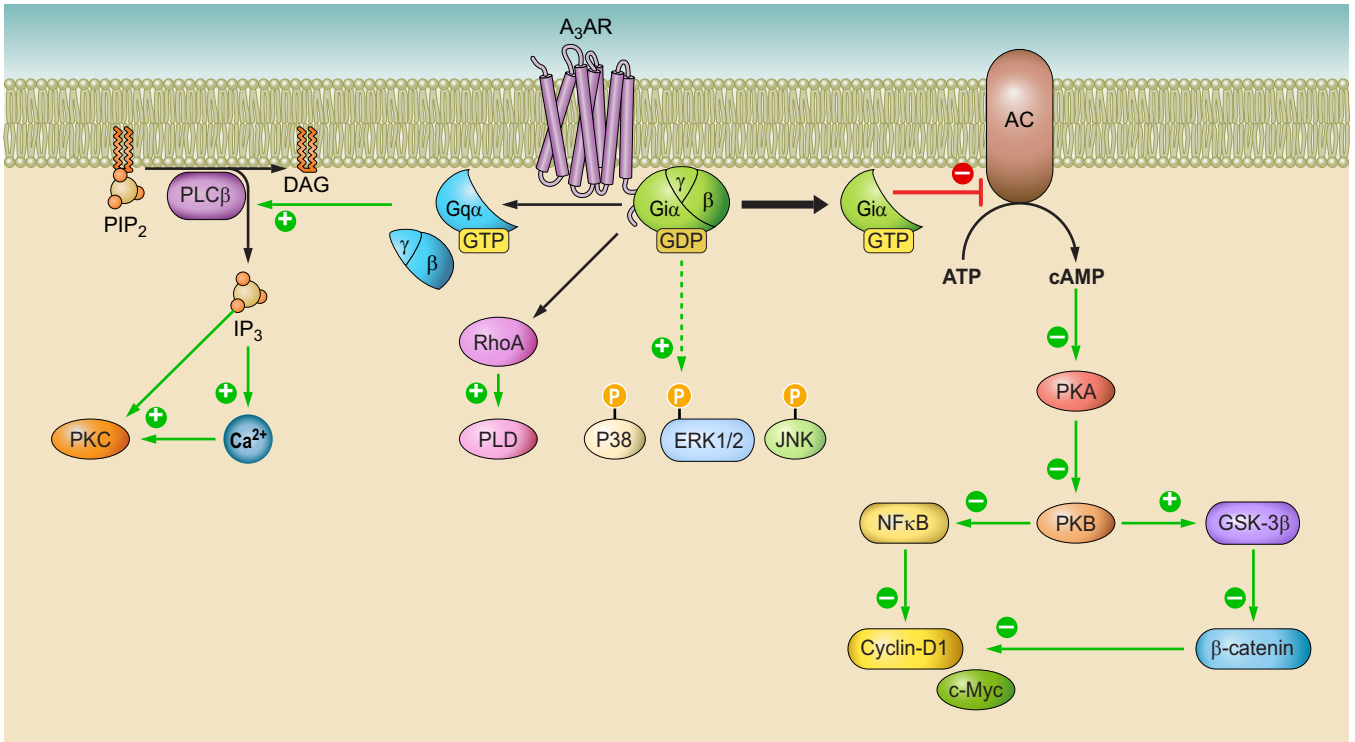

FIGURE 5. Overview of A_3AR intracellular signaling pathways. A_3AR stimulation triggers decrease of adenylate cyclase (AC) activity and cAMP production, activation of glycogen synthase kinase-3β (GSK-3β), and consequent decrease of β-catenin, cyclin D1, and c-Myc. Increase induced by A_3AR activation of phospholipase C (PLC)-β and Ca^{2+}, as well as of RhoA and phospholipase D (PLD) is shown. Mitogen-activated protein kinases p38, ERK1/2, and JNK1/2 phosphorylation are induced by A_3AR activation.

found in the cerebral cortex, hippocampus, heart, lung, and blood vessels. In addition, A_{2A}AR is expressed on both pre- and postsynaptic neurons—astrocytes, microglia, and oligodendrocytes—where it orchestrates a number of functions related to excitotoxicity, spanning neuronal glutamate release, glial reactivity, blood-brain barrier (BBB) permeability, and peripheral immune cell migration. In the peripheral immune system, A_{2A}ARs are particularly greatly expressed in leukocytes, platelets, and the vasculature, where they mediate numerous anti-inflammatory, antiaggregatory, and vasodilatory effects, respectively (79a).

In the brain, A_{2A}ARs are associated with the activation of a particular neuron-specific type of G_s protein known as G_{olf}, which is also linked to AC (206). cAMP-dependent PKA is the most common effector raised by A_{2A}AR activation; this phosphorylates and activates numerous proteins, including receptors, phosphodiesterases, cAMP-responsive element-binding protein (CREB), and dopamine- and cAMP-regulated phosphoprotein (DARPP-32) (318). In the rat tail artery, the A_{2A}AR facilitates the release of norepinephrine through activation of both PKC and PKA (118).

Finally, several literature reports on different cellular models suggest that A_{2A}AR is involved in the modulation of MAPK signaling (26, 56). A_{2A}AR may also interact with different accessory proteins, D_2-dopamine receptors, α-actinin, ADP-ribosylation factor nucleotide site opener (ARNO), ubiquitin-specific protease (USP4), and translin-associated protein X (TRAX) through its long COOH terminus, which would explain the contrasting results found in terms of A_{2A}AR-mediated effects (26) **(FIGURE 6)**.

The A_{2B}AR is greatly expressed essentially in the periphery, where they are found in the bowel, bladder, lung, vas deferens, and different cell types including fibroblasts, smooth muscle, endothelial, immune, alveolar epithelial, chromaffin, taste cells, and platelets. At the central level they are found in astrocytes, neurons, and microglia (100, 203, 307), and increasing evidence indicates a role for this subtype in the modulation of inflammation and immune responses in selected pathologies like cancer, diabetes, as well as renal, lung, and vascular diseases. This contrasts previously held assumptions attributing poor physiological relevance to A_{2B}AR, due to its low affinity for adenosine in comparison with the other ARs (380). In support of a pathological role for A_{2B}AR, its expression is upregulated in different injurious conditions such as hypoxia, inflammation, and cell stress. In fact, a hypoxia-responsive region, which includes a functional binding site for hypoxia-inducible factor (HIF), has been detected within the A_{2B}AR promoter, explaining its transcriptional regulation from HIF-1, the master regulator of cellular responses to hypoxia (94, 197).

A_{2B}AR signaling pathways involve AC activation through G_s proteins, leading to PKA phosphorylation and enrollment of different cAMP-dependent effectors like exchange proteins, which are directly activated by cAMP (Epac). Interestingly, a role for A_{2B}ARs in enhancing gap junction coupling through the cAMP pathway has been observed in cerebral microvascular endothelial cells (20). In addition, A_{2B}ARs can stimulate PLC through the G_q protein, resulting in Ca^{2+} mobilization, and can regulate ion channels through their $\beta\gamma$ subunits. Moreover, this subtype acts as stimulator of MAPK activation in several cell models in both central and peripheral systems (380) **(FIGURE 7)**.

In addition, A_{2B}ARs have multiple binding partners that modulate A_{2B}AR responses and functions; these include netrin-1, E3KARPP-EZRIN-PKA, SNARE, NF-κB1/P105, and α-actinin-1. Netrin-1, the neuronal guidance molecule, induced during hypoxia, reduces inflammation by activating A_{2B}AR, which inhibit neutrophils migration (333). SNARE protein interacting with A_{2B}AR, mostly that located inside the cell, recruits the receptor to

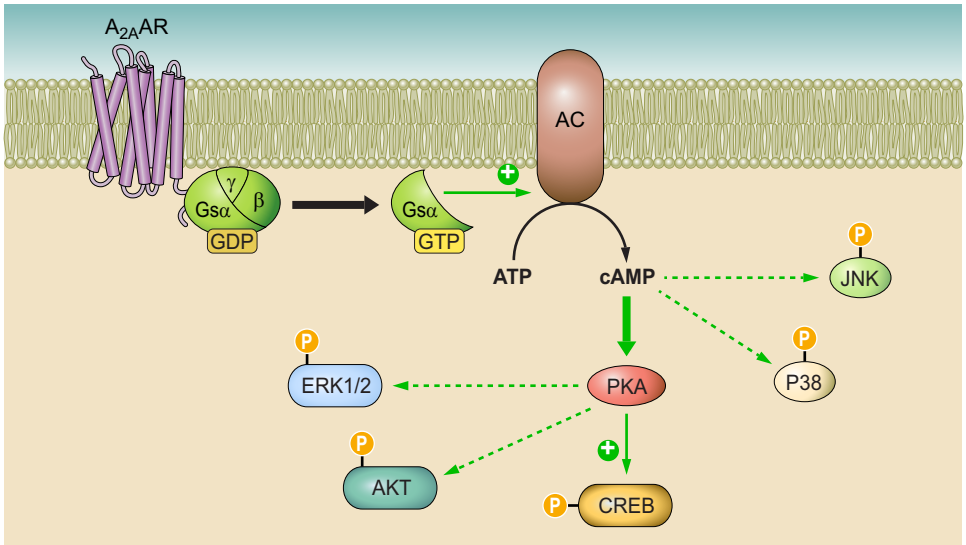

FIGURE 6. Overview of A_{2A}AR intracellular signaling pathways. A_{2A}AR stimulation increases adenylate cyclase (AC) activity, cAMP production, protein kinase A (PKA), and cAMP-responsive element-binding protein (CREB) phosphorylation. AKT and mitogen-activated protein kinases p38, ERK1/2 and JNK1/2 are activated following by A_{2A}AR recruitment.

