

Adenosine Receptors

Key References

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Overview

There are four known subtypes of adenosine receptors referred to as A₁, A_{2A}, A_{2B} and A₃. All are members of the superfamily of G protein-coupled receptors and each bears the characteristic motif of seven transmembrane spanning domains. Modulation of adenosine receptors by selective agonists and antagonists has potential for the treatment of various cardiovascular inflammatory and neurological diseases. For example, adenosine is released in large amounts during myocardial ischemia and is capable of exerting potent cardioprotective effects in the heart by activating A₁ and A₃ receptors. A synthetic adenosine receptor agonist might therefore be beneficial to the survival of the ischemic heart. A₃ receptor agonists are also a target for cancer therapy. A_{2A} receptor agonists suppress excessive inflammation and reperfusion injury and may be useful also in physiologic stress testing. In the asthmatic lung, however, adenosine acts as an irritant and bronchoconstrictor, such that a synthetic adenosine receptor antagonist would be desirable.

Selectivity for A₁ receptors is typically accomplished through modification of the N⁶-position that gave rise to compounds such as CPA, CHA, and R-PIA, although substantial A₃ receptor affinity was later detected for these agonists. The 2-chloro analog CCPA displays slightly greater A₁ receptor affinity than the parent CPA. S(-)-ENBA is a highly potent and selective A₁ receptor agonist. The affinities of these N⁶-substituted derivatives at A₃ receptors are often intermediate between their respective A₁ and A_{2A} affinities. Although most N⁶-substituted adenosine agonists are A₁ selective, the agonist DPMA is 30-fold selective for the rat A_{2A} receptor. Small alkyl amide substitution at the 5'-

position, as in NECA, provides increased potency at all of the adenosine receptors. NECA is also among the most potent agonists at all four subtypes of adenosine receptors and is therefore non-selective. CGS21680 is a moderately A_{2A}-selective adenosine agonist in rat, but not human, possessing a 140-fold selectivity for A_{2A} versus A₁ receptors in rat. Aryl amines related to the agonist CGS21680 (e.g. PAPA-APEC) or the antagonist ZM241,385 can be radioiodinated to provide A_{2A} receptor selective radioligands.

The most recently discovered member of the adenosine receptor family, the A₃ receptor, has a unique pharmacological profile, tissue distribution and effector coupling. In recent years, selective A₃ adenosine receptor agonists and antagonists have been described. Previously, APNEA had been used as an agent to activate A₃ receptors in the presence of non-A₃ antagonists, although APNEA is actually 8-fold selective for A₁ receptors. IB-MECA is 50-fold selective for A₃ versus either A₁ or A_{2A} receptors *in vitro* and appears to be highly A₃ selective *in vivo*. The related 4-amino derivative may be radioiodinated giving rise to [¹²⁵I]-I-AB-MECA which is widely used as a high affinity radioligand for A₃ receptors. 2-Chloro substitution, in combination with modifications at N⁶ and 5'-positions, e.g. in CI-IB-MECA (selective for rat A₃ vs A₁ and A_{2A} receptors by 2500- and 1400-fold, respectively), further enhances A₃ selectivity.

Adenosine receptor antagonists, of which xanthines and numerous classes of fused heterocyclic compounds are representative, have been under development as anti-asthmatic, anti-arrhythmic, renal-protective, anti-Parkinson's and cognition

enhancing drugs. A₃ receptor antagonists have potential in treating glaucoma or inflammatory disorders.

The classical xanthines, theophylline (1,3-dimethylxanthine) and caffeine (1,3,7-trimethylxanthine) are non-selective adenosine receptor antagonists possessing low micromolar affinity. Selective antagonists for A₁ receptors include many 8-aryl and 8-cycloalkyl xanthine derivatives, such as CPX which is ~500-fold selective for A₁ versus A_{2A} receptors. Certain non-xanthine antagonists, such as N-0841, are A₁ selective, whereas SCH-58261 is a highly potent and selective A_{2A} receptor antagonist. CSC and other 8-styrylxanthines, such as KW 6002, are selective for A_{2A} receptors versus both A₁ and A_{2B} receptors. However, in dilute solution, these compounds suffer from sensitivity to photoisomerization.

