

DRUG DISCOVERY

A Pharmacological Characterization of Adenosine Receptors

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ABSTRACT

Adenosine receptors (AR) are member of the G-protein Coupled Receptors (GPCR) superfamily, with four subtypes currently recognised, A₁, A_{2A}, A_{2B} and A₃ receptors. Because of various potential physiological implications of stimulating AR, the main purpose of the present review was to briefly describe the pharmacological properties of these receptors and how they could be activated. Since these receptors are G-protein-coupled receptors, and so exert their effects by coupling to heterotrimeric G proteins, it is important to follow the G proteins functions and how they regulate the intracellular response of activated receptors, as well as their ability to couple to multiple second messenger signaling pathways. The responses to adenosine (ADO) are governed by the selective activation of distinct G proteins by AR subtypes. The A_{2A} and A_{2B} both couple via G_s to adenylyl cyclase (AC) stimulation (A_{2B} can also couple to G_q subtype), while the A₁ and A₃ are mainly coupled to G_i protein subtype to G_i to inhibit AC (although coupling via G_o and G_{q/11} respectively). A₁ and A_{2A} are considered high affinity receptors while A_{2B} and A₃ receptors are considered as low affinity receptors. Because of its potent actions on many organs and systems, adenosine is an obvious target for the development of new drugs.

Key words: Adenosine (ADO), Adenosine Receptors (AR), G protein coupled receptors (GPCR), AR subtypes.

Abbreviations: ADO - Adenosine; AR - Adenosine Receptors; GPCR - G protein coupled receptors; cAMP - Cyclic adenosine 3,5 monophosphate; CPA - N6-cyclopentyladenosine; MAPK - Mitogen activated protein kinase; PSVT - Paroxysmal supraventricular tachycardia; HEL - human erythroleukaemia.

1. BACKGROUND

The diversity in intracellular signalling downstream of adenosine receptors (AR) is dependent on the receptor subtype activated by adenosine (ADO). Under physiological conditions ADO is shown to be present extracellularly at concentrations that can stimulate both the higher affinity A₁ and A_{2A}. Under pathological conditions, ADO rises to concentrations that can also stimulate the lower affinity A_{2B} and A₃. Because AR are G-protein Coupled Receptors (GPCR), the conventionally-accepted mechanism is that, in their resting stage, G proteins exist as heterotrimers, with GDP bound to α subunit (Figure 1). Following the occupying of the receptor by an agonist molecule, a conformational change occurs, involving the cytoplasmic domain of the receptor, which causes the G protein to bind to it (Neves et al., 2002), as the $\alpha\beta\gamma$ trimer. Association of the $\alpha\beta\gamma$ trimer with receptor causes the bound GDP to be replaced with GTP which, in turn, causes dissociation of the G-protein trimer, releasing α -GTP and $\beta\gamma$ subunits; these are the

active form of the G-protein (Hamm, 1998), which diffuse in the membrane. Dissociation of these subunits mediates diverse physiological responses via their effect on certain types of intracellular target and influencing the cellular signalling events through the second messenger pathways (Figure 1). The α -subunit has intrinsic GTPase activity, which provides a self-limiting mechanism to G protein-mediated responses; once the GTP bound to the α subunit has been hydrolysed to GDP, the α subunit re-associates with $\beta\gamma$ subunits, thus completing the G protein cycle (Rang et al.2003).

2. SIGNAL TRANSDUCTION OF ADENOSINE RECEPTORS ACTIVATION

The A₁ and A₃ are mainly coupled to G_i protein subtype (although coupling via G_o and G_q respectively, have also been described) (Fredholm et al., 1994), while A_{2A} and A_{2B} can couple to G_s or to G_{q/r} subtype. As stated below

Receptor: A molecular structure or site on the surface or interior of a cell that binds with substances such as hormones, antigens, drugs, or neurotransmitters.