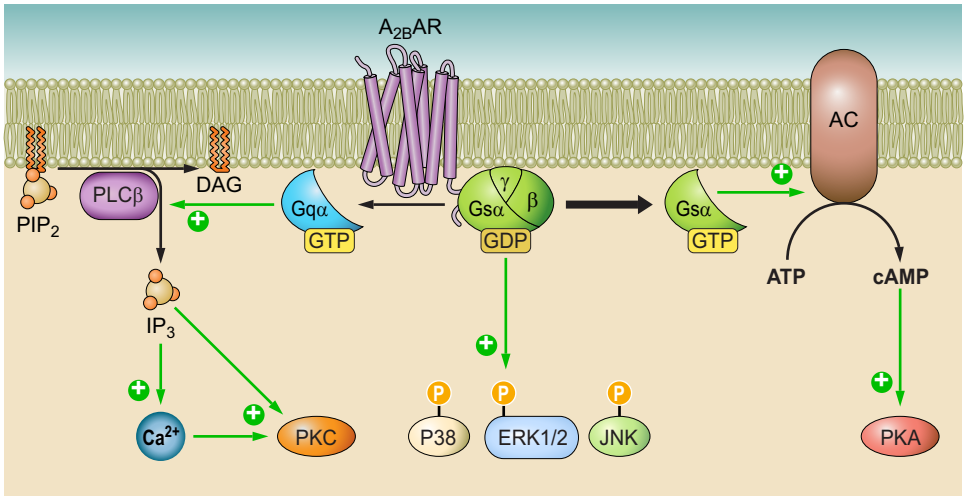

FIGURE 7. Overview of $A_{2B}AR$ intracellular signaling pathways. $A_{2B}AR$ stimulation increases adenylate cyclase (AC) activity, cAMP production, and protein kinase A (PKA) phosphorylation. $A_{2B}AR$ enrollement activates phospholipase C (PLC)-β and increases Ca^{2+}. Mitogen-activated protein kinases p38, ERK1/2, and JNK1/2 phosphorylation are induced by $A_{2B}AR$ activation.

the plasma membrane following agonist binding (417). After this interaction, a multiprotein complex with E3KARP (NHERF2) and ezrin stabilizes $A_{2B}AR$ in the plasma membrane (364). Interestingly, binding of $A_{2B}AR$ to P105 inhibits NF-κB activity, thereby explaining its anti-inflammatory effects (379). Furthermore, α-actinin-1 might favor $A_{2A}AR$ and $A_{2B}AR$ dimerization, thus inducing $A_{2B}AR$ expression on the cell surface (277).

V. ADENOSINE RECEPTORS AND PATHOLOGICAL ASPECTS IN

A. Neurological Diseases

The role of adenosine in diseases affecting the nervous system is related to its influence on a range of mediators including channels, receptors, second messengers, and neurotransmitters, through activation of ARs. While all the four ARs subtypes are present in the brain, the cerebral effects of adenosine are mainly mediated by A_1AR and $A_{2A}AR$, the subtypes predominantly expressed in the brain.

1. A_1AR

The A_1AR subtype is widely and homogeneously distributed in the brain, mainly in excitatory synapses, and plays an important role in the control of physiological synaptic transmission. In particular, A_1AR activation depresses excitatory transmission through N-type calcium-channel inhibition and neuronal hyperpolarization by regulation of potassium current (146, 427). This causes a reduction in glutamate release and inhibition of NMDA effects, which maintains an A_1ARs-dependent inhibitory tonus in the brain (414a, 414b, 444), an effect that is beneficial in several central disease states, including epilepsy, pain, and cerebral ischemia (37). At this proposal, adenosine is recognized as an endogenous anticonvulsant molecule, able to reduce the frequency of action potentials induced by electrical stimulation through enrollment of overexpressed A_1ARs (148). Several studies have reported protection against seizures resulting from an increase in adenosine levels produced by a ketogenic diet, which apparently inhibits adenosine kinase (ADK) (244). It seems that this effect may also be related to adenosine interfering with the *S*-adenosyl methionine (SAM)-induced DNA methylation pathway—involved in epileptogenesis—as a result of ADK reduction, adenosine increase, SAH accumulation, and SAM inhibition (234). These data constitute the rationale supporting ADK inhibitors as therapeutic agents. However, although these may increase adenosine and reverse such epigenetic changes, their toxic side effects have not yet been overcome (35). As an alternative, adenosine-based treatments have been proposed. For example, adenosine delivery might find a use either as a preventative treatment or following surgical resection of an epileptogenic focus (420).

The neuroprotective effects of A_1ARs have been studied in several models of inflammatory and neuropathic pain, in which A_1AR agonists exhibited antinociceptive and/or antihyperalgesic properties. A_1AR activation reduces pain by acting on spinal, supraspinal, and peripheral neurons as well as in glial cells. The molecular pathways involved in pain mitigation include the classical signaling mechanisms described for A_1AR-AC and PKA reduction; PLC induction; Ca^{2+} and K^+ channel regulation; and ERK, CREB, calmodulin kinase (CaMKIIα) inhibition, as well as reduction of excitatory amino acid release (349). In addition, the pathway involving the nitric oxide/cGMP/protein kinase G/K_{ATP} channel has been demonstrated to be a molecular effector of A_1AR-mediated pain suppression, via the induction of nociceptive neuron hyperpolarization and inhibition of microglia hyperactivation (185). However, as systemic A_1AR agonist administration may have central and cardiovascular side effects, several have failed in clinical trials. Nonetheless, partial agonists or allosteric modulators could represent a solution to this problem; indeed, allosteric en-

hancers, acting only on the ternary complex constituted by agonist-A_1AR-G protein, have been shown to minimize side effects in sites expressing A_1AR, but not in those involved in injury. Unfortunately, a trial of an allosteric modulator (2-amino-4,5,6,7-tetrahydrobenzo[b]thiophen-3-yl)-(4-chlorophenyl)methanone (T62) in postherpetic neuralgia was terminated (330), but more recently, a potent derivative of T62, 2-amino-4-[(4-(phenyl)piperazin-1-yl)methyl]-5-(4-fluorophenyl)thiophen-3-yl-(4-chlorophenyl)methanone (TRR469), produced antinociception without motor effects in models of acute and neuropathic pain under chronic treatment (412). Interestingly, administration of an A_1AR agonist with endomorphin decreases mechanical and thermal hyperalgesia, and A_1AR/opioid blockade counteracts the analgesic effects of electroacupuncture, a popular Chinese clinical practice used for pain relief (224). Prompted by the positive data obtained with TRR469 in pain models, its anxiolytic activity has been investigated. Specifically, this compound displayed an anxiolytic behavior similar to diazepam, without sedative drawbacks and ethanol interaction (408, 409). A_1AR's inhibitory effect on the release of glutamate is fundamental for prevention/protection against ischemic damage. However, A_1AR only seems to be effective in the early hours after damage, and chronic stimulation is responsible for the opposite effects. Indeed, a role for A_1AR has been retrieved during preconditioning—a state of tissue protection by exposure to sublethal insults—probably occurring through modulation of NMDA preconditioning-mediated increase of glutamate uptake (65).

In view of their effect on glutamate release, A_1AR selective agonists or allosteric modulators have also been proposed as antineurodegenerative agents (141). Interestingly, activation of A_1AR has been reported to reduce intraocular pressure (IOP) by increasing metalloproteinase-2 (MMP-2) secretion. This effect results in the digestion of collagen type IV, a main element of extracellular matrix in the trabecular meshwork (TM), thus contributing to an increase in outflow facility at the TM and IOP reduction. It is relevant that aqueous humor of patients affected by ocular hypertension is characterized by higher levels of adenosine in comparison with normotensive patients, thus suggesting a potential role of adenosine in IOP control. Trabodenoson (INO-8875), a very selective A_1AR agonist entered in phase I/II clinical trial, and at 500 μg, the highest dose tested, it showed a good profile of safety, tolerability, and IOP-lowering efficacy in patients with ocular hypertension or primary open-angle glaucoma (210, 279). Now the compound is under examination in a higher range of doses in phase III clinical trials (229). Moderate hyperemia was the most recurrent side effect, suggesting a promising pharmacological profile.

Overall, the therapeutic potential of A_1AR mimetics has been compromised by a series of obstacles that need to be overcome. If we are, in fact, to obtain successful A_1AR agonists, for example, their cardiovascular side effects, related to atrioventricular block, need to be eliminated (306). Another crucial point in this regard is the desensitization of A_1AR; this reduces the neuroprotective activity of A_1AR agonists, which could otherwise be administered after injuries (173). This limits the time window for the potential neuroprotection of A_1AR-activating agents in ischemia, inflammation, excitotoxicity, and neurodegenerative diseases, as the increase in adenosine concentrations occurring in these pathological conditions can cause AR desensitization and downregulation.

2. A_{2A}AR

A_{2A}ARs are recognized as the main AR subtype located in the striatum, where they colocalize with dopamine D2 receptors (D2R). This results in A_{2A}AR/D2R heteromers with a crucial role in the modulation of motor function (40, 46, 120). In fact, the observation that A_{2A}AR activation decreases the binding affinity of D2R for agonists was the first proof of concept for the use of A_{2A}AR antagonists as novel therapeutic agents in PD (100). Indeed, these drugs have been demonstrated to improve motor function in numerous PD animal models by reducing A_{2A}AR's inhibition of D2R activity in GABAergic neurons of the striato-pallidal pathway (123). High concentrations of A_{2A}AR antagonists reduce D2R agonists' affinity and function, as well as D2R antagonists' affinity, but these allosteric modulations disappear following agonist and antagonist coadministration.