At A₃ receptors, the dihydropyridine derivative MRS 1191 (not active at L-type calcium channels) and the triazoloquinazoline MRS 1220 (not selective in rat) are both relatively potent A₃ receptor antagonists, possessing K_i values of 31 and 0.65 nM, respectively, at the human subtype. The nucleoside MRS 1292 and the pyridine derivative MRS 1523 are selective A₃ adenosine receptor antagonists in the rat and human.

Adenosine Receptors

CURRENTLY ACCEPTED NAME	A ₁	A _{2A}	A _{2B}	A ₃
ALTERNATE NAMES	R _i	A _{2a} , R _a	A _{2b}	
STRUCTURAL INFORMATION	326 aa (human)	412 aa (human)	332 aa (human)	318 aa (human)
RECEPTOR SELECTIVE AGONISTS	Adenosine amine congener (A111), CPA (C8031), CHA (C9901), CCPA (C142, C7938), CVT-510	CGS21680 (C141), DPMA (D130), HE-NECA (H8034), ^a ATL-146e, CVT-3146	NECA (E2387) ^b	IB-MECA (I146), CI-IB-MECA (C277)
RECEPTOR SELECTIVE ANTAGONISTS	CPX (C101), CPT (C102), N-0840 (N154), WRC-0571	KW 6002, 8-(3-Chlorostyryl) caffeine (C197), SCH-58261 (S4568), ZM241,385	XAC (X103), ^b Alloxazine (A242), MRS 1754 (M6316), MRE 2029-F20	I-ABOPX, ^c MRS 1191 (M227), MRS 1220 (M228), MRS 1523 (M1809), VUF 5574 (V5888), MRS 1292, MRE 3008F20
SIGNAL TRANSDUCTION MECHANISMS	G _i (cAMP modulation) increased K ⁺ , decreased Ca ²⁺	G _s (increase cAMP)	G _s (increase cAMP) increased Ca ²⁺	G _i (cAMP modulation) increased Ca ²⁺
RADIOLIGANDS OF CHOICE	[³ H]-CHA [³ H]-CPX [³ H]-R-PIA	[³ H]-CGS21680 [¹²⁵ I]-PAPA-APEC [³ H]-SCH-58261	[³ H]-MRS 1754 [³ H]-CPX [³ H]-MRE 2029-F20	[¹²⁵ I]-APNEA [¹²⁵ I]-AB-MECA [³ H]-PSB-11
TISSUE EXPRESSION	Cerebral cortex, hippocampus, atria, kidney, testis	Platelets, endothelial cells, striatum, neutrophils	Fibroblasts, colon, aorta, mast cells	Eosinophils, heart, lung, pineal
PHYSIOLOGICAL FUNCTION	Inhibition of neurotransmitter release, bradycardia, ischemic preconditioning	Vasodilatation, inhibition of platelet aggregation	Smooth muscle relaxation, release from mast cells	Ischemic preconditioning
DISEASE RELEVANCE	Cardiac arrhythmia, diabetes, stroke	Parkinson's disease, inflammation, arthritis	Asthma, diabetes	Cardiac ischemia, cancer, arthritis, glaucoma

Abbreviations

AB-MECA: N⁶-(4-Aminobenzyl)-9-[5-(methylcarbamoyl)-β-D-ribofuranosyl]adenine
ATL-146e: 4-[3-[6-Amino-9-(5-ethylcarbamoyl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-9H-purin-2-yl]-prop-2-ynyl-cyclohexanecarboxylic acid methyl ester
CCPA: 2-Chloro CPA
CGS21680: 2-p-(2-Carboxyethyl)phenethylamino-5'-N-ethylcarboxamidoadenosine
CHA: N⁶-Cyclohexyladenosine
CI-IB-MECA: 2-Chloro-N⁶-(3-iodobenzyl)-9-[5-(methylcarbamoyl)-β-D-ribofuranosyl]adenine
CPA: N⁶-Cyclopentyladenosine
CPT: 8-Cyclopentyl-1,3-dimethylxanthine
CPX: 8-Cyclopentyl-1,3-dipropylxanthine
CVT-510: N-(3(R)-Tetrahydrofuran-6-aminopurine riboside
CVT-3146: 1-(6-Amino-9-β-D-ribofuranosyl-9H-purin-2-yl)-N-methyl-1H-pyrazole-4-carboxamide (regadenosine)
DBXRM: 1,3-Dibutylxanthine 7-riboside 5'-N-methylcarboxamide
DPMA: N⁶-[2-(3,5-Dimethoxyphenyl)-2-(2-methylphenyl)ethyl]adenosine
S(-)-ENBA: (2S)-N⁶-[2-endo-Norbornyl]adenosine

