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A_1 adenosine receptors and their ligands: overview and recent developments

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Abstract

Potent adenosine receptor (AR) agonists and antagonists with high selectivity for the A_1AR subtype have been developed during the past decades. However, some of the compounds considered to be selective may not be as selective in humans as in rats, and may not be very selective versus the new AR subtypes A_3 or A_{2B}. Partial agonists have been developed that may exhibit fewer side effects than full agonists. Low water solubility of many A_1 antagonists remains a problem. A_1 AR antagonists can be classified as neutral antagonists or inverse agonists; the pharmacological consequences of inverse agonism versus neutral antagonism will have to be the subject of future investigations. Some medicinal plants (e.g. *Hypericum perforatum* and *Valeriana officinalis*) contain compounds that are antagonists or partial agonists at A_1 ARs; effects on ARs may contribute to their pharmacological activity. ^{18}F- and ^{11}C-labeled A_1 AR antagonists have been developed for positron emission tomography studies.

Keywords: A_1 adenosine receptors; A_1 antagonists; A_1 agonists

The family of adenosine receptors (ARs), which are G-protein coupled receptors, consists of four subtypes designated A_1, A_{2A}, A_{2B}, and A_3 [1]. The A_1 AR is the best known and the most comprehensively studied AR subtype. It has been cloned from different species, including humans. A_1 ARs are coupled to adenylate cyclase in an inhibitory manner, and they may also be coupled to other second messenger systems, such as activation of phospholipase C (PL C), stimulation of K^+ channels, or inhibition of Ca^{2+} channels. The A_1 AR is found in high density in the brain (cortex, hippocampus), and in lower density in peripheral organs and tissues, such as heart, kidney, lung, and fat cells [1]. During the past 20 years a large number of A_1 AR agonists and antagonists have been developed [2,3]. Recently, human recombinant ARs expressed in mammalian cell lines (CHO, HEK) have found wide application in the screening of new ligands [4]. Re-evaluation of compounds at all four human AR subtypes has shown that ligands that had been considered to be A_1-selective may not be selective in a comparison of human A_1 versus human A_3 ARs, in some cases due to species differences (e.g. lower affinity for human than for rat receptors), or due to high affinity of the compounds for the new A_3 or A_{2B} ARs [3,5].

A_1 agonists have therapeutic potential, for example as analgesic, antiepileptic, and neuroprotective agents [3]. A_1-selective antagonists are developed as kidney-protective diuretics, and for the treatment of dementias, depression, and asthma. Further potential applications have been claimed [2].

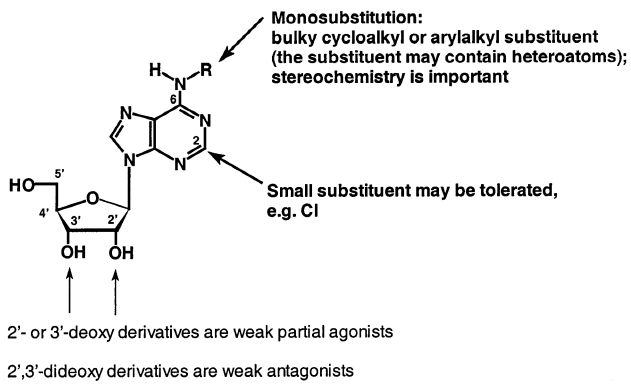

Fig. 1. General structure of A_1 adenosine receptor agonists.

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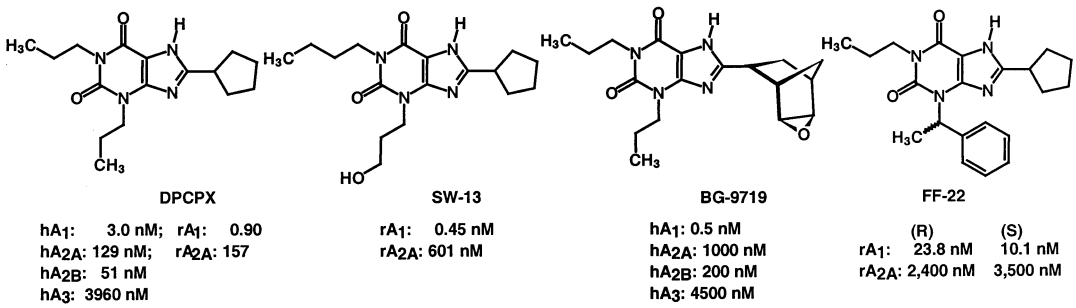


Fig. 2. A_1-selective adenosine receptor antagonists: xanthines (h = human; r = rat); data are taken from Refs. [4,6,7], or are from our own laboratory.