This behavior has been explained by demonstrating the existence of A_{2A}AR/D2R heterotetramers—composed of A_{2A}AR and D2R homodimers—in which allosteric interactions between an agonist or antagonist of A_{2A}AR and an agonist of D2R occur, depending on the quaternary structure of the A_{2A}AR/D2R heteromer. This model is important from a clinical point of view, as regards adaptation of the application of A_{2A}ARs antagonists in the treatment of PD (36).

Thus far, several molecules that block A_{2A}ARs have been developed and brought to the clinical arena. Istradefylline is the only such drug that has been approved, but only in Japan, in combination with levodopa (L-DOPA), and is currently awaiting global approval following new clinical trials performed by Kyowa Hakko Kirin. Indeed, the American Food and Drug Administration has thus far not approved this drug, due to its lack of efficacy with respect to L-DOPA. Similarly, another A_{2A}AR antagonist, Preladenant, did not significantly decrease off-time in comparison with a placebo. However, it has been suggested that both of these trials may have been compromised by study design or execution issues, as their positive controls also failed (154, 284).

Tozadenant, on the other hand, appears more promising, and following positive results from phase IIb trials, a phase III clinical study has begun into this A_{2A}R antagonist (153).

Furthermore, a functional link between A_{2A}AR and α-synuclein (α-Syn) has recently been reported, which may open new avenues. Indeed, A_{2A}AR knockout (KO) mice prevented α-Syn-induced toxicity (182), and α-Syn aggregation and associated toxicity were reduced by A_{2A}AR blockade, suggesting a strong relationship between these two proteins, which are both harmful in PD (103). More extensively, the involvement of aberrant A_{2A}AR signaling has been found in the pathogenesis of synucleinopathy, as its genetic deletion reduces hippocampal pathological α-Syn aggregation (163).

A_{2A}AR is widely distributed in synapses, where it plays an important role in synaptic plasticity, facilitating glutamate release and potentiating NMDA receptor effects. Indeed, in presynaptic A_{2A}/A_1AR heteromers, A_{2A}AR regulates the A_1-induced inhibition of glutamate transmission, modulating corticostriatal glutamate levels in a timely fashion. In addition, A_{2A}ARs inhibit the glutamate uptake transporter GLT-1 and stimulate glutamate release in astrocytes. Therefore, A_{2A}ARs in neurons and glia are also significant in the pathogenesis of neuropsychiatric illnesses such as major depression and schizophrenia (205, 437). Indeed, in rodent depression models of learned helplessness (LH), A_{2A}AR antagonists improved escape deficit in LH rats with a similar efficacy to desipramine or fluoxetine, a tricyclic antidepressant and a selective serotonin (5-HT) reuptake inhibitor, respectively (438). Moreover, A_{2A}ARs may be a therapeutic target in other neuronal diseases such as Alzheimer's disease (AD), Huntington's disease (HD), epilepsy, acute and chronic stress, and memory fear (73, 211, 362, 396). Interestingly, A_{2A}AR expression increases in the astrocytes of both AD patients and aging mice expressing human amyloid precursor protein (hAPP). Furthermore, young and aging transgenic mice lacking A_{2A}AR in astrocytes have an increased long-term memory, an effect that has also been observed in aging mice expressing hAPP (298). In addition, by inhibiting glutamate uptake, A_{2A}AR causes the synaptic dysfunction and excitotoxic cell death that underlies many neurodegenerative diseases; through its upregulation, A_{2A}AR also reduces amyloid-β Aβ (1–42) glutamate transporters and uptake (245, 246).

A_{2A}AR silencing improves spatial memory deficits and long-term hippocampal depression induced by Tau pathology, as well as normalizing the glutamate/GABA ratio in the hippocampus, and providing a reduction in neuroinflammatory markers and Tau hyperphosphorylation (211). Genetic silencing, as well as antagonism, in a mouse model of AD, also reestablished long-term synaptic potentiation (LTP) in CA3 pyramidal cells which had been blocked by neuronal upregulated A_{2A}AR activation (407). Overexpression of A_{2A}ARs has also been revealed in animal models of HD, and A_{2A}AR antagonists have been found to reverse cognitive deficits in HD mice, presumably by controlling long-term depression deregulation (223, 402).

A_{2A}ARs are promoters of proinflammatory functions in the CNS (37, 194). In particular, they are involved in process retraction by the microglia during neurodegeneration and neuroinflammation, playing a role in the functional change of microglia into an activated proinflammatory phenotype (299). Accordingly, A_{2A}ARs induce microglia proliferation (126, 140), and their antagonism prevents hippocampal neuroinflammation (327), interleukin (IL)-1β-induced exacerbation of neuronal toxicity (361) and retinal microglia reactivity, providing protection to retinal neuronal cells (239). Importantly, blockade of A_{2A}ARs has been shown to confer neuroprotection against a broad spectrum of CNS insults (73). Specifically, the effects mediated by A_{2A}ARs on glutamate release, neuronal inflammation, and glial activation support a role for A_{2A}ARs in cerebral ischemia, in which their blockade has been shown to induce neuroprotection (141). In contrast, A_{2A}AR activation 2 days after ischemic insult decreases infiltration of blood cells, ischemic brain damage, and activation of glial cells, thereby improving neurological deficiency, measurable up to 7 days after injury. These findings indicate a protective function of A_{2A}ARs caused by peripheral immunosuppressive effects that mitigate central inflammatory process (255). Indeed, central A_{2A}ARs increase neurotrophic factor levels, including nerve growth factor (NGF) from the microglia as well as brain-derived neurotrophic factor (BDNF) from hippocampal and cortical neurons. This may explain the neurological protective effects of their activation (140, 353); it seems that the protective effects induced by A_{2A}AR antagonism, on the other hand, occur 24 h after ischemia as a consequence of a decreased excitotoxicity, while 7 days after ischemia this protection is surmounted by a second phase of damage induced by migration of blood cells causing neuroinflammation (256).

In line with the neurotoxic and proinflammatory role of A_{2A}ARs, it may be that caffeine, the most widely used drug in the world, exerts its effects, at least in part, through antagonism of A_{2A}AR; this interaction could be responsible for the numerous beneficial prophylactic effects of caffeine against PD, AD, amyotrophic lateral sclerosis (ALS), attention deficit hyperactivity disorder (ADHD), brain injury, incidence of suicide, depression, and stroke (73, 88, 212, 235, 433). Indeed, epidemiological studies have indicated that caffeine offers protection against a range of different neurodegenerative diseases, an effect that has been attributed to A_{2A}AR antagonism in animal models of PD (19, 57, 334, 435). In addition, several studies have displayed a protective effect of caffeine intake against cognitive impairment in both humans and animals (76, 85). Indeed, Aβ levels of brain and plasma decrease in AD transgenic mice following consumption of caffeine, which also inhibits memory deficits in beta-amyloid injected mice (47, 75). Moreover, plasma caffeine levels in human subjects with mild cognitive impairment (MCI) who later progressed to dementia were lower than those whose MCI remained sta-

ble, providing preliminary evidence for a link between high caffeine levels and protection against dementia (47, 426). Caffeine consumption has also been correlated with a reduction in the mood and memory dysfunction caused by chronic stress, through modulation of neuronal A_{2A}AR; it also reverts performance deficits in rats after treatment with reserpine (186, 271). In addition, administering caffeine to helpless mice (HM), an animal model of depression, appeared to restore memory deficits through upregulation of functional hippocampal A_{2A}AR. By regulating synaptic glutamate release, it reverted the depletion of synaptic markers in the hippocampus, without affecting helpless or anxiety behavior (236).

3. A_{2B}AR

There are fewer A_{2B}ARs expressed in the CNS and spinal cord than there are on astrocytes, in which A_{2B}AR expression is upregulated following lipopolysaccharide (LPS) and hypoxic stimulation (133). In human astroglial cells, A_{2B}ARs induce astrogliosis, and after short-term tumor necrosis factor (TNF)-α treatment, undergo to desensitization, a mechanism of cell defense (391). As for the role of A_{2B}ARs in the brain, it has been reported that their blockade inhibits the inflammatory cascade and neuronal injury following global cerebral ischemia by interfering with the p38 pathway (145). It therefore appears that in this condition, mirroring the behavior of A_{2A}ARs, A_{2B}AR signaling may be harmful due to its action on brain cells. Whatever the case, A_{2B}ARs may have a potential indirect role in hypoxia/ischemia as a consequence of angiogenesis resulting from increased endothelial cell functions (97, 307).

Other observations point towards a pronociceptive and proinflammatory role for A_{2B}ARs in the periphery (349). Recently, it has been shown in two different chronic pain models that A_{2B}ARs on myeloid cells contribute to pain perception by stimulating IL-6 receptor signaling and promoting immune-neuronal interactions (164). Even more recently, secretion of IL-6 and a consequent increase in cell proliferation mediated by A_{2B}ARs and a pathway involving p38 has been observed in microglial cells, suggesting that this subtype may have a proinflammatory role (258). That being said, an anti-inflammatory effect, linked to IL-10 production and TNF-α inhibition, has also been provoked by A_{2B}AR activation (201, 264).

4. A_3AR

Even though A_3ARs in the brain are not as abundant as in the periphery, these receptors are influential in several neuronal diseases. In cerebral ischemia, for example, A_3ARs play an initial protective role in synergy with A_1ARs by inhibiting excitatory synaptic transmission. Once again, however, longer activation raises excitotoxicity and the risk of damage, possibly via the activation of PKC and consequent calcium increase. This suggests that the protective or deleterious role of A_3ARs depends on the severity and duration of the ischemic episode (257). In addition, plastic changes in A_3ARs may occur following prolonged stimulation by either agonists or antagonists before and after ischemia/hypoxia with similar results (320). This counterintuitive response may be the result of rapid A_3AR desensitization occurring after sustained receptor activation by an exogenous A_3AR agonist and concomitant endogenous adenosine, which is increased during ischemia (307).