G protein coupled receptors (GPCR)

G-protein-coupled receptors (GPCRs) constitute a large and diverse family of proteins whose primary function is to transduce extracellular stimuli into intracellular signals. They are among the largest and most diverse protein families in mammalian genomes. On the basis of homology with rhodopsin, they are predicted to contain seven membrane-spanning helices, an extracellular N-terminus and an intracellular C-terminus. This gives rise to their other names, the 7-TM receptors or the heptahelical receptors. GPCRs transduce extracellular stimuli to give intracellular signals through interaction of their intracellular domains with heterotrimeric G proteins, and the crystal structure of one member of this group, bovine rhodopsin, has recently been solved. The presence of GPCRs in the genomes of bacteria, yeast, plants, nematodes and other invertebrate groups argues in favor of a relatively early evolutionary origin of this group of molecules. The diversity of GPCRs is dictated both by the multiplicity of stimuli to which they respond, as well as by the variety of intracellular signalling pathways they activate. These include light, neurotransmitters, odorants, biogenic amines, lipids, proteins, amino acids, hormones, nucleotides, chemokines and, undoubtedly, many others. In addition, there are at least 18 different human G α proteins to which GPCRs can be coupled. These G α proteins form heterotrimeric complexes with G β subunits, of which there are at least 5 types, and G γ subunits, of which there are at least 11 types.

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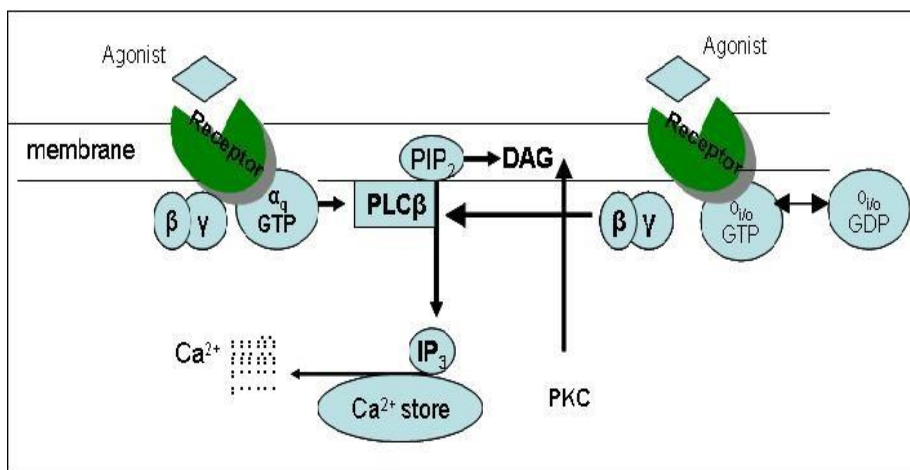


Figure 1

The conventional structure of GPCR with their coupling effectors. The adenosine receptors have seven transmembrane domains (α helices), and have the ability to couple to G proteins. The COOH is believed to be intracellular while NH₂ remains extracellular. The G protein consists of a trimer (α , β & γ), each of which has specific roles to activate its target effector, with α subunit being able to bind and switch between GTP and GDP. When the agonist binds to the receptor, the G protein replaces GDP with GTP and α subunit dissociates from $\beta\gamma$ dimer, and bind to effector (AC). Also activation of PLC β by adenosine receptors. Both G_q and G_{i/o} proteins regulate the function of PLC β . The G_q subunit of G_q activates PLC directly, whereas G _{$\beta\gamma$} subunits typically released from G_{i/o} also activate PLC. Hydrolysis of PIP₂ generates DAG and IP₃.