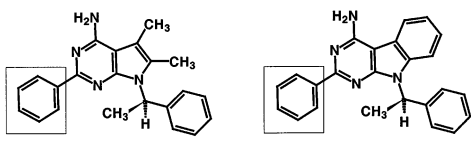
AR agonists are derivatives of the physiological agonist adenosine; the ribose is essential for agonistic activity (Fig. 1). A_1-selectivity is achieved by monosubstitution of the exocyclic amino group with bulky substituents, such as cyclohexyl or endonorbornyl; polar residues are tolerated. Removal of either the 2′- or the 3′-hydroxyl group of A_1 agonists leads to partial agonists with reduced AR affinity (Fig. 1) [3,5]. Since the treatment with A_1 AR agonists may lead to fast desensitization of the receptors, partial agonists may be therapeutically advantageous. Furthermore, indirect A_1 agonists have been developed, such as adenosine kinase inhibitors or allosteric enhancers of adenosine binding [3].

Different structural classes of compounds (bi- or tri-cyclic heterocyclic compounds) possess antagonistic activity at ARs. Important classes of A_1-selective antagonists comprise xanthine derivatives with bulky 8-substituents (Fig. 2), adenine derivatives with bulky N^6-substituents, aza- and deaza analogs of adenine (Table 1), pyrazolo[1,5-*a*]pyridines, and other heterocyclic compounds [2]. Recent developments include the introduction of polar functions to increase water solubility of the compounds (e.g. **BG9719** [6] and **SW-13**, Fig. 2). Polar substituents are tolerated at the 3- and at the 8-residue, but not at the 1-substituent of xanthines (see Fig. 3).

A_1 antagonists with chiral residues in different positions have been prepared to investigate the stereochemical requirements for ligand recognition. A 1-methylbenzyl substituent in 7-deazaadenines (amino-substituted pyrrolo[2,3-*d*]pyrimidines and pyrimido[4,5-*b*]indoles) either at the pyrrole nitrogen (e.g. ADPEP and analogs, see Table 1) or at the exocyclic amino group (e.g. DPEAP, Table 1) is recognized highly stereoselectively ($R \gg S$) [8]. In xanthines, a 1-methylbenzyl substituent in the 3-position was tolerated, but it showed only a negligible degree of stereoselectivity ($S > R$, see Fig. 2 compound **FF-22**). Structure–activity relationships for xanthine derivatives at A_1 ARs are summarized in Fig. 3.

Amino-substituted pyrrolo[2,3-*d*]pyrimidines, such as **ADPEP**, and pyrimido[4,5-*b*]indoles, such as **APEPI**, examples for A_1-selective non-xanthine AR antagonists,

Table 1
Pyrrolo[2,3-*d*]pyrimidines and pyrimido[4,5-*b*]indoles: bioisosteric replacement of the 2-phenyl substituent



Substituent	Type	$K_i \pm$ SEM (μM)	
		A_1	A_{2A}
Phenyl (ADPEP)	A	0.0047	3.7
Phenyl (APEPI)	B	0.0026	6.2
2-Pyridyl	A	2.1	>10
2-Pyridyl	B	0.54	>10
3-Pyridyl	A	>10	>10
3-Pyridyl	B	0.092	>10
4-Pyridyl	A	0.046	1.3
4-Pyridyl (APPPI)	B	0.021	>10
2-Thienyl	A	0.019	5.4
2-Thienyl	B	0.036	>3