Other evidence also supports a role of A_3ARs in brain ischemia through immunomodulation. Specifically, A_3ARs affect glial functions by regulating cell migration and TNF-α production in microglial cells (61, 217, 295). Furthermore, it has been found that in astrocytes A_3ARs decrease HIF-1 expression in both normoxic and hypoxic conditions, thereby inhibiting proinflammatory genes including those for inducible nitric oxide synthse and A_{2B}AR. This suggests an anti-inflammatory role of this AR subtype in the CNS (133).

A_3ARs involvement has also been investigated in pain conditions, albeit with mixed results. Even though some studies, performed with nonselective ligands as well as KO mice, have attributed them a pronociceptive function, several other studies have suggested A_3ARs as an antinociceptive drug target (176, 350, 428). Indeed, A_3ARs agonists show beneficial effects in neuropathic pain models by their inhibition of mechano-allodynia onset after chronic constriction injury and by increasing the potency of classical analgesic drugs including morphine and gabapentin (60, 225). Importantly, the antinociceptive activity of these agents has been evidenced in neuropathic pain induced by chemotherapy in animal models of bone metastasis associated with breast cancer (131, 175, 177, 404). As ongoing clinical trials of A_3AR agonists in other medical diseases are revealing an absence of side effects during their administration, the recent discovery of their antinociceptive role is a highly encouraging avenue of exploitation in drug development.

B. Cardiovascular Diseases

In the heart, adenosine is associated with regulatory functions, including control of cardiac contractility and adrenergic responsiveness, impulse generation and conduction, coronary vascular tone, and cardiac substrate utilization (156). In particular, adenosine indirectly modifies cardiac contractility via the modulation of adrenergic responses and the inhibition of norepineprhine release from cardiac nerves (89). It is well known that adenosine reduces heart rate and impulse generation in supraventricular tissues and the His-Purkinje system (90), but it also modifies vascular tone and regulates vasculogenesis and angiogenesis by modulating vascular cell growth (2). In addition, adenosine may also regulate glucose metabolism and fatty acid availability,

an effect that has important consequences on myocardial metabolism and responses to hypoxic or ischemic stress (155).

1. A_1ARs

A_1AR expressed in smooth muscle cells and cardiomyocytes in atria and ventricular tissues may be exploited by several cardiovascular therapies for diseases like angina pectoris, control of cardiac rhythm, and ischemic injury during acute coronary syndrome or heart failure (44). Indeed, A_1AR activation regulates tissue transglutaminase activity in cytoprotection, and in cardiomyocyte-like cell survival during hypoxia-induced cell death (415). Moreover, several literature reports suggest that A_1ARs mediate antiadrenergic effects via the inhibition of β-adrenoceptor-stimulated PKA activation and G_s cycling (98). It has also been reported that A_1ARs may inhibit β-adrenergic signaling through PKC and PLC activation, leading to the modulation of p38-MAPK and HSP27 (99).

In ischemic heart tissue, an unexpected A_1AR-mediated positive inotropic response to adenosine has been observed in atria from coronary heart disease patients; indeed, adenosine activity via A_1ARs has for some time been associated with a negative inotropic effect in human atrial preparations (127). Nevertheless, A_1AR activation does mediate negative chronotropic effects involving the inhibition of K^+ and Ca^{2+} currents, as well as the hyperpolarization-activated "funny" current (30).

It is well reported that A_1ARs stimulate smooth muscle proliferation and are involved in promoting stenosis, their expression being increased in proximity to vascular stents; in this context, they play a role in atherosclerosis and vascular remodeling (96). Furthermore, several studies report A_1AR involvement in atrial fibrillation in infarct and coronary artery bypass graft patients (442). The electrophysiological action of A_1ARs and their involvement in arrhythmogenesis has led to the use of adenosine (Adenocard) as a therapeutic agent for supraventricular tachycardia, and as an "off-label" drug in electrophysiological diagnostics (32). More selective A_1AR agonists have been shown in clinical trials to be efficacious type IV antiarrhythmics for supraventricular tachycardia and atrial fibrillation (314).

Nonetheless, the cardiovascular effects of A_1ARs could be associated with several side effects and receptor desensitization that may represent a potential impediment to the chronic use of full agonists (331). That being said, the development of partial A_1AR agonists, low efficacy ligands that elicit only a submaximal response, could be used to trigger some of the physiological responses of receptor activation inducing less A_1AR desensitization than full agonists, making them ideal for chronic treatment with broader dose ranges (5). In fact, neladenoson, a prodrug of a partial A_1AR agonist, has recently demonstrated potential cardioprotection without negative effects on heart rate, atrioventricular conduction, or blood pressure in clinical trials (254). A_1ARs are also involved in myocardial tissue protection during ischemia-reperfusion (421), and the activation of A_1ARs exerts protective effects following ischemia-reperfusion injury in both male and female hearts through an increase in protein *S*-nitrosylation (358). Interestingly, the postconditioning-dependent reduction in infarct size is modulated via A_1AR activation, and targeted deletion of these receptors results in a loss of cardioprotective effects (431).

In the ischemic myocardium, A_1ARs are able to slow conduction via G_i protein activation (434), and A_1AR stimulation attenuates cardiac hypertrophy and prevents heart failure following adrenergic stimulation in both a rat neonatal cardiac myocyte model and in mice (62, 321). Intriguingly, recent research has revealed a threefold greater A_1AR expression in the right atrium with respect to the left; this suggests that the right atrium is more sensitive to repolarization in response to adenosine than the left (221).

2. A_{2A}ARs

Some evidence suggests that A_{2A}ARs have a direct inotropic effect and are able to counteract the antiadrenergic action of A_1AR activation (388). However, A_{2A}ARs are primarily involved in coronary vascular control through their expression in the smooth muscle and endothelium, where they induce vasodilation. The A_{2A}AR-mediated coronary response seems to involve PKA activation, and some studies have indicated the participation of p38 MAPK and IP_3 signaling (1, 384). It has also been reported that adenosine prompts the generation of large amounts of nitric oxide, a well-known vasodilator, through A_{2A}AR-mediated activation of endothelial nitric oxide synthase (326). Increased A_{2A}AR expression has been detected in a streptozotocin mouse model of type 1 diabetes, resulting in augmented coronary flow in the heart (209). Indeed, A_{2A}AR activation mediates a significant increase in coronary flow in isolated mouse hearts, via a mechanism that is partially mediated by Nox2-derived H_2O_2 (454).

The cardioprotective actions of A_{2A}ARs are primarily due to their potent anti-inflammatory effects, and it has been proposed that A_{2A}AR stimulation results in cardioprotection by reducing neutrophil accumulation (181). Cardioprotection is abolished in mice with CD4+ T cells lacking A_{2A}AR (440), while A_{2A}AR activation provided protection against infarction in isolated myocardium by inhibiting mast cell degranulation (332). Furthermore, an A_{2A}AR agonist has been recently shown to prevent the development of cardiac dysfunction and cardiac remodeling in a dose-dependent fashion following myocardial infarction in spontaneously hypertensive rats (74a). Increased A_{2A}AR expression, on the other hand, has been associated with spontaneous calcium release from the sarcoplasmic reticulum in

atrial fibrillation patients, and blocking A_{2A}ARs results in calcium inhibition (226). Moreover, stimulation of A_{2A}ARs in human atrial myocytes can induce beat-to-beat irregularities in the calcium transient. This suggests a novel role for A_{2A}AR antagonists in atrial fibrillation: maintaining uniform beat-to-beat responses at higher beating frequencies (273).

A_{2A}ARs could be also very important in atherosclerosis onset and treatment, due to their role in inhibiting foam cell formation. This effect seems to be related to the ability of A_{2A}AR to stimulate the expression of proteins involved in reverse cholesterol transport (329). In particular, it has been reported that A_{2A}AR activation increases the expression and function of cholesterol 27-hydroxylase, resulting in enhanced ABCA1-dependent cholesterol efflux (33). Nevertheless, despite several papers reporting the repression of foam cell formation among isolated cells by A_{2A}ARs, their deletion in apolipoprotein E-deficient mice inhibits the formation of atherosclerotic lesions, suggesting a pro-atherogenic role for A_{2A}ARs (416). That being said, upregulation of A_{2A}ARs has also been reported in apolipoprotein E KO mice, leading to speculation that they may represent a compensatory mechanism for counteracting the compromised endothelial function (450).

The beneficial actions of A_{2A}ARs include the inhibition of neointimal formation following arterial injury (248). A_{2A}ARs may also exert a protective function by switching macrophages from inflammatory to angiogenic phenotypes (144). Furthermore, in dermal microvascular endothelial cells of human flaps, hypoxic postconditioning protects against apoptosis induced by reoxygenation via activation of A_{2A}ARs (48).

3. A_{2B}ARs

It has been reported that the activation of A_{2B}ARs inhibits cardiac fibroblast proliferation, as well as vascular smooth muscle cell growth and collagen synthesis (91, 92). Recently, an A_{2B}AR agonist has been shown to reduce transforming growth factor (TGF)-β1- and angiotensin II-mediated collagen synthesis in isolated neonatal rat cardiac fibroblasts, suggesting that A_{2B}AR activation has an antifibrotic effect (405). A role for A_{2B}ARs has also been proposed in the inhibition of postinfarct remodeling, an action that seems to involve modulation of caspase-1 activity (389).