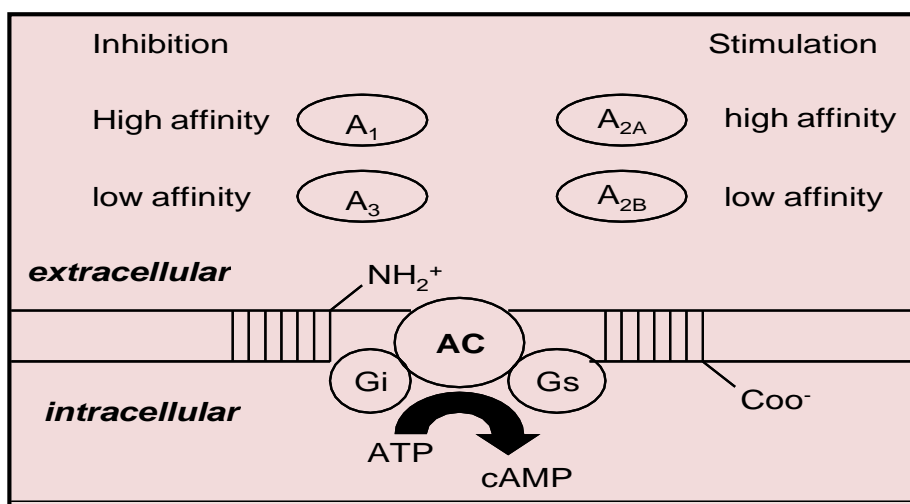


Figure 2

A summary of the adenosine receptor classification with indicated coupling and affinities. Among the four AR subtypes, the A₁- & A₃ are negatively coupled to AC via G_i and/or G_o while A_{2A}- & A_{2B} are positively coupled to AC via G_s. Consequently, the decrease or increase in cAMP levels leads to either inactivation or activation of protein kinase A (PKA), respectively (Hancock, 2005-9)

(Figure.2), A₁ and A_{2A} are considered high affinity receptors while A_{2B} and A₃ receptors are considered as low affinity receptors. It seems that A_{2B} and A₃ are much more active in pathophysiological events when extracellular ADO concentration rises above the normal concentrations. The most widely recognized primary signalling mechanism of A₁ receptors is inhibition of adenylcyclase (AC) causing a decrease in cyclic adenosine 3,5 monophosphate (cAMP) (Cooper et al., 1980). The other signalling pathways of A₁ receptors are activation of PLC resulting in an increase in IP₃, DAG and calcium mobilization (Megson et al., 1995). In addition, the A₁ receptors is coupled to activation of ATP-sensitive K⁺ channels (K_{ATP} channel) in guinea pig ventricular myocytes (Ito et al., 1994), and inhibition of calcium channels (Ca²⁺) has been described in dorsal root ganglion neurons (Sweeney & Dolphin, 1995), both of which inhibit neuronal activity. The protective effect of ADO during ischemia has been reported to be mediated primarily via the A₁ receptors (Matherne et al., 1997).

Conventionally A₃ receptors are coupled to G_i or G_o and also interact with G_{q11} subtypes of G protein (Palmer et al., 1995), and the classic second messenger system is inhibition of AC with a consequent decrease in cAMP accumulation (Figure 3). Other signalling pathways are also involved, including an increase in PLC (Abbraccio et al., 1995) and PLD activity (Ali et al., 1996), and the elevation of IP₃ levels, [Ca²⁺]_i and the activation of PKC. The A₃ receptors has also been shown to regulate chloride channels (Mitchell et al., 1999). Although the accepted signal cascade of both A_{2A} receptors (Olah, 1997) and A_{2B} receptors (Olah & Stiles, 1995) is to increase cAMP generation via a positive coupling to AC by G_s protein, there is increasing evidence to demonstrate that it is not the only second messenger pathway that can activated by these subtypes (Fredholm et al., 2000). In human endothelial cells, Mitogen activated protein kinase (MAPK) (eg ERK, SAPK) have been shown to be activated by A_{2A} receptors through a tyrosine kinase, which appears to play an important role in cell differentiation, proliferation and death (Sexl et al., 1997). The activation of PLC with stimulation of IP₃ levels and calcium elevation has been observed to be a further signal transduction pathway by which the A_{2B} receptors may evoke the cellular response. For instance, NECA was found to stimulate an increase in [Ca²⁺]_i and cAMP accumulation in the human mast cell HMC-1 cells (Linden et al., 1999). In human erythroleukaemia (HEL) cells, activation of A_{2B} receptors evoked a Ca²⁺ influx, apparently not related to PIP₂ hydrolysis (IP₃), but via a pertussis toxin-insensitive and cholera toxin-insensitive G protein coupling (G_s) (Feoktistov et al., 1994). In contrast, in human T lymphocytes, A_{2B} receptors activation by NECA results in cAMP generation, with no alteration in [Ca²⁺]_i (Mirabet et al., 1999). Similarly, in HEK293 cells transfected with A_{2A} receptors, CGS21680 (A_{2A} selective agonist) produced an increase in cAMP accumulation without changing [Ca²⁺]_i levels (Furlong et al., 1992).

