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ADENOSINE RECEPTOR: A REVIEW ON THE STATE OF THE ART IN PHARMACOLOGY

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Abstract

Adenosine is a ubiquitous endogenous autacoid whose goods are touched off through the registration of four G proteincoupled receptors A1, A2A, A2B, and A3. Due to the rapid-fire generation of adenosine from cellular metabolism, and the wide distribution of its receptor subtypes in nearly all organs and apkins, this nucleoside induces a multitude of physiopathological goods, regulating central nervous, cardiovascular, supplemental, and vulnerable systems. It's getting clear that the expression patterns of adenosine receptors vary among cell types, advancing weight to the idea that they may be both labels of pathologies and useful targets for new medicines. This review offers an overview of current knowledge on adenosine receptors, molecular relations and cellular functions, distribution, physiology and signal transduction. Eventually, we punctuate the rearmost findings on motes able of targeting adenosine receptors and report which stage of medicine development they've reached.

Keywords Adenosine receptors, inflammation, CNS, Signal transduction.

Introduction

The first substantiation of a part for adenosine in cellular physiology dates back to 1927, when the presence of an adenine emulsion suitable to decelerate the heart meter and rate was discovered in excerpts from cardiac apkins. Fifty times Latterly, this finding led to the preface of adenosine in the opinion and treatment of supraventricular tachycardia. Since also, scientists from different areas — gauging physiology, biochemistry, pharmacology, chemistry and immunology — have been fastening their sweats on probing adenosine's numerous places in health and complaint, thereby generating a new field of exploration [1,2,3].

Adenosine receptors(ARs) are G protein- coupled receptors(GPCRs) that smell an imbalance of demand and force of energy/ oxygen/ nutrients. Extracellular adenosine attention rise in response to hypoxia and other stress, to act upon four subtypes of ARs(A1AR, A2AAR, A2BAR, and A3AR). As shown with mice lacking all four AR subtypes, extracellular adenosine is substantially a detector of towel damage or peril, rather than a homeostatic controller under birth conditions. Elevated adenosine can correct an energy imbalance during torture of an organ, for illustration by decelerating the heart rate by A1AR activation or adding the blood force to heart muscle by the A2AAR [4,5]. Still, there are conditions in which habitual adenosine overproduction

can be dangerous, leading to increased inflammation, fibrosis, cytokine release, brain dopamine reduction, and order damage. also, exogenous AR agonists, antagonists, or allosteric modulators can be applied for remedial benefit, and thousands of similar agents have been reported by medicinal druggists working toward that thing [7,8]. Clinically important goods of adenosine also include repression of the vulnerable response, glomerular filtration, seizures and pain. Adenosine 50- triphosphate are released outof the cells under stress conditions or damage is the source of important of the extracellular adenosine. There's generally a rudimentary position of AR stimulation, that is for A1AR, A2AAR and A3AR at minimum nM attention, while A2BAR activation generally occurs at advanced (mM) adenosine attention. thus, AR antagonists have distinct natural goods in vivo. Purinergic signaling is also to be considered in the larger environment of ligand (ATP)-reopened P2X receptors or G protein- coupled P2Y receptors that respond to extracellular mono- and di-nucleotides [9,10,11].

The endogenous purine nucleoside adenosine is an integral element of ATP which regulates colorful pathophysiological functions of the body. The conflation of adenosine substantially depends on the metabolic conditions of a cell. In normal physiological conditions, the attention of extracellular adenosine remains low(20- 300 nM), whereas its attention increases to micromolar situations(up to 30 μM) under colorful metabolic stress/ demand similar as exercise, hypoxia, inflammation, including colorful complaint countries like epilepsy and cancer among others. before, adenosine was recognised as a hormone or secondary metabolite, but its capability to restore the imbalance between energy
demand and vacuity under several pathophysiological conditions has earned it a new term " retaliatory metabolite ". Adenosine also prevents ischaemic damage by preconditioning of cells and promotesanti-inflammatory response and angiogenesis [12,13,14].