In fact, there is growing evidence regarding the cardioprotective action of A_{2B}ARs. In particular, the cardioprotection exerted by A_{2B}ARs has been associated with the inhibition of GSK-3β and the permeability transition pore (430), whereas another report has suggested that A_{2B}ARs lead to myocardial metabolic adaptations by inducing stabilization of the circadian rhythm protein period 2 (Per2) (93). Moreover, it has been reported that A_{2B}ARs cardioprotection may be related to the modulation of TNF-α and neutrophil function (192), and in vivo experiments have implicated A_{2B}ARs in cardioprotection in ischemic pre- and postconditioning (207, 315). In fact, a novel tissue-specific approach has recently been used to indicate that A_{2B}ARs exert different functions related to ischemic preconditioning and/or reperfusion in different tissues. In particular, A_{2B}AR is important for ischemic preconditioning-mediated cardioprotection in vascular endothelial cells and cardiac myocytes, while A_{2B}AR signaling was critical in inflammatory cells during ischemia/reperfusion (354).

Literature data suggest that A_{2B}ARs may also be beneficial in atherosclerosis, reducing vascular injury. Indeed, the deletion of A_{2B}ARs in apolipoprotein E-deficient mice worsens the atherosclerosis induced by a high-fat diet (203). Furthermore, increased expression of A_{2B}ARs has been reported in macrophages following interferon (IFN)-γ and arterial injury, resulting in the inhibition of macrophage activation (429). In the same vein, a study performed in A_{2B}AR KO mice has suggested that, through the stimulation of A_{2B}AR, adenosine suppresses IFN-γ-induced major histocompatibility class II (MHC II) transcription activation and collagen transcription repression in mouse vascular smooth muscle cells by downregulating MHC II transactivator (436). More recently, it has been reported that A_{2B}AR signaling suppresses MHC II transactivator expression in human aortic smooth muscle cells by manipulating the interaction between STAT1 and the epigenetic machinery (432). Moreover, A_{2B}AR activation under hypoxic conditions promotes foam cell formation and induces an increase in IL-8 secretion in an ERK 1/2, p38, and Akt kinase-dependent fashion (258).

4. A_3ARs

A considerable body of evidence shows that A_3ARs limit injury processes within myocardial tissue and mediate beneficial anti-inflammatory actions during reperfusion (155). In this regard, A_3AR agonists could protect against postischemic neutrophil-mediated injury and may be involved in the regulation of bone marrow-derived cells (125). In this context, the activation of A_3ARs has been shown to induce a biphasic hemodynamic response that is partially mediated by A_{2A}AR activation. Specifically, the cardioprotective effect of IB-MECA, a well-known A_3AR agonist, has been ascribed to the initial activation of A_3AR followed by A_{2A}AR stimulation in bone marrow-derived cells (387). It has been found that Cl^-IB-MECA protects against cardiotoxicity induced by doxorubicin through restoration of the oxidant/antioxidant status and consequential reduction of inflammatory responses and the resultant apoptotic signals (124). Moreover, an A_3AR agonist significantly reduces infarct size in both isolated perfused rat hearts and primary rat cardiac myocytes subjected to ischemia/hypoxia and reperfusion/reoxygenation by upregulating the status of p-ERK1/2 and p-AKT. During the reoxygenation phase,

A_3AR stimulation significantly reduces apoptosis and necrosis, indicating a role for the prosurvival signaling pathways that decrease caspase-3 activity (166).

It has been also reported that A_3ARs stimulate the proliferation of human coronary smooth cells by the activation of PLC and the induction of the transcriptions factors EGR2 and EGR3 (158), while others have reported that A_3AR activation induces coronary vasodilation, and that the expression of A_3ARs in cardiovascular tissues is altered in hypertension. In particular, a reduction of A_3ARs has been noted in hypertensive hearts, which is presumably associated with the limited vasodilator responses to A_3AR agonists observed in coronary vessels (159). Similarly, A_3AR expression has recently been detected in the renal microcirculation. Stimulation of these receptors led to dilation of a preconstricted afferent arteriole by norepinephrine and reduced the vasoconstrictive effect of both A_1AR activation and angiotensin (ANG) II on the afferent arteriole (230).

C. Inflammatory and Autoimmune Diseases

1. A_1AR

The role of A_1ARs on immune cells is not univocal, as both pro- and anti-inflammatory effects have been revealed, depending on both the cell type and the pathological state involved.

In multiple sclerosis (MS), for example, A_1AR activation seems to play a protective role, as A_1AR-deficient mice present exacerbated demyelination, axonal injury, and increased reactivity of microglia/macrophages in comparison to wild-type (WT) animals. Interestingly, reduction of A_1AR expression in microglia during experimental autoimmune encephalomyelitis (EAE) was followed by neuroinflammation, and EAE severity was reduced through caffeine treatment and consequent increase in A_1AR levels in the microglia (394). Moreover, in endotoxemic mice and LPS-activated macrophages, stimulation of A_1ARs decreases TNF-α, nitrite, and nitrate production (151).

Accordingly, several studies have also reported a protective effect of A_1AR activation in renal and hepatic ischemia/reperfusion (I/R) injury (180, 189, 322, 398). A_1AR-null mice presented high creatinine levels and aggravated renal histology, and prestimulation of A_1ARs in WT mice decreased various inflammatory markers of renal inflammation, including myeloperoxidase activity, renal tubular neutrophil infiltration, ICAM-1, IL-1β, and TNF-α. This suggests that preischemic stimulation of A_1ARs exerts protective effects versus renal I/R injury (216). Interestingly, an allosteric enhancer of A_1AR-induced strong renal protection against I/R damage by decreasing inflammation, necrosis, and apoptosis (305).

In contrast with the protective effects described above, A_1AR activation in leukocytes increases neutrophil chemotaxis and endothelial adhesion, as recently confirmed with ticagrelor, which potentiated neutrophil chemotaxis and phagocytosis by increasing adenosine concentration (10, 69, 70). Such A_1AR-mediated effects have been thoroughly investigated in airway inflammation, in particular in preclinical models of asthma (316). However, initial findings reporting a reduction in bronchoconstriction with an antisense oligonucleotide or following A_1AR antagonist treatment have not been confirmed in clinical trials performed in patients with asthma (21, 52, 280). That being said, antagonism of A_1ARs has more recently been found to block acute lung injury induced by infection with *Yersinia pestis*. This suggests that it may be useful as an adjunctive therapy for antibiotics in infections by this Gram-negative bacillus (423, 424).

Furthermore, blockade of A_1ARs may beneficially modulate glucose homeostasis by affecting oxidative stress and immune cells effects (309). Specifically, A_1AR-deficient mice present a reduction in oxidative stress, IL-1β, IL-6, TNF-α, and IL-12, and lesser infiltration of T cells in visceral adipose tissue. It may, therefore, offer protection against age-dependent metabolic disorders such as glucose intolerance, insulin resistance, and obesity (439). The hypothesized mechanism behind this is inhibition of NOX activity, which would be an important finding, considering the increase of adenosine and A_1AR expression induced by oxidative stress (309).

2. A_{2A}AR

As for the function of A_{2A}ARs in inflammation, this is paradoxical; it is proinflammatory in the CNS but coordinates several anti-inflammatory signaling pathways in the peripheral system (37). In general, A_{2A}AR stimulation reduces neutrophils' inflammatory functions and inhibits cytokine production, T cell activation, eosinophil and monocyte secretion, and mast cell migration (178). Indeed, mice lacking A_{2A}ARs develop a more pronounced inflammatory response, suggesting that it may play a role in regulation of the immune response (297). In this context, A_{2A}AR activation is involved in different inflammatory pathologies affecting the brain, joints, bone, lung, kidney, and bowel (8).

In MS A_{2A}AR is upregulated in the CNS tissue, but its activation induces contrasting effects, depending on which stage of the disease is underway. Specifically, the early phase of EAE, a model for MS, is characterized by a peripheral immune response that is inhibited by A_{2A}AR activation, but later on there is an involvement of CNS cells, in which A_{2A}AR activation is deleterious (168).

Methotrexate (MTX), the gold standard therapy for rheumatoid arthritis (RA), increases adenosine production, and its efficacy is predicted by the ability of Treg cells to produce

the nucleoside (55, 71, 150, 312). A_{2A}AR activation delays arthritis progression by hampering oxidative and nitrosative damage, and reducing levels of TNF-α, IL-1β, and IL-6 (247). Furthermore, mice with collagen-induced RA present A_{2A}AR upregulation in neutrophils and monocytes at the arthritic knee joint, which is mirrored by an increase in CD73 in the macrophages, neutrophils, and monocytes of the synovial fluid. Hence, a phosphorylated class of selective prodrugs for A_{2A}ARs has been developed requesting CD73 presence to be activated. These have been shown to reduce joint inflammation through selective interaction with A_{2A}ARs on immune cells, thereby escaping the cardiovascular side effects typical of systemic A_{2A}AR agonist administration (113). In a similar vein, adenosine is known to play a role in the suppression of inflammatory bone resorption. In addition, MTX reduces bone degradation in RA patients and mediates anti-inflammatory effects through A_{2A}ARs (55, 250, 251), which inhibit osteoclast differentiation and modulate bone regeneration by reducing NF-κB activation (252, 253).