2.1. MAPK Pathways Adenosine receptors

2.1.1. p42/p44 (ERK1/2) Cascade

Activation of the ERK1/2 (p42/44 MAPK) cascade pathway via adenosine receptors has been intensively studied in a variety of systems (Figure 4). For example, the selective A₁ agonist N6-cyclopentyladenosine (CPA) has been reported to increase MAP kinase activity in CHO-A1 cells (Dickenson et al., 1998).

CGS21680 has also been reported to stimulate MAP kinase activity in HEK293 and CHO cells transfected with A_{2A}AR (Seidel et al., 1999). The stimulation of endogenous A_{2B}ARs by NECA has also been suggested to evoke activation of ERK1/2 in HEK293 cells (Gao et al., 1999), and in HMC-1 (Feoktistov et al., 1999). CHO-A3 cells have also been reported to produce concentration-dependent increases in ERK1/2 MAPK in response to IB-MECA, an A₃ high affinity agonist (Graham et al., 2001). The diverse effects of ADO on mitogenesis, depending on the receptor subtype activated, may be related to changes in MAPK. For instance, all the human AR transfected into CHO cells are able to activate ERK1/2 at physiologically relevant concentrations of the endogenous agonist ADO as well as its analogue NECA (Schulte & Fredholm, 2000). Interestingly in this study, NECA acting on A_{2B} was much more potent in stimulating ERK1/2 phosphorylation (EC₅₀ = 19 nM) than cAMP formation (EC₅₀ = 1.4 μ M). While this report supports the accumulated evidence of activation of MAPK activation via all adenosine receptors, it was

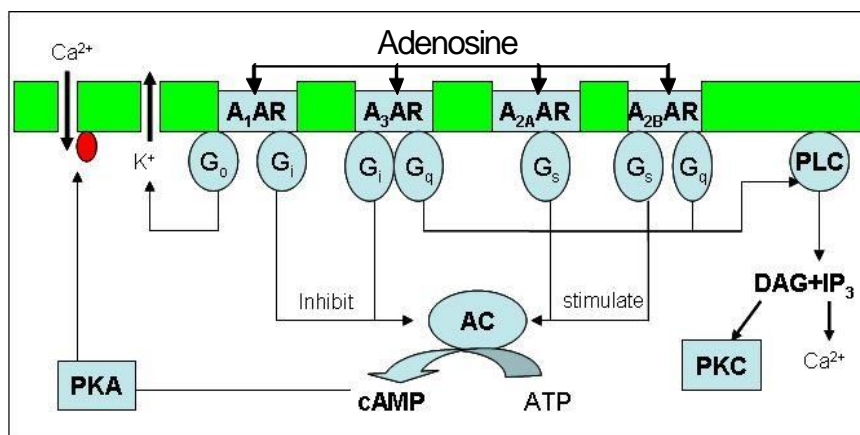


Figure 3

Signal transduction pathways associated with the activation of the human adenosine receptors. All AR are coupled to AC, A_{2A} & A_{2B} via G_s while A₁ & A₃ via G_i. Activation or inhibition of this pathway results in either increase or decrease of cAMP and subsequent stimulation or inhibition of PKA, respectively. A_{2B} & A₃ are also coupled to PLC via G_q. Activation of this pathway results in increase in DAG and IP₃. DAG stimulates PKC. IP₃ activates mobilization of calcium from intracellular stores. A_{2B} potentiate calcium influx directly by coupling with G_s, and via cAMP and activation of PKA. A₁ are also coupled via G_o to K⁺ channel.