Adenosine: Origin and Metabolism

In 1981, when excreted adenosine was linked as a cell density signal suitable to induce the conformation of regenerating bodies, following starvation, in the bacterium Myxococcus xanthus. latterly, its product was linked to energy metabolism, thanks to physiological substantiation of an increase of adenosine in leukocytes and heart cells during ATP catabolism. Indeed, adenosine has been observed to play a " coadjutor " part in the protection of working cells, like neurons and cardiomyocytes, against stressful conditions by enabling them to acclimate their energy input and acclimatize their exertion to reduce ATP demand. This effect is substantially brought about by reducing energy- consuming Conditioning, similar as the heart inotropic effect, and by adding nutrients oxygen support through vasodilation. This rebutted the being thesis of its origin as a alternate runner from the cAMP pathway, and latterly urged the preface of the term " retaliatory metabolite " to describe this useful nucleoside. Under normal physiological conditions, extracellular adenosine situations are in the range of 20 and 300 nM, rising to a low level micromolar range under extreme physiological situations like ferocious exercise or low atmospheric oxygen situations(e.g., at high altitude) — and high

micromolar situations(30 M) in pathological conditions similar as ischemia [15,16].

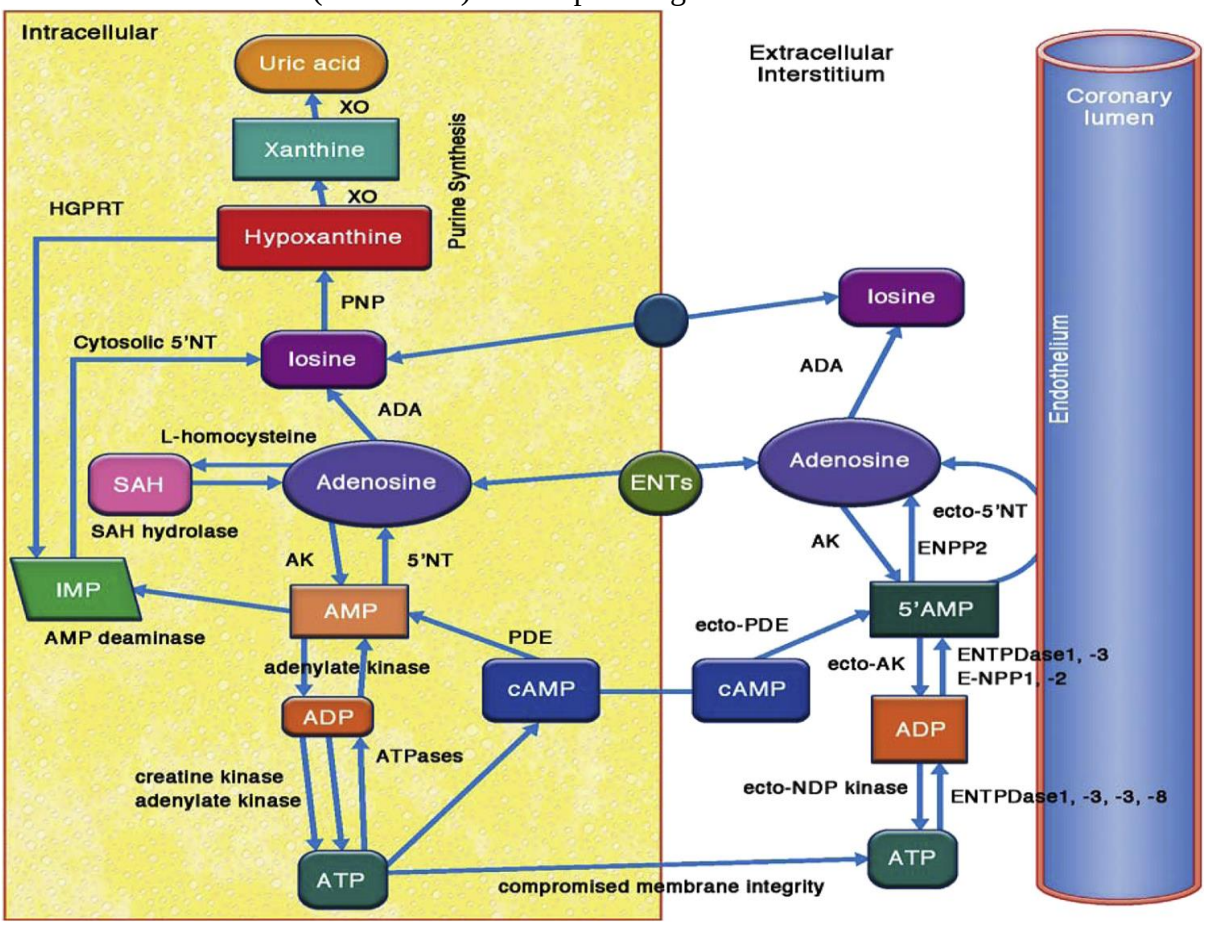


Figure 1. The Metabolism of Adenosine Schematic diagram to represent the intracellular and extracellular metabolism of adenosine. ADA ¼ adenosine deaminase (deamination); ADP ¼ adenosine 50- diphosphate; AK ¼ adenosine kinase (phosphorylation); AMP ¼ adenosine 50-monophosphate; ATP ¼ adenosine 50-triphosphate; cAMP ¼ cyclic adenosine 30,50- monophosphate; ENPP2 ¼ ecto-nucleotide pyrophosphatase/phosphodiesterase; ENTPDase ¼ ecto-nucleoside triphosphate diphosphohydrolase; ENTs ¼ equilibrative nucleoside transporters; HGPRT ¼ hypoxanthine phosphoribosyl transferase; IMP ¼ inosine 50-monophosphate; NDP ¼ nucleoside diphosphate; 50-NT ¼ 50-nucleotidase (dephosphorylation); PDE ¼ phosphodiesterase; PNP ¼ purine nucleoside phosphorylase; SAH ¼ S-adenosylhomocysteine; XO ¼ xanthine oxidase.

The top medium responsible for the extracellular production of adenosine is dephosphorylation of precursor realities ATP, ADP, and AMP. These are released by cell types under stressful circumstance via specific hydrolyzing enzymes nominated ectonucleoside triphosphate diphosphohydrolase (CD39) with the ecto- 5 = - nucleotidase CD73), without which nucleotide attention would be fairly stable. still, under physiological conditions, adenosine is basically began intracellularly, from hydrolysis of AMP and S-adenosylhomocysteine SAH) via the endo- 5 = - nucleotidase, with the SAH hydrolase, independently [17,18]. Once generated, extracellular adenosine is captured at the intracellular position via the SLC28 family of cation- linked concentrative nucleoside transporters(CNTs) and the SLC29 family of energy-independent, equilibrative ENTs, this makes free passage of adenosine across the cell membrane. The direction of adenosine release from cells is stated by the attention difference across the membrane. The part of ENTs in this transfer is tough than that of CNTs. Indeed, the four isoforms of ENT transport nucleosides into or out of cell membranes on the base of adenosine attention, while the three isoforms of CNT(1 – 3) grease adenosine affluence against a attention grade, using the sodium ion Grade as a source of energy. typically the flux is from extracellular to intracellular terrain, while during hypoxia, it is reversed, as nicely reported [19,20,21].