Through its generation from ATP by lung T cells and action on overexpressed A_{2A}ARs, adenosine also inhibits inflammation following acute lung injury (ALI) (119). As mentioned, A_{2A}ARs play a fundamental role in the suppressive mechanism of regulatory T cells (Tregs). Accordingly, airway inflammation was significantly higher in Cd39(−/−) mice in comparison to wild-type animals, which possess Tregs with stronger A_{2A}ARs-dependent inhibitory effects on airway inflammation (222). Furthermore, A_{2A}AR activation during sensitization in response to initial allergen exposure decreased lung T helper (Th1 and Th17) cell numbers, and enhanced Treg expansion in response to rechallenge, suggesting an interesting idea that coadministration of A_{2A}ARs agonists may increase the efficacy of immunotherapies used for allergic asthma and rhinitis prevention (308). Indeed, a reciprocal inhibitory regulation between miR-214 and A_{2A}ARs has been reported to increase proinflammatory TNF-α and IL-6 cytokines; blocking miR-214 and contemporaneously stimulating A_{2A}ARs exerts several anti-inflammatory effects, rather than modulating just one of them, as demonstrated by the inhibition of neutrophil infiltration and coexpression of inflammatory cytokines (448). Interestingly, however, in spite of several reports attributing the inhibitory effect of adenosine on proinflammatory cytokines to A_{2A}AR-dependent NF-κB inhibition (233), novel findings suggest that the pathway involved is instead the inhibition of MAPKs, through A_{2A}ARs-dependent regulation of dual specific phosphatase 1, in macrophages (199). This lends weight to the idea that targeting A_{2A}ARs may be a promising treatment for human inflammatory lung diseases, especially in those in which inflammation is a strong component. Indeed, proinflammatory stimuli mitigate their own effects by upregulating A_{2A}ARs (6), and this observation has led to the development of selective agonists; these, inhaled or administered intranasally to avoid cardiovascular and systemic side effects such as tachycardia and hypotension, are being clinically trialled in asthma, allergic rhinitis, and chronic obstructive pulmonary disease (COPD) therapies. Unfortunately, however, the compounds Glaxo Wellcome GW328267X and Pfizer UK432097 have been discontinued due to lack of efficacy (178).

Nonetheless, through A_{2A}AR activation, adenosine is an important modulator of immune cell functions in renal injury. The A_{2A}AR is present on both renal and hematopoietic cells and has a high level of expression in the glomerulus, and it has been demonstrated that A_{2A}ARs on hematopoietic cells protect the kidney from ischemia reperfusion injury (IRI) (79, 414). Moreover, the presence of A_{2A}ARs on macrophages is important in kidney inflammation, as recently demonstrated in A_{2A}AR-deficient mice, in which a lack of A_{2A}AR increased inflammation; this led to glomerular damage, suggesting that endogenous A_{2A}ARs on macrophages are crucial for hampering progressive kidney fibrosis (393). In addition, adenosine produced by Treg has demonstrated a protective effect in an animal model of kidney IRI, an effect that was linked to the presence of CD73 and A_{2A}ARs on Treg (191). Furthermore, adenosine also acts via A_{2A}AR activation to prevent renal IRI by controlling dendritic cells; indeed, cells lacking A_{2A}ARs are more sensitive to kidney damage (220).

Increasing attention has been paid towards adenosine-mediated modulation of gut functions, as well as its anti-inflammatory effects, in the pathogenesis of intestinal disorders spanning inflammatory intestinal ischemia, irritable bowel diseases (IBDs), postoperative ileus, diarrhea, dysmotility, and abdominal pain (17). In this context, A_{2A}AR activation has been shown to decrease inflammation in the intestinal mucosa due to reduced leukocyte infiltration and cytokine production (294). A_{2A}ARs also reduced colonic motility in a rat model of experimental colitis, and adenosine deaminase inhibitors exert anti-inflammatory effects in chronic colitis through the activation of both A_{2A}ARs and A_3ARs (14, 15); the effects of A_{2A}AR signaling are due to both lymphoid and nonlymphoid cell recruitment (208). In addition, polydeoxyribonucleotide (PDRN), an A_{2A}AR agonist, has been shown to replace the structural integrity of tissue in two experimental animal models of colitis, suggesting that activation of this receptor subtype may be exploited to develop new drugs for treating IBD (302).

Adenosine is also involved in several events that occur during wound healing via A_{2A}ARs activation. These include vasodilatation, angiogenesis, matrix production, and inflammation (150). Specifically, treatment with topical selective A_{2A} agonists inhibits the inflammatory response, associated with a large reduction in inflammatory cell infiltrate and a decrease in LTB4 and CXCL-1 levels and TNF-α, while promoting the growth of dermal fibroblasts (18, 130).

A_{2A}AR-dependent promotion of wound closure appears to be due to raised tissue plasminogen activator (tPA) leading to fibrin proteolysis (274). Interestingly, a clinical trial for PDRN in diabetic foot ulcers showed its dramatic efficacy in earlier ulcer closure, producing a significant reduction in ulcer area (369, 370). Conversely, the use of an A_{2A}AR antagonist has been suggested to prevent irradiation-induced dermal changes, such as fibrosis and atrophy (313). Indeed, A_{2A}AR stimulation increases the synthesis of collagen type I and type III, essential mediators of fibrosis and scarring, through pathways involving cAMP/PKA/p38-MAPK/Akt and in the case of collagen III also involving β-catenin (357). Importantly, antagonism of A_{2A}AR blocks the WNT/β-catenin signaling pathway, thus reducing dermal fibrosis in diseases such as scleroderma, hypertrophic scarring, and keloid (447). It has been reported that A_{2A}AR and A_{2B}AR subtypes are up- and downregulated, respectively, in psoriatic epidermis; this leads to contrasting effects in keratinocyte proliferation, which is stimulated by A_{2A}ARs and inhibited through A_{2B}ARs via modulation of intracellular calcium increase and p38 phosphorylation, respectively (11). In addition, A_{2A}AR/A_{2B}AR agonists have also been shown to induce anti-inflammatory effects in this condition. However, these do not appear to be due to AR-mediated interaction. Future research will therefore need to address the relevance of A_{2A}AR agonists as anti-inflammatories and/or A_{2A}AR antagonists as antiproliferative agents (265). Another possibility to exploit the anti-inflammatory effect of A_{2A}AR activation is by means of pulsed electromagnetic fields (PEMFs) exposure. Indeed, various literature data suggest that PEMFs are able to upregulate A_{2A}AR in different cells and tissues (400, 403, 411). In particular, the augmented A_{2A}AR density and functionality could explain the PEMFs-mediated reduction of proinflammatory cytokines, inhibition of osteolysis and cartilage damage, and chondroprotective effects (105).

3. A_{2B}AR

Acting through A_{2B}ARs, adenosine has a complex role in immune cells, producing either pro- or anti-inflammatory effects depending on the organ affected and the signaling involved. Nevertheless, A_{2B}ARs are expressed in almost all immune cells and thereby affect a series of inflammatory diseases, from MS, wound healing, fibrosis, asthma, and COPD to colitis and diabetes (38). For instance, a role for A_{2B}AR antagonists in therapy for MS has been suggested, following studies reporting that pharmacological A_{2B}AR blockade improved EAE symptoms and decreased CNS damage, and that in A_{2B}AR-KO mice this pathology was less critical due Th17 cell differentiation block. Accordingly, A_{2B}AR worsens experimental autoimmune uveitis (EAU) by increasing Th17 cell effects (58). Interestingly, an overexpression of A_{2B}ARs has been observed in both the peripheral leukocytes of MS patients and in mice bearing EAE lymphoid tissues (343, 418).

Like A_{2A}ARs, A_{2B}ARs play an important role in wound healing and remodeling processes. They enable the body to limit potential infections and replace tissue integrity through successive inflammation, neovascularization, neoepithelialization, scar formation, and remodeling, which often involve A_{2B}AR activation. Indeed, A_{2B}AR increases angiogenesis and remodeling in cardiac mesenchymal stromal cells after myocardial injury by shifting them into myofibroblasts (340). Furthermore, A_{2B}ARs raise IL-6, IL-8, and vascular endothelial growth factor (VEGF) proangiogenic proteins in cardiac stromal cells, acting as a proangiogenic factor in the injured heart (338, 342). In general, A_{2B}ARs are well known to promote VEGF synthesis and angiogenesis in numerous cell types, including cardiac mesenchymal stemlike cells (264, 338), retinal and skin endothelial cells, mast cells, tumor-infiltrating hematopoietic cells, as well as cancer cells, through the involvement of transcription factors like HIF-1 and JUN-B (129, 336). Interestingly, HIF-1 signaling associated with A_{2B}ARs has been observed in an in vitro cellular model of foam cells, in which this transcription factor was modulated by adenosine through A_{2B}ARs, inducing ERK1/2, p38 MAPK, and Akt phosphorylation and thereby increasing foam cell formation. Simultaneous blockade of both A_{2B}AR and A_3AR has been shown to reduce adenosine-stimulated foam cell formation, indicating that antagonists may be useful in the treatment of atherosclerosis (129). Similarly, A_{2B}AR blockers have been reported to contrast fatty liver formation after alcohol ingestion in mice (311). However, subsequent studies report that atherosclerosis induced by a high-fat diet was higher in the absence of A_{2B}AR in apolipoprotein E-deficient mice, which showed increased levels of liver and plasma cholesterol and triglycerides (204).

Interestingly, a head-to-head comparison of animals with A_{2B}AR knock-down in either the myeloid lineage, endothelial cells, or alveolar epithelial cells has revealed that alveolar epithelial A_{2B}AR signaling is relevant for lung protection; that study also demonstrated that an aerosolized A_{2B}AR agonist attenuated lung inflammation (160). Accordingly, A_{2B}AR involvement has been linked to the reduction of cell migration and microvascular permeability obtained through CXCR4 and CXCR7 inhibition in an animal model of acute pulmonary inflammation (198). A_{2B}AR activation takes place in pathologies characterized by chronic inflammation and fibrosis; these include asthma and COPD, in which a role for antagonists has been hypothesized (53). Specifically, A_{2B}ARs increase Th-17 differentiation in chronic lung injury and facilitate differentiation of alternatively activated macrophages, thereby contributing to pulmonary fibrosis (425). Interestingly, they are also upregulated in the lung tissues of patients affected by this pathology (356, 453). In asthma and COPD, on the other hand, A_{2B}ARs increase cytokine production, stimulate eosinophil degranulation, and regulate human mast cells' IL-4 secretion, thereby increasing allergic inflammation (337,

341). Accordingly, a profibrotic role has been also observed in the kidney, where A_{2B}AR inhibition reduces renal hypoxic fibroblast growth, as well as profibrotic cytokine release, thereby hampering renal fibrosis development (383). In addition, A_{2B}AR activation leads to an increase in inflammatory molecules, such as SMA-α, IL-6, TGF-β, CTGF, and fibronectin, in renal fibroblasts (419).