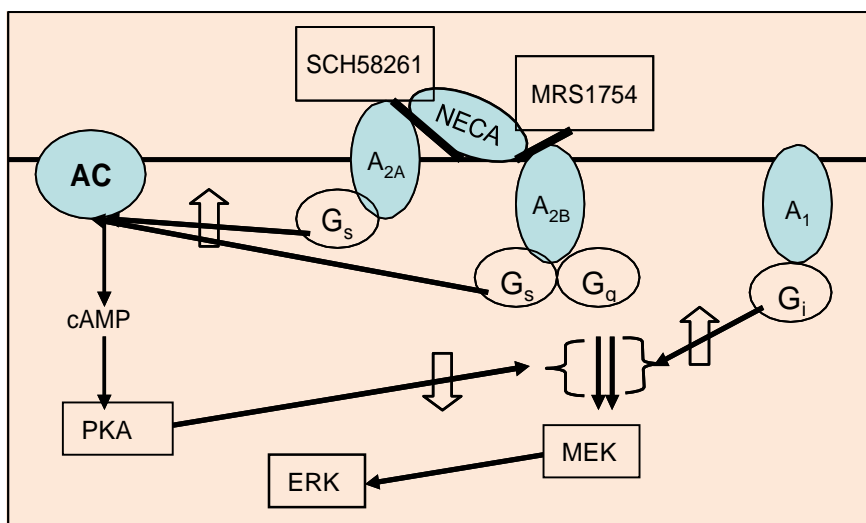


Figure 4

The ERK phosphorylation pathways via AR. It appears that involvement of the G_s-coupled A_{2A} in reduction of ERK phosphorylation via increase of AC and PKA activity ([can be blocked by either A_{2A} antagonist [SCH58261] or PKA inhibitor [H89]), while A_{2B} receptors enhance ERK activity (can be inhibited by A_{2B} antagonist [MRS1754] and MEK inhibitor [PD98059]).

conducted in transfected CHO cells and not cells with natively expressed receptors.

2.1.2 p38 & JNK (SAPK) Cascade

These pathways are activated by interleukin-1 (IL-1), tumor necrosis factor-α (TNF-α) and stress (heat) and is suggested to be involved in regulation of gene expression and cell differentiation (Seger & Krebs, 1995). Stimulation of A_{2B}AR via NECA has been reported to regulate the ERK, JNK and p38 MAPK signalling cascades in HMC-1 cells (Feoktistov et al., 1999) and p38 MAPK phosphorylation in porcine coronary smooth muscle (Teng et al., 2005). A₁ stimulation has also been shown to activate both ERK1/2 and p38 phosphorylation in DDT1MF-2 cells (Robinson & Dickenson, 2001), and p38 in pig myocardial stunning (Yoshimura et al., 2004).

3. ADENOSINE RECEPTOR AGONISTS

Because of various potential physiological implications of stimulating ARs, a large number of agonists have been

synthesized (Table 1); the vast majority of them are structurally related to the physiological agonist ADO. The classic non-selective adenosine receptor agonist NECA stimulates A_{2B}AR with low potency, 2 μM, but shows greater potency for other subtypes, high nanomolar (A₃) or low nanomolar (A₁ & A_{2A}) (Feoktistov & Biaggioni, 1997). Many A₁ agonists have been synthesized, with N⁶-substituted ADO derivatives being the most potent and selective, with K_i values in the range of 0.6 to 1.3 nM, which include N⁶-cyclopentyladenosine (CPA), N⁶-cyclohexyladenosine (CHA), and R-PIA (Jacobson et al., 1992). Both IB-MECA and its derivative 2CI-IB-MECA are considered as selective agonists for human A₃AR. 2CI-IB-MECA is considered as a highly selective agonist (K_i = 0.33 nM) for A₃AR, with 2500 and 1400 fold selectivity versus A₁ and A_{2A}AR, respectively (Kim et al., 1994).

The distinction between high-affinity A_{2A} and low-affinity A_{2B} mediated responses was confirmed by the introduction of the ADO analogue CGS21680, which binds with nanomolar affinity to A_{2A} (Jarvis et al., 1989) and does not bind to A_{2B} up to micromolar concentrations (Stehle et al., 1992). CGS21680 is also 180 fold selective towards A₁ (Jarvis et al., 1989) and is unable to displace binding to A₃ receptors at micromolar concentrations (Zhou et al., 1992). CGS21680 is therefore, considered to be a prototypical A_{2A} agonist, and is used pharmacologically to define the A_{2A} subtype. However, there is a problem using CGS21680 as an A_{2A} agonist & pharmacological tool, because it has been previously reported that it also binds to sites unrelated to A_{2A} (Johansson et al., 1993; Lindstrom et al., 1996). Highly selective and potent agonists have been designed for A₁, A_{2A} & A₃, however, no selective agonist has been found so far, and only non-selective agonists are available for A_{2B}, and NECA is currently the most potent agonist at this subtype, having low micromolar affinity (Alexander et al., 1996; Klotz et al., 1998). Because it is non-selective, therefore, it is less useful in the characterization of A_{2B} in cells or tissues in which A_{2A} are also expressed.