Distribution, Physiological effects and Signal Transduction

ARs are setup throughout the nervous, cardiovascular, respiratory, gastrointestinal, urogenital, and vulnerable systems as well as in bone, joints, eyes, and skin — a pattern of distribution that denotes their significant control of neuronal, cardiac, metabolic, and renal conditioning. Each AR is characterized by unique cell and distribution, secondary signaling transductors, and physiological goods. A1AR and A3AR signals are intermediated through Gi and Go members of the G protein family, through which they reduce AC exertion and cAMP situations, while A2AARs and

A2BARs are coupled to Gs proteins, through which they stimulate AC and increase cAMP situations, thereby leading to the activation of a plethora of intercerors, depending on the signaling sent by cAMP in specific cells [22,23].

A. A1AR and A3AR Gi and Go-Coupled Receptors

The A1AR subtype is present in the central nervous system CNS), substantially in the brain cortex, cerebellum, hippocampus, autonomic whim-whams outstations, spinal cord, and glial cells. This broad distribution reflects the wide range of physiological functions regulated by A1AR, gauging neurotransmitter release, dampening of neuronal excitability, control of sleep/ insomnia, pain reduction, as well as opiate, anticonvulsant, anxiolytic, and locomotor depressant goods [24,25]. This subtype is also present at high situations in the heart gallerias, order, adipose towel, and pancreas, where it stimulates negative chronotropic, inotropic, and dromotropic goods, reduces renal blood inflow and renin release, and inhibits lipolysis and insulin stashing, independently. It is also present on airway epithelial and smooth muscle cells, where it stimulates a bronchoconstrictor effect, and in several vulnerable cells similar as neutrophils, eosinophils, macrophages, and monocytes, where it promotes basically proinflammatory goods [26,27].

A1AR also induces phospholipase C(PLC)- activation, thereby adding inositol- trisphosphate(IP3) and intracellular Ca2 situations, which stimulate calcium-dependent protein kinases(PKC). At the neuronal and myocardial position, A1AR stimulates potassium (K) pertussis poison-sensitive and KATP channels, while reducing Q-, P-, and N- type Ca2 channels. likewise, the involvement of A1AR in the intracellular phosphorylate waterfall of the mitogen- actuated protein kinase (MAPK) family — including extracellular signal has been reported. Pharmacological agents that increase the activation of A1AR would be useful for the treatment of CNS, cardiovascular, and seditious pathologies. A1AR debit goods, due to their wide distribution, broad diapason of physiological goods, and miscellaneous signaling pathway transduction, can fortunately be eased through allosteric enhancers, which stabilize the complex formed by agonist- A1AR- G protein motes. This enhances the agonist action only at the point affected by injury, where adenosine attention is increased [28,29,30].