In the colon, A_{2B}ARs is the most abundant adenosine receptor subtype. They modulate chloride secretion, fibronectin, and IL-6 production in intestinal epithelial cells, and interestingly, A_{2B}ARs are upregulated in colitis, in which contrasting results concerning their function have been reported (195). For example, A_{2B}ARs are known to play an important role in reducing mucosal inflammation, as demonstrated by animal studies in which knock-down of the receptor increases the severity of colitis due to intestinal epithelial barrier function failure. Specifically, A_{2B}AR signaling in epithelial cells is pivotal for reducing colonic inflammation by determining phosphorylation of a vasodilator-stimulated phosphoprotein (4). In contrast, however, clinical aspects, histological outcomes, and myeloperoxidase activity were less pronounced in A_{2B}AR-deficient mice affected by colitis (196), and subsequent studies have demonstrated that A_{2B}ARs on nonimmune cells are crucial for colitis insurgence (167).

The role of A_{2B}AR in glucose homeostasis is also controversial. Earlier studies showed that A_{2B}AR blockers had hypoglycemic effects in animal models of adenosine-mediated hepatic glucose production (147). Accordingly, A_{2B}AR stimulation increased rat liver glucose levels by acting on glycogenolysis and gluconeogenesis (441). Furthermore, A_{2B}AR antagonists improved insulin resistance by reducing IL-6 and other cytokines involved in glucose and fat metabolism in diabetic mice, and also reduced caspase-1 activation in rat retinal cells (104, 392, 413). However, some papers have suggested A_{2B}AR agonists as therapeutic agents for diabetes, on the basis of a link between A_{2B}AR, insulin receptor substrate 2 (IRS-2), and insulin pathways, as well as Akt phosphorylation (179).

4. A_3AR

A_3AR is a crucial player in terms of the modulatory effects mediated by adenosine on inflammation and is widely distributed in immune cells (16, 131, 150, 172). Unsurprisingly, therefore, a role for A_3AR in infections has been suggested; indeed, a reduction in neutrophil recruitment to the lung and peritoneum has been reported in A_3AR-KO mice affected by sepsis (169). In this context, it has been shown that A_3AR is localized in a polarized manner on the leading edge of neutrophil cell membranes, whereby it induces chemotaxis and migration. In more detail, ATP and adenosine cooperate to trigger and quicken pathogen-induced chemotaxis and migration through P2Y2 and A_3AR activation (45, 59, 66, 215). Interestingly, A_3AR also modulates cytoskeletal remodeling following its aggregation into plaquelike microdomains and helps neutrophils to capture pathogens by inducing membrane protrusions termed cytonemes (67). Nevertheless, it has been reported that A_3AR inhibits neutrophil chemotaxis and oxidative burst (41, 137, 398a). On a related note, it has very recently been reported that adenosine induces hypothermia through A_3AR activation; it leads to a drop in total energy expenditure, physical inactivity, and preference for cooler environmental temperatures by stimulating histamine release, acting on central H1 receptors on peripheral mast cells by way of A_3AR. This is particularly noteworthy because hypothermia can help to reduce inflammation, and in particular the cytokine increase provoked by sepsis (49, 50).

In pathologies characterized by autoimmune inflammation, on the other hand, A_3AR may represent a new biological predictive marker. Specifically, it is upregulated in the peripheral blood mononuclear cells (PBMCs) of patients with RA, Crohn's disease, and psoriasis. This is due to a TNF-α increase and upregulation in the related A_3AR transcription factors NF-κB and CREB (293). In lymphocytes obtained from RA patients, A_3ARs decreased NF-κB signaling, as well as the production of inflammatory cytokines and matrix metalloproteinases. Interestingly, their level of expression was inversely related to the DAS28 and DAS scores used to evaluate disease activity in RA (401). Accordingly, A_3AR stimulation in arthritis rat models prevents cartilage injury, osteoclast/osteophyte generation, bone damage, and lymphocyte pannus production (24, 325).

The signaling pathway of the anti-inflammatory effect of A_3AR in RA patients involves NF-κB and TNF-α in the synoviocytes (292). In fact, results from in vitro and in vivo studies have already prompted the launch of A_3AR agonists in clinical trials for the therapy of different inflammatory diseases. These compounds have been shown to be safe and well tolerated in preclinical and human studies, and specifically, the agonist IB-MECA (Piclidenoson, CF101) has been tested in phase II trials on RA patients (phase II, NCT00280917; phase II, NCT01034306; phase II, NCT00556894), in whom it displayed a significant antirheumatic action. Remarkably, basal receptor expression correlated with the patients' reaction to the drug, suggesting that A_3AR may be a biological marker for prognosticating patients' response to CF101 (112). In addition, CF101 was efficacious in clinical trials on plaque psoriasis (phase II, NCT00428974; phase II/III, NCT01265667) (77, 78), where it showed a better profile than the PDE4 inhibitor apremilast (Otezla). Moreover, its optimum safety profile makes it a promising drug for chronic psoriasis therapy. In contrast, however, CF101 did not showed efficacy in trials for ocular hypertension (NCT01033422) and dry eye disease (phase II, NCT00349466; phase III, NCT01235234) and, in combination with methotrexate (NCT00280917), for RA. That being said, new trials in RA (phase III,

NCT02647762) and osteoarthritis of the knee (phase II, NCT00837291) are in the planning stages.

Several studies in the literature support a role for A_3AR in asthma due to its expression in mast cells. Specifically, earlier works ascribed A_3AR a crucial role in rodent mast cell activation and degranulation, and more recently, this effect has been demonstrated in both primary human and LAD2 mast cells (142, 219, 323, 328, 346, 368, 449). Interestingly, a disparity in adenosine-dependent degranulation has been revealed in primary human mast cells from lung and skin, which may explain the allergic response induced by adenosine in the lung but not in the skin (142). Due to its potentiating effect on FcεRI-induced degranulation, A_3AR is also involved in bronchoconstriction induced by adenosine in asthmatics. Indeed, in asthma, A_3AR stimulation in human mast cells raised the levels of a series of proinflammatory mediators, including IL-8, IL-6, VEGF, amphiregulin, and osteopontin (304, 452). In addition, A_3AR activation reduced its own expression, thereby inducing suppression of its basal inhibition on cytokine production (335).

Adenosine also modulates monocyte-macrophage functions through A_3AR, which is responsible for both inflammatory mediator production and healing. For example, A_3AR stimulation inhibits the respiratory burst, IL-1β, TNF-α, chemokine macrophage inflammatory protein (MIP) 1α, interferon regulatory factor 1, inducible nitric oxide synthase, and CD36 gene expression (27, 42, 217, 249, 344, 363, 386), but adenosine reduced the expression of adhesion molecules on monocytes and decreased cytokine production, effects that were potentiated by an A_3AR antagonist (381). In addition, A_3AR stimulation increases TNF-α production in activated macrophages (114).

A functional A_3AR is expressed in dendritic cells, antigen-presenting entities that activate naive T lymphocytes and trigger primary immune responses (135, 200). In particular, the A_3AR in the immature human dendritic cells has been found to induce elevated Ca^{2+} levels, actin polymerization, and chemotaxis, while in mature dendritic cells, the A_3AR is downregulated and decreases TNF-α release (87, 303).

D. Cancer

1. A_1AR

Several studies have evaluated the effects of A_1AR activation in cancer, but its role remains difficult to pin down. Data are mostly derived from old studies, often performed with nonselective ligands, and both pro- and antitumoral effects have been reported (132, 187). Specifically, antiproliferative effects have been observed in colon cancer, breast cancer, glioblastoma, and leukemia cells. In addition, proapoptotic effects, through an increase in caspase activity, have been reported in astrocytoma and colon cancer cells. In line with these data, A_1AR has displayed a crucial role in reducing glioblastoma proliferation and increasing chemotherapy sensitization by stimulating cell apoptosis (76). However, it also displays protumoral effects due to an increase in melanoma chemotaxis and breast proliferation, as well as P27 reduction in cervical carcinoma cells. Furthermore, recent data have demonstrated significantly raised VEGF R2-dependent angiogenesis through stimulation of A_1AR in an animal model of melanoma (202).

2. A_{2A}AR and A_{2B}AR

Adenosine is an important regulator of several aspects of tumorigenesis—spanning angiogenesis, tumor cell growth, and metastasis—affecting immune system cells, like T and natural killer, myeloid-derived suppressor and dendritic cells, as well as macrophages, tumor and endothelial cells, where both A_2ARs subtypes are involved (7, 13, 296). Adenosine concentration is significantly increased in hypoxic tumors due to hypoxia-dependent CD73 overexpression and AK downregulation (296).

Interestingly, CD73 expression is associated with poor prognosis in leukemia, brain, breast, ovarian, and prostate tumors (12, 16, 38, 131, 214, 227, 355, 395). Specifically, silencing or inhibition of CD73 reduced cell growth of melanoma, breast, prostate, and fibrosarcoma tumors (371–373, 385). The antitumoral effect of CD73 can be explained by the effects of adenosine in immune cells and represents one of the first pieces of evidence on the involvement of this nucleoside in cancer. Indeed, it is well recognized that immune cells are important in the fight against cancer and that adenosine, which is increased in hypoxic tumors, is able to impair cytolytic effector immune cell recognition of cancer cells, suppress $\alpha4\beta7$ integrin-dependent adhesion of T lymphocytes to colon adenocarcinoma cells, and reduce the expression of CD2 and CD28 on T cells (34, 45, 238).