4. ADENOSINE RECEPTOR ANTAGONISTS

Potent and selective antagonists, xanthines & non-xanthines, have been developed for all the adenosine receptors. A₁ could be considered the best characterized subtype of the adenosine receptor family (Dhalla et al., 2003). The first selective A₁ antagonist DPCPX, which competitively antagonized both the inhibition of AC activity via A₁ and the stimulation via A_{2A} with K_i-values of 0.45 nM at the A₁AR in rat fat cells, and 330 nM at the A_{2A} in human platelets, shows a more than 700-fold A₁-selectivity (Lohse et al., 1987). DPCPX is a highly selective antagonist for A₁ versus A_{2A} (up to 500-fold) and 20-fold versus A_{2B} (Johansson et al., 2001). The non-xanthine AR antagonist CGS15943 was the first high-affinity A_{2A} antagonist described (Francis et al., 1988; Ghai et al., 1987), but it also interacts with appreciable affinity with A₁, A_{2B} & A₃ making it a high affinity non-selective AR antagonist (Kim et al., 1996; Kim et al., 1998). The non-xanthine A_{2A} antagonist SCH58261 (Lindstrom et al., 1996) was the first radioligand available for the characterization of the A_{2A} in platelets (Dionisotti et al., 1996). SCH58261 has been reported to be 50-fold A_{2A}/A₁ selective without appreciable affinity at A_{2B} or A₃ (Zocchi et al., 1996). SCH58261 has been reported to be ineffective on HEL cells (A_{2B}) up to a concentration of 100 nM, whereas it inhibited the CGS21680 activated cAMP accumulation in HMC-1 cells (A_{2A}) (Feoktistov & Biaggioni, 1997). It was also described as a potent and selective A_{2A} antagonist in human neutrophil membranes (Varani et al., 1998). Of particular interest for the current body of work, SCH58261 has been described to be useful in the discrimination of A_{2B} in cells also expressing A_{2A} receptors.

Table 1 Binding affinity of agonists and antagonists at human adenosine receptor subtypes (K_i values, nM), adapted and modified from (Fredholm et al. 2001)

	A ₁ AR	A _{2A} AR	A _{2B} AR	A ₃ AR
NECA	14	20	330	6.2
CGS21860	290	27	361,000	67
CGS15943	3.5	4.2	16	51
DPCPX	3.9	129	50	4,000
ZM241385	260	0.8	32	>10,000
SCH58261	290	0.6	-	>10,000
MRS1754	400	500	2	570
MRS1220	52	11	-	0.65

Table 2 Summarizes the diverse agonists and antagonists available for identification AR subtypes and their G-protein coupling

	A ₁ AR	A _{2A} AR	A _{2B} AR	A ₃ AR
	NECA			
universal Selective agonist	CPA, CHA CCPA, R-PIA	CGS21860, HE-NECA, CV1808, DPMA, APEC WRC-0470,	None currently available	2-CI-IB-MECA
G protein	G _{i/o}	G _s	G _{s/q/11}	G _{i/o/q/11}
Effect of G-protein coupling	↓ cAMP ↑ IP ₃ /DAG (PLC) ↑ Arachidonate (PLA2) ↑ Choline (PLD)	↑ cAMP ↑ ERK1/2	↑ cAMP ↑ IP ₃ /DAG ↑ ERK1/2 ↑ [Ca ²⁺] _i	↓ cAMP ↑ IP ₃ /DAG (PLC)
	CGS15943			
universal Selective antagonist	DPCPX, N0861 8cyclopentyl-theophylline	ZM241385, SCH58261, CSC, KF17387	MRS1754 MRS1706	MRS1220, F20, RS1067, MRE3008 MRS1191, MRS1097 MRS1523, L268605