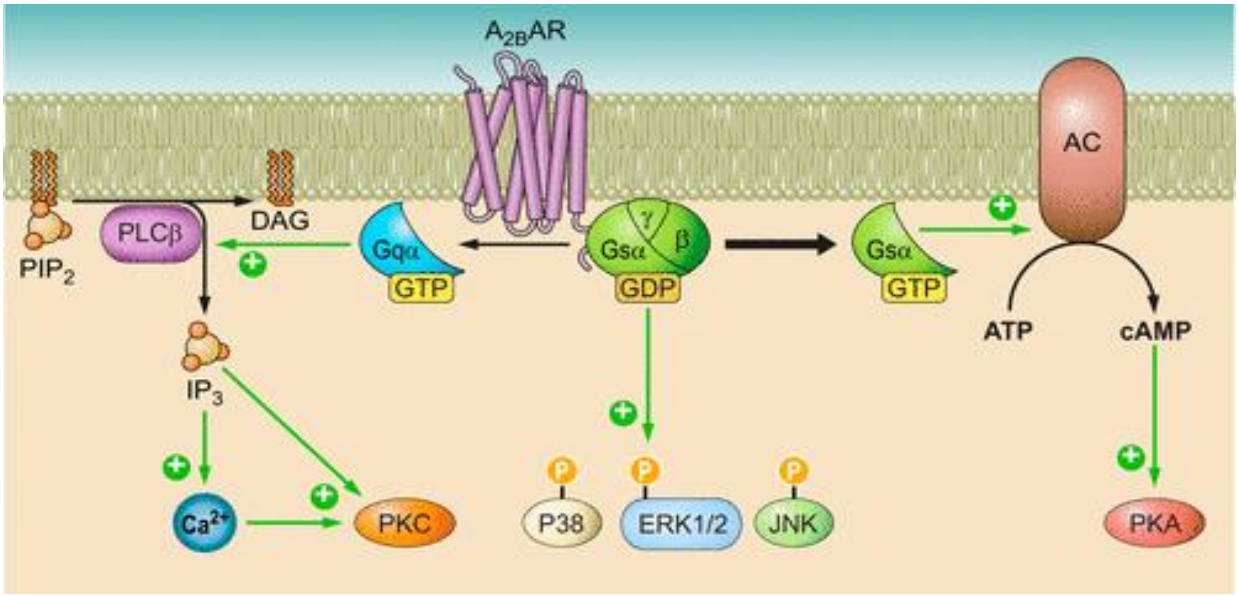


Figure: Overview of A1AR intracellular signaling pathways.

A3ARs spark a variety of intracellular signaling by preferentially coupling to Gi proteins, by which they reduce cAMP situations, and, at high attention of A3AR agonists, to Gq proteins or G subunits, thereby converting an increase in both PLC and calcium. A reduction in cAMP results in PKA inhibition, which leads to rise in glycogen synthase kinase- 3(GSK- 3); downregulation of beta- catenin, cyclin D1; and reduction of nuclear factor(NF)- B DNA- binding capability. Another pathway from GPCR signaling — including monomeric G protein RhoA and phospholipase D is important for A3AR- intermediated neuro- and cardio protection. A3ARs are also known to regulate MAPK, PI3K/ Akt, and NF- B signaling pathways, by which they plyanti-inflammatory goods. Stimulation or inhibition of HIF- 1 has been also observed to have protumoral and neuromodulator goods in cancer cells and astrocytes, independently [31].

B. A2AAR and A2BAR Gs-Coupled Receptors

The A2AAR subtype occurs in the centrally as well as peripherally, but its topmost expression is in the striatum, the olfactory excrescence, and the vulnerable system, while lower situations are found in the cerebral cortex, hippocampus, heart, lung, and blood vessels. A2AAR is expressed on both preened postsynaptic neurons — astrocytes, microglia, and oligodendrocytes where it orchestrates a number of functions affiliated to excitotoxicity, gauging neuronal glutamate release, glial reactivity, blood- brain hedge(BBB) permeability, and supplemental vulnerable cell migration. In the supplemental vulnerable system, A2AARs are particularly greatly expressed in leukocytes, platelets, and the vasculature, where they intervene multitudinous- inflammatory, antiaggregatory, and vasodilatory goods, independently [32,33].