Several studies have been performed to identify the receptor subtypes mediating these effects. At first, adenosine reduction of anti-CD3-activated killer lymphocyte adhesion to colon adenocarcinoma cells was attributed to A_3AR activation (237). However, subsequent studies found that, instead, A_{2A}AR activation was implicated in the ability of adenosine to stimulate cAMP and inhibited lymphokine-activated killer (LAK) cell destruction of cancer cells (324). However, a huge number of studies have reported that adenosine via A_{2A}AR is also involved in stimulation of Treg responses and induction of T cell anergy, as well as inhibition of natural killer (NK) activity, thereby promoting tumor escape from the immune system and metastasis (80, 242, 243, 365, 366, 446). Therefore, A_{2A}AR antagonists may be useful in novel approaches for increasing the immune response against cancer, by interfering with adenosine-mediated immunosuppression in tumors; indeed, phase I clinical trials to investigate their effects on the immune system have already begun (29).

These molecules have the advantage that they have been already tested in human clinical trials for PD, where they showed a lack of toxicity. However, novel molecules targeting A_{2A}AR for cancer that are unable to cross the BBB must be developed to obviate neurological side effects (152). This aim of this promising line of research will be able to take advantage of the new knowledge acquired on A_{2A}AR molecular structure (51, 178, 443), and reports that a double blockade of both CD73 and A_{2A}AR powerfully limits cancer growth and metastasis (8, 9, 445).

A_{2B}AR has also been implicated in tumor development. Initially, this receptor was considered a "bad copy" of A_{2A}AR, due to its low adenosine affinity. However, it has more recently been discovered that its expression is significantly increased by HIF-1α, indicating its involvement in cancer promotion (197). Indeed, recent findings on several aspects of tumorigenesis suggest that it may be not pleonastic towards A_{2A}AR.

In general, by stimulating cAMP, A_{2B}AR, like A_{2A}AR, induces depression of immune responses, promoting immunoescape (28). Its protumoral effect has been observed in the stimulation of myeloid-derived suppressor cells, as well as in the activation of M2 macrophages— crucial for angiogenesis, proliferation, and metastasis— but not on NK cell functions (28, 72, 339). In addition, stimulation of A_{2B}AR induces development of an anomalous phenotype of proangiogenic dendritic cells (290); suppresses RAS-related protein 1 (RAP1) prenylation, important in cell-cell adhesion; and increases the Fra-1 component of activator protein 1 (AP-1) transcription factor, relevant for cell proliferation, motility, and invasiveness, thereby promoting cell scattering (82, 291). Accordingly, A_{2B}AR activation has been shown to increase experimental and spontaneous metastasis in cancer mouse models, and to worsen the efficacy of classical chemotherapy drugs. This mechanism does not appear to involve NK or the myeloid-dependent pathway, but instead drives cancer metastasis through a reduction of cell adhesion and MAPK-dependent signaling activation (272). Thus far, stimulation of metastasis through A_{2B}AR has been reported in melanoma, ovarian, blood, and breast carcinomas (28, 54). It has also been recently reported that bladder urothelial carcinoma (BUC) expresses high levels of A_{2B}AR, which is associated with poor prognosis of patients. Accordingly, inhibition of A_{2B}AR decreased the proliferation, migration, and invasion of BUC cells and blocked the cell cycle at the G_1 phase (451).

3. A_3AR

Adenosine exerts antitumoral effects by acting directly on neoplastic cells, essentially through A_3AR, which is greatly expressed in several tumors from lymphoma, astrocytoma, glioblastoma, melanoma, and sarcoma, to thyroid, lung, breast, colon, liver, pancreas, prostate, and renal carcinomas (25, 64, 128, 134, 136, 138, 162, 174, 183, 184, 193, 240, 241, 266, 268, 269, 276, 278, 281, 289, 300, 345, 376, 399, 410). Interestingly, A_3AR upregulation in human colorectal and hepatocellular carcinomas is reflected in the PBMCs. These, by mirroring receptor status in remote tumor tissue, may make A_3ARs useful tumor markers (25, 128, 240).

The role of A_3AR has been investigated in different types of cancer cells, with contrasting results attesting both pro- and antiproliferative effects, as well as modification of cell migration and apoptosis (3, 74, 132, 134, 136, 171, 174, 188, 228, 260, 267, 276, 282, 382, 399). Intriguingly, initial studies reported the lack of occurrence of tumor metastases in striated muscles, and it has also been found that muscle cells secrete adenosine and endogenous A_3AR agonists, which would explain the anti-cancer and chemoprotective activity of muscle-conditioned media. This finding, in addition to explaining the rarity of tumor metastases in muscle, may suggest proof of concept for the development of A_3AR agonists as anti-cancer drugs (23, 111). Moreover, A_3AR has been shown to reduce telomerase activity and produce cytostatic effects in tumor cells (106, 107, 109, 110). Indeed, the therapeutic efficacy of orally administered A_3AR agonists IB-MECA and Cl^-IB-MECA has already been demonstrated through in vivo experimental animal studies, including syngeneic, xenograft, orthotopic, and metastatic models of colon, prostate, melanoma, and hepatocellular carcinomas. These drugs reduced cell proliferation and enhanced the effect of cyclophosphamide in syngeneic and lung metastatic models of murine melanoma (107). It is also interesting to note that A_3AR agonist administration reduced in vivo growth of melanoma cells by increasing IL-12 and the cytotoxic effects of mouse NK cells (149). Furthermore, ex vivo A_3AR stimulation in CD8+ T cells ameliorated immunotherapy of melanoma (275). IB-MECA has also been shown to reduce cancer growth and potentiate the chemotherapeutic effect of 5-fluorouracil and taxol in colon and prostate xenograft models. Furthermore, Cl^-IB-MECA blocks the development of hepatocellular cancer, liver inflammation, and pain in breast tumor-derived bone metastases (25, 64, 107, 404).

That being said, contrasting results on the behavior of A_3AR in tumor development that support the utility of A_3AR antagonists in cancer treatment have also been reported. Specifically, A_3AR appears to promote HIF-1α accumulation in melanoma, glioblastoma, and colon carcinoma cell lines, leading to an increase in angiogenic factors (259, 261, 262). This has been confirmed in animal models of melanoma, in which A_3AR activation enhanced microvessel density, proangiogenic molecules, cytokine production, and macrophage tumor infiltration (202). Furthermore, A_3AR increases MMP-9 production and activity, resulting in an increase of cell invasion in glioblastoma, as previously shown in macrophages (136, 406). Moreover, an increase in MRP1 expression via A_3AR activation in

glioblastoma cells has been blocked by A_3AR antagonist administration, which increased the antitumoral effect of the chemotherapy drug vincristine (390).

Even though both agonists and antagonists have been studied at the preclinical level, only A_3AR agonists, in particular Cl^-IB-MECA (Namodenoson, CF102), have progressed to clinical trials for advanced hepatocellular carcinoma treatment. Phase I and phase II (NCT00790218) clinical trials have thus far shown that the agonist is safe, well tolerated, and able to increase a median overall survival by 7.8 mo in patients, a subset of whom were given CF102 as second-line therapy, due to disease progression under sorafenib (374). A global phase II trial in this patient population is currently underway, and other trials are planned for CF102 in hepatocellular carcinoma treatment (phase II, NCT02128958).

VI. DISCUSSION AND PERSPECTIVES

Adenosine is an endogenous modulator with several potential therapeutic applications, due to its ubiquitous presence and ability to interact with major physiological processes. In the CNS, for example, activation of A_1ARs could be beneficial in different pathologies such as epilepsy and acute, chronic, and neuropathic pain. Furthermore, although data regarding the role of A_3ARs in cerebral ischemia are controversial, the inhibitory effect of A_1ARs on glutamate release is fundamental for protection from ischemic damage. Moreover, A_{2A}AR antagonists are promising therapeutic agents for PD, due to their interaction with D2R. Indeed, istradefylline has been approved in combination with levodopa and is commercially available in Japan. Other therapeutic targets for A_{2A}AR in the CNS include AD, HD, epilepsy, acute and chronic stress, and fear memory. Interestingly, caffeine, the most widely drug used in the world, seems to be protective in a number of neurological and psychiatric pathologies that involve ARs.

In the cardiovascular system, on the other hand, adenosine via A_1ARs is already commercially available as Adenocard, a therapeutic agent for supraventricular tachycardia. Partial agonists of A_1ARs are also undergoing clinical trials designed to assess their cardioprotective action and lack of side effects. As for A_{2A}ARs, these are primarily involved in vasodilation, through their expression in smooth muscle and endothelial cells, while A_{2B}ARs and A_3ARs have therapeutic potential in the heart, for cardiac fibrosis and infarct, respectively.

In addition, evidence from several sources indicates that adenosine and its receptors are promising targets for cancer therapy. In particular, A_{2A}AR antagonists may represent a novel approach to increasing the immune response against tumors by counteracting adenosine-mediated immunosuppression, especially in hypoxic conditions, in which the concentration of adenosine rises dramatically. Moreover, an antitumoral effect of adenosine has been attributed to the activation of A_3ARs acting directly on cancer cells. Indeed, the A_3AR agonist CF102 is showing promise in clinical trials for advanced hepatocellular carcinoma.

In the peripheral system, the majority of the anti-inflammatory and immunosuppressive effects of adenosine are mediated by A_{2A}AR and A_3AR subtypes. For this reason, A_{2A}AR and A_3AR agonists could represent interesting novel pharmacological agents for the treatment of inflammation-based and autoimmune diseases. In this regard, several clinical trials have demonstrated the efficacy and tolerability of the A_3AR agonist CF101, and new trials are planned for RA and psoriasis.

Overall, the extensive studies performed in the adenosinergic field reveal adenosine and its receptors as outstanding pharmacological targets for the future development of novel drugs with many potential therapeutic applications in human pathologies.

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DISCLOSURES

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