Another non-xanthine derivative, ZM241385 (Alexander & Millns, 2001; Kelly et al., 2004) also has high affinity for A_{2A} (Poucher et al., 1995), and selectivity, which is up to 1000 fold and 90 fold versus A₁ & A_{2B}, respectively, and does not interfere with A₃AR (Keddie et al., 1996). However, [³H]ZM241385 has been reported as a radioligand to label recombinant human A_{2B} in HEK293, that do not express A_{2A}, with a K_d value of 33.6 nM (Ji & Jacobson, 1999). It displayed moderate affinity for A_{2B} (K_i 50 nM) in CHO_{A_{2B}} cells (Ongini et al., 1999) indicating usefulness as an A_{2A}/A_{2B} antagonist with moderate A_{2A} receptors selectivity. Much progress in this field could be achieved by the development of selective A_{2B} antagonists. Because of the low affinity of this receptor for agonists, the design of selective and potent A_{2B} antagonists seems to be more promising than the development of selective agonists. Over the last decades, various ADO antagonists have been introduced and modified in the search for A_{2B} antagonists. A high affinity A_{2B} antagonist is the xanthine derivative MRS1754 considered to be the most potent and selective human A_{2B}AR antagonist (Kim et al., 2000). Indeed, the tritiated form [³H]-MRS1754 was found to bind specifically to the human A_{2B}AR expressed in HEK-293 cells (Ji et al., 2001).

After discovering a significant role for the A₃ in cell cycle regulation and cell growth, generating a receptor antagonist for this subtype became a focus for medicinal chemistry research (Brambilla et al., 2000). A highly potent (0.65 nM) and selective human A₃AR antagonist MRS1220 was made possible by chemical modification of CGS15943 (Kim et al., 1996). The A₃ has very low affinity (high micromolar range) for the natural AR antagonists, caffeine and theophylline. However, MRS1220 showed affinity (subnanomolar range) at the human A₃ with 80- & 16-fold selectivity versus A₁ and A_{2A}, respectively (Baraldi et al., 2000).

5. ADENOSINE ACTION & THERAPEUTIC APPLICATIONS

As mentioned previously, the extracellular purine ADO is an important signaling molecule that mediates diverse biological effects, including neurotransmission, exocrine and endocrine secretion, smooth muscle contraction, pain, the immune response, inflammation, platelet aggregation, and modulation of cardiac function, via its receptors (Moro et al., 2006). It is evident that several characteristics of the AR subtypes are, at least in part, elucidated; although more research is necessary to better elucidate the pathophysiological role of these receptors. A series of selective agonists and antagonists are now known, which will greatly enable studies of the roles of these receptors in various diseases. In fact, over the past decade the research in this field has hugely expanded and it seems likely that more roles will be discovered in the future.

A large number of AR agonists and antagonists have been synthesized providing greater or lesser selectivity for

established AR (Table 2). If the selectivity of AR ligands can be improved; it might provide a new approach for treatment of many illnesses, and would also be helpful in limiting possible unwanted effects. Several such compounds are currently undergoing clinical trials for treatment of cardiovascular disorders, pain and diabetic foot ulcer, although the wide distribution and low density of some ARs, or low brain penetration, short half life and lack of effect of these compounds has led to problems. In the cardiovascular system, ADO acting at A₁ is being used successfully as a diagnostic tool and for reversing paroxysmal supraventricular tachycardia (PSVT). There is great attention on the development of A₁ & A₃ agonists for myocardial ischemia (Jacobson & Gao, 2006), while the recently-developed A_{2A} agonists Regadenoson (CVT3146) (Hendel et al., 2005), Binodenson (WRC-0470) (Barrett et al., 2005) and ALT-146e are being evaluated in clinical trials for coronary imaging and vasodilation (Jacobson & Gao 2006). The A₁ agonists, GW-493838 (Zambrowicz et al., 2003) and T-62 (Li et al., 2003) have entered clinical trials for treatment of migraine and neuropathic pain, respectively. The A_{2A} agonist MRE-0094 is in clinical trials for the treatment of chronic diabetic neuropathic foot ulcers (Jacobson & Gao 2006). In the nervous system, both theophylline and caffeine are well recognized central stimulatory drugs, indeed, most of their stimulant effects are thought to result from antagonism of AR. The role of theophylline and enprofylline in the treatment of asthma and neonatal dyspnea is likely to derive also from adenosine receptor, presumably A_{2B} receptor, antagonism (Feoktistov et al., 1998). Employing the antagonistic relationship between striatum dopamine D₂ & A_{2A} provides a new approach by using of A_{2A} antagonist, such as istradefylline (KW-6002) and V2006 (both in clinical trial), in the treatment of Parkinson's syndrome (Weiss et al., 2003). Another A₁ antagonist in clinical trial is BG9928, which is indicated to improve renal function and congestive heart failure (Auchampach et al., 2004).