HE-NECA: 2-Hexynyl-adenosine-5'-N-ethyluronamide
I-ABOPX: 3-(3-Iodo-4-aminobenzyl)-8-(4-oxacetate)-phenyl-1-propyl xanthine
IB-MECA: N⁶-(3-Iodobenzyl)-9-[5-(methylcarbamoyl)-β-D-ribofuranosyl]adenine
KW 6002: (E)-1,3-Diethyl-8-(3,4-dimethoxyphenylethyl)-7-methyl-3,7-dihydro-1H-purine-2,6-dione
MRE 2029-F20: N-Benzo[1,3]dioxol-5-yl-2-[5-(2,6-dioxo-1,3-dipropyl-2,3,6,7-tetrahydro-1H-purin-8-yl)-1-methyl-1H-pyrazol-3-yloxy]-acetamide
MRE 3008F20: 5N-(4-methoxyphenylcarbamoyl)amino-8-propyl-2-(2-furyl)pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine
MRS 1191: 3-Ethyl 5-benzyl 2-methyl-6-phenyl-4-phenylethynyl-1,4-(±)-dihydro-pyridine-3,5-dicarboxylate
MRS 1220: 9-Chloro-2-(2-furyl)-5-phenylacetylaminol[1,2,4]-triazolo[1,5-c]quinazoline
MRS 1292: (2R,3R,4S,5S)-2-[N⁶-(3-Iodobenzyl)adenos-9'-yl]-7-aza-1-oxa-6-oxo-spiro[4.4]nonan-4,5-diol
MRS 1523: 2,3-Diethyl-4,5-dipropyl-6-phenylpyridine-3-thiocarboxylate-5-carboxylate

MRS 1754: 8-[4-[[[(4-Cyano)phenylcarbamoylmethyl]oxy]phenyl]-1,3-di-(n-propyl)xanthine
N-0840: N⁶-Cyclopentyl-9-methyladenine
NECA: N-Ethylcarboxamidoadenosine
PAPA-APEC: 1-[6-Amino-2-[[2-[4-[3-[[2-[[[(4-aminophenyl)acetyl]amino]ethyl]amino]-3-oxopropyl]phenyl]ethyl]amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-β-D-ribofuranuronamide
PIA: R(-)-N⁶-(2-Phenylisopropyl)adenosine
SCH-58261: 5-Amino-7-(β-phenylethyl)-2-(8-furyl)pyrazolo[4,3-e]-1,2,4-triazolo(1,5-c)pyrimidine
VUF 5574: N-(2-Methoxyphenyl)-N'-(2-(3-pyridyl)quinazolin-4-yl)urea
WRC-0571: 8-(N-Methylisopropyl)amino-N-(5'-endohydroxy-endonorbornyl)-9-methyladenine
XAC: 8-[4-[[[(2-Aminoethyl)amino]carbonyl]methyl]oxy]phenyl]-1,3-dipropylxanthine; Xanthine amine congener
ZM241,385: 4-[2-(7-Amino-2-(2-furyl)[1,2,4-triazolo[2,3-a][1,3,5]triazin-5-yl-amino]ethyl phenol

FOOTNOTES

- HE-NECA is also a potent agonist at A₃ receptors.
- NECA and XAC are among the most potent agents at this adenosine receptor subtype. However, these compounds are not subtype selective.
- Rat A₃ receptor is relatively insensitive to xanthine blockade.