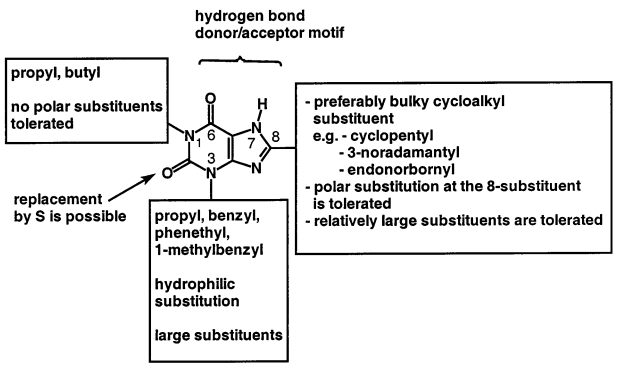


Fig. 3. Structure–activity relationships of xanthines as A_1-adenosine receptor antagonists.

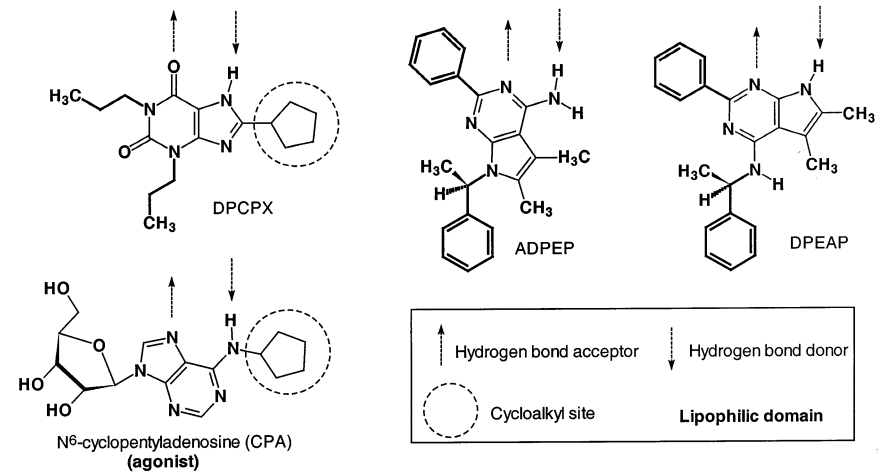


Fig. 4. Pharmacophore model for A_1 adenosine receptor agonists and antagonists.