6. CONCLUSION

Adenosine is an important regulatory metabolite that exerts diverse biological effects in neurons, although the problem in translating this knowledge into therapeutic potential is the nature of adenosine receptors, which widespread in whole body. Even if drugs were developed that could selectively target a receptor mediating a specific action, the problem remains of selectively targeting the receptor at the site of action. However, investigating the factors that could inhibit or induce adenosine receptor gene expression and function, together with regulating the synthesis, release, reuptake or degradation of the purine transmitter, is likely to expand our knowledge of the regulation of adenosine-evoked responses. In summary, it is evident that several characteristics of the AR subtypes are, at least in part, elucidated; although more research is necessary to better

Neurotransmitter:
A chemical in the brain that transmits messages between neurons, or nerve cells.

elucidate the pathophysiological role of these receptors. In fact, over the past decade the research in this field has hugely expanded and it seems likely that more roles will be discovered in the future.

SUMMARY OF RESEARCH

1. Adenosine receptors (AR) are member of the G-protein Coupled Receptors (GPCR) superfamily, with four subtypes currently recognised, A₁, A_{2A}, A_{2B} and A₃ receptors
2. The A_{2A} and A_{2B} both couple via G_s to adenylyl cyclase (AC) stimulation (A_{2B} can also couple to G_q subtype), while the A₁ and A₃ are mainly coupled to G_i protein subtype to G_i to inhibit AC (although coupling via G_o and G_{q/11} respectively)
3. A₁ and A_{2A} are considered high affinity receptors while A_{2B} and A₃ receptors are considered as low affinity receptors Because of its potent actions on many organs and systems, adenosine is an obvious target for the development of new drugs
4. AR play a role in multiple physiological functions and further studies necessary to elucidate further their pathophysiological role of these receptors

FUTURE ISSUES

More Research on Adenosine and Adenosine receptor will help will help understand their pathophysiological roles?

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Dhalla et al. (2003): Adenosine's diverse physiological functions are mediated by four subtypes of receptors (A(1), A(2A), A(2B) and A(3)). The A(1) adenosine receptor pharmacology and therapeutic application of ligands for this receptor are the subjects of this review. A(1) receptors are present on the surface of cells in organs throughout the body. Actions mediated by A(1) receptors include slowing of heart rate and AV nodal conduction, reduction of atrial contractility, attenuation of the stimulatory actions of catecholamines on beta-adrenergic receptors, reduction of lipolysis in adipose tissue, reduction of urine formation, and inhibition of neuronal activity. Although adenosine analogs with high efficacy, affinity, and selectivity for the A(1) receptor are available, the ubiquitous distribution and wide range of physiological actions mediated by A(1) receptors are obstacles to development of therapeutic agents that activate these receptors. However, it may be possible to exploit the high A(1) "receptor reserve" for some actions of adenosine by use of weak (partial) agonists to target these actions while avoiding others for which receptor reserve is low. The presence of high receptor reserves for the anti-arrhythmic and anti-lipolytic actions of adenosine suggests that partial A(1) agonists could be used as anti-arrhythmic and anti-lipolytic agents. In addition, allosteric enhancers of the binding of adenosine to A(1) receptors could be used therapeutically to potentiate desirable effects of endogenous adenosine. Antagonists of the A(1) receptor can increase urine formation, and because they do not decrease renal blood flow, are particularly useful to maintain glomerular filtration in patients having edema secondary to reduced cardiac function.

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RELATED RESOURCE

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