Therapeutic Potentials of Adenosine Receptors: The State of The Art

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The endogenous purine nucleoside adenosine is an integral component of ATP which regulates various pathophysiological functions of the body [1]. The synthesis of adenosine mainly depends on the metabolic conditions of a cell. In normal physiological conditions, the concentration of extracellular adenosine remains low (20-300 nM), whereas its concentration increases to micromolar levels (up to 30 μM) under various metabolic stress/demand such as exercise, hypoxia, inflammation, including various disease states like epilepsy and cancer among others [1, 2]. Earlier, adenosine was recognised as a hormone or secondary metabolite, but its ability to restore the imbalance between energy demand and availability under several pathophysiological conditions has earned it a new term “retaliatory metabolite” [3]. Adenosine also prevents ischaemic damage by preconditioning of cells and promotes anti-inflammatory response and angiogenesis [4].

In physiological conditions, adenosine is mainly produced intracellularly through the hydrolysis of adenosine monophosphate (AMP) and/or S-adenosyl-homocysteine (SAH) by endo-5′-nucleotidase and/or SAH hydrolase, respectively [5]. Extracellularly, adenosine is released with micromolar concentration by different types of cells under metabolic stress/demand through dephosphorylation of ATP, ADP and AMP by hydrolysing enzymes viz. ectonucleosidase triphosphate diphosphohydrolase (CD39) and ecto-5′-nucleotidase (CD73), respectively [6]. Transport of adenosine across the cell membrane takes place either via three isoforms of energy-dependent cation-linked (Na+) concentrative nucleoside transporters (CNTs 1-3) or by four isoforms of energy-independent equilibrative nucleoside transporters (ENTs 1-4). Normally the transport of adenosine takes place from extracellular to intracellular region, except during hypoxia where the flux is reversed [7-9]. Intracellularly, adenosine undergoes biotransformation either by phosphorylation to AMP via adenosine kinase (AK) and/ or deamination to inosine through adenosine deaminase (ADA). It should be noted that AK is the main mechanism of adenosine biotransformation under physiological conditions, while its clearance via ADA preferentially takes place under pathological conditions. Adenosine clearance from extracellular region mainly occurs either by ecto-ADA or influx through ENTs [10, 11].

![Diagram](Image)

**Fig. (1).** Overview of synthesis, biotransformation, and cellular transportation of adenosine including its signal transduction cascade by interaction with A₁, A₂A, A₂B and A₃ receptors.

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Adenosine exhibits a myriad of biological functions mainly by interacting with four G-protein coupled receptors (GPCRs) termed as A₁, A₂A, A₂B, and A₃ adenosine receptors (ARs) [12-14]. Among these four receptors, A₁, A₂A, and A₃ ARs have moderate to high affinity for adenosine (10 nM-1 μM), while A₂B AR shows low affinity and requires high concentration (10 μM) of adenosine for activation [13, 15]. Biological actions of A₁ and A₃ ARs are mainly mediated by inhibition of adenylyl cyclase (AC) activity followed by reduction of cyclic AMP (cAMP) and inhibition of protein kinase A (PKA). In contrast, A₂A and A₂B ARs mediated physiological actions are linked to the activation of AC activity followed by consequent increase of cAMP and protein kinase A (PKA) [1, 2, 16]. Stimulation of A₁, A₂B and A₃ ARs also activate phospholipase C (PLCβ) and Ca²⁺, while inducing mitogen activated protein kinases P38, ERK1/2 and JNK phosphorylation. Activation of A₁ AR facilitates both the opening and closing of K⁺ and Ca²⁺ channels, respectively [14]. An overview of synthesis, biotransformation, and cellular transportation of adenosine including its signal transduction cascade by interaction with A₁, A₂A, A₂B and A₃ receptors are presented in Fig. 1.

ARs are distributed ubiquitously throughout the body in the form of homomers, heteromers or oligomers, and are being investigated as potential drug targets in several pathological conditions for the treatment of various diseases [1, 17]. Extensive research efforts from pharmaceutical industries and academia lead to the design and discovery of numerous promising agonists/partial agonists, antagonists and allosteric modulators of ARs with wide spectrum of therapeutic applications [18-29]. However, only limited number of drugs targeting ARs could reach the market. This is mainly due to the complexity of signalling as well as ubiquitous distribution of ARs in both the healthy organs and in diseased tissues, which has imposed a great challenge to the researchers for the development of drugs with specific therapeutic action, while culminating side effects [16, 30]. Adenosine itself has been used for the treatment of paroxysmal supraventricular tachycardia (PSVT) as an A₁ AR agonist, including its use in myocardial perfusion imaging as an A₂A AR agonist. Istradefylline, the A₂A AR antagonist is available only in Japan for the treatment of Parkinson’s disease. A₁ AR antagonists: Theophylline, Dooxofylline and Bamifylline are available in the market for the treatment of asthma [1, 14]. A list of clinically available drugs targeting ARs for various therapeutic interventions is presented in Fig. 2.

![Adenosine, Theophylline, Dooxofylline, Bamifylline](image)

**Fig. (2).** Therapeutic applications and mechanism of action (MoA) of clinically approved drugs targeting adenosine receptors (ARs).

This thematic issue highlights the current state of the art in the development of potential agonists/partial agonists, antagonists and allosteric modulators of ARs in different stages of preclinical and clinical trials, mainly focusing on their essential roles in cancer, central nervous system (CNS) disorders, pain, inflammation, rheumatoid arthritis, and other autoimmune diseases. Borah et al., discussed the progress and probable future of P1 receptor ligands that are under clinical trials as promising novel therapeutic agents [31]. Choudhry et al., briefly highlighted the pathophysiological roles of adenosine on ARs in the modulation of different CNS disorders. In particular, modulation of A₁ and A₂A ARs has shown to affect different CNS disorders such as cognitive disorders, psychiatric diseases, and neurodegenerative diseases [32]. Gorain et al., and Pratap et al., discussed the biological mechanism of ARs in mediating various types of cancers and highlighted the progress in the development of both agonists and antagonists as potential anticancer chemotherapeutic agents. Authors further emphasised that A₂A and A₃ ARs are the most promising targets as compared to other subtypes for the cancer chemotherapy [33, 34]. Pal et al., shed light on the therapeutic potential of A₂A and A₃ ARs as promising targets for the treatment of rheumatoid arthritis (RA), as these two receptors have been found to be overexpressed in the inflammatory tissue and lymphocytes of RA patients. Molecules that are under development in various phases of clinical trials have been also discussed. In particular, A₁ AR agonists like CF502 and CF101 and A₂A AR agonists like CGS 21680 and LASSBio-1359 have been found to be promising for the treatment of RA [35]. Shakya et al., discussed the development of various new chemical entities targeting ARs for the treatment of diseases like inflammation, neuroinflammation, autoimmune and related disorders [36]. Finally, Jamwal et al., provided a summary of pharmacology and structure activity relationship (SAR) of various ARs ligands as potential therapeutic agents for the treatment of various diseases [37].

**Keywords:** Adenosine A₁, A₂A, A₂B and A₃ receptors, agonists, partial agonists, allosteric modulators, antagonists.
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