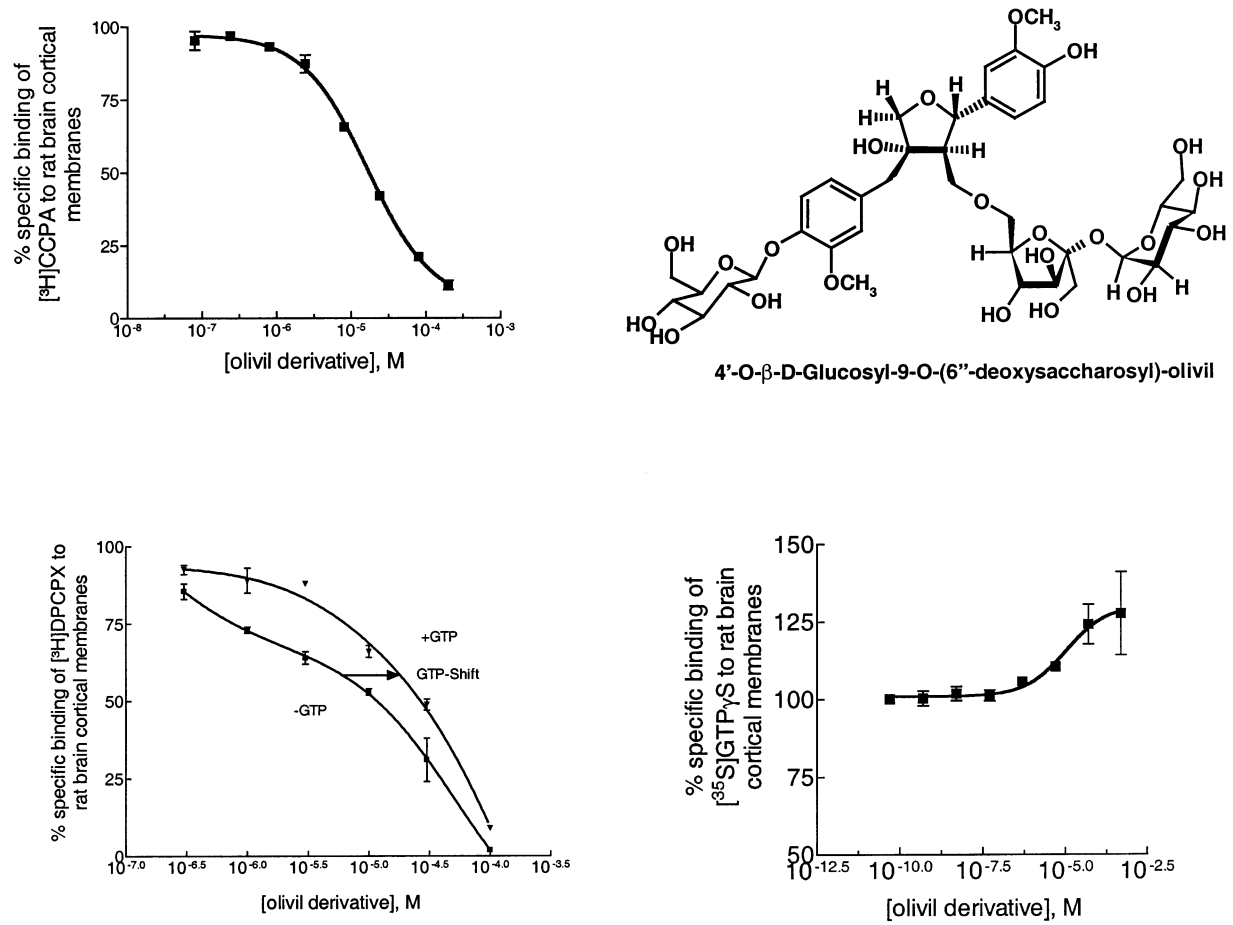


Fig. 5. Characterization of an isolated lignan constituent of the medicinal plant *Valeriana officinalis* as a ligand (partial agonist) of A_1 adenosine receptors.

have been shown to require a 2-phenyl group for high affinity [8]. This phenyl residue has been bioisosterically replaced by various heterocycles (Table 1) [9]. 2-Thienyl and *p*-pyridyl residues were suitable replacements for the 2-phenyl group. *p*-Pyridyl substitution in the 2-position of pyrimido[4,5-*b*]indoles (e.g. **APPPI**) leads to highly potent and selective A_1 antagonists with fluorescent properties (Table 1).

A pharmacophore model for A_1 AR ligands has been developed. Important features are a hydrogen bond

donor–acceptor motif, two lipophilic domains (for antagonists), a (cyclo)alkyl site, and a ribose domain for agonists (Fig. 4) [2].

A variety of natural products has been found to possess A_1 affinity and may serve as novel lead structures for A_1 ligands. The lignan 4′-*O*-β-D-glucosyl-9-*O*-(6″-deoxysaccharosyl)olivil (Fig. 5), a constituent of *Valeriana officinalis*, a sedative medicinal plant, was found to be a partial agonist at A_1 ARs by means of GTP shift experiments and GTPγS binding studies (Fig. 5). Various constituents of *Hypericum perforatum*, the extract of which is used as a mild antidepressive medication, have been shown to be AR antagonists [10].

The subdivision of receptor ligands into agonists on the one hand, and antagonists on the other hand has turned out to be too simple. In fact, ligands have been characterized with properties ranging from full agonists, to partial agonists (with different degrees of intrinsic activity), to neutral antagonists. Recently, it has been shown that many A_1 antagonists, e.g. DPCPX, exhibit inverse intrinsic activity, and thus may be characterized as inverse agonists rather than antagonists [11]. Xanthine derivatives labeled with positron emitters (e.g. ^{18}F, ^{11}C) for diagnostic positron emission tomography studies have been developed. These compounds may be useful diagnostics, e.g. for CNS and heart diseases, in which A_1 ARs are involved [12,13].

Besides rational methods of drug development (e.g. CADD, QSAR), combinatorial chemistry and high throughput screening methods are increasingly used for the discovery of novel lead compounds for the development of subtype-selective AR agonists and antagonists.

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