The A2BAR is greatly expressed basically in the fringe, where they're set up in the bowel, bladder, lung, vas deferens, and different cell types including fibroblasts, smooth muscle, endothelial, vulnerable, alveolar epithelial, chromaffin, taste cells, and platelets. At the central position they are set up in astrocytes, neurons, and microglia, and adding substantiation indicates a part for this subtype in the modulation of inflammation and vulnerable responses in named pathologies like cancer, diabetes, as well as renal, lung, and vascular conditions. This contrasts preliminarily held hypotheticals attributing poor physiological applicability to A2BAR, due to its low affinity for adenosine in comparison with the other ARs. In support of a pathological part for A2BAR, its expression is upregulated in different pernicious conditions similar as hypoxia, inflammation, and cell stress. In fact, a hypoxia- responsive region, which includes a functional list point for hypoxia- inducible factor (HIF), has been detected within the A2BAR protagonist, explaining its transcriptional regulation from HIF- 1, the master controller of cellular responses to hypoxia [34,35,36].

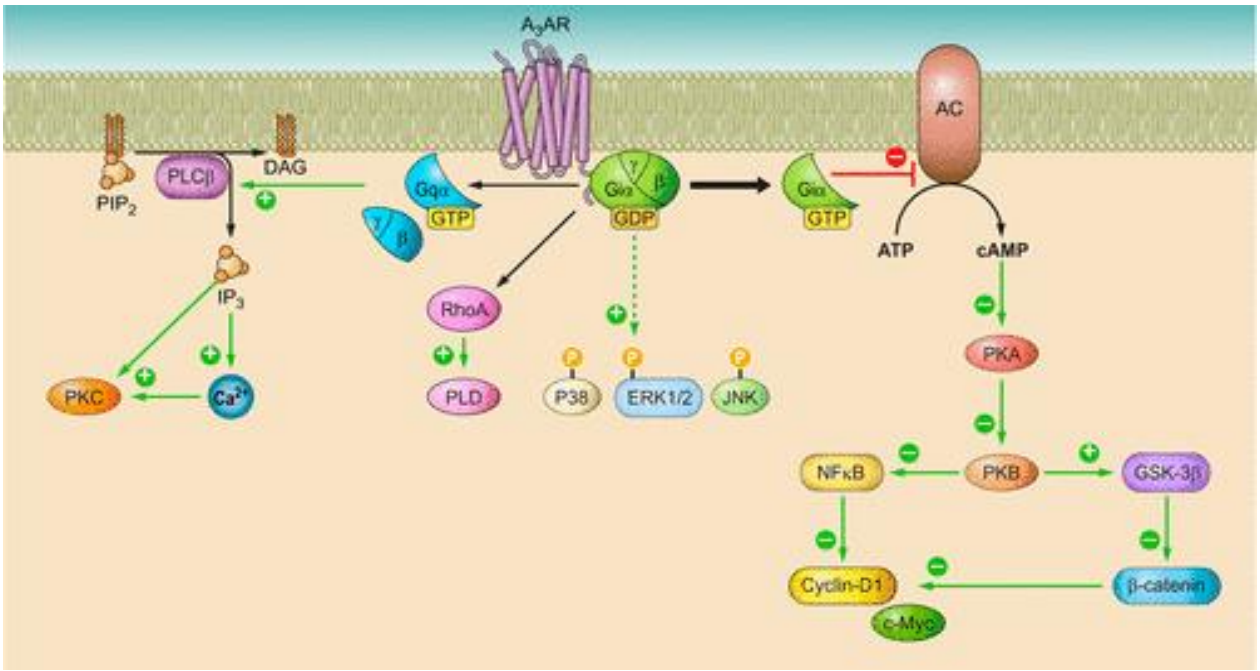


Figure: Overview of A2AAR intracellular signaling pathways.

A2BAR signaling pathways involve AC activation through Gs proteins, leading to PKA phosphorylation and registration of different cAMP-dependent effectors like exchange proteins, which are directly actuated by cAMP(Epac). Interestingly, a part for A2BARs in enhancing gap junction coupling through the cAMP pathway has been observed in cerebral microvascular endothelial cells. In addition, A2BARs can stimulate PLC through the Gq protein, performing in Ca2 rallying, and can regulate ion channels through their subunits. also, this subtype acts as precursor of MAPK activation in several cell models in both central and supplemental systems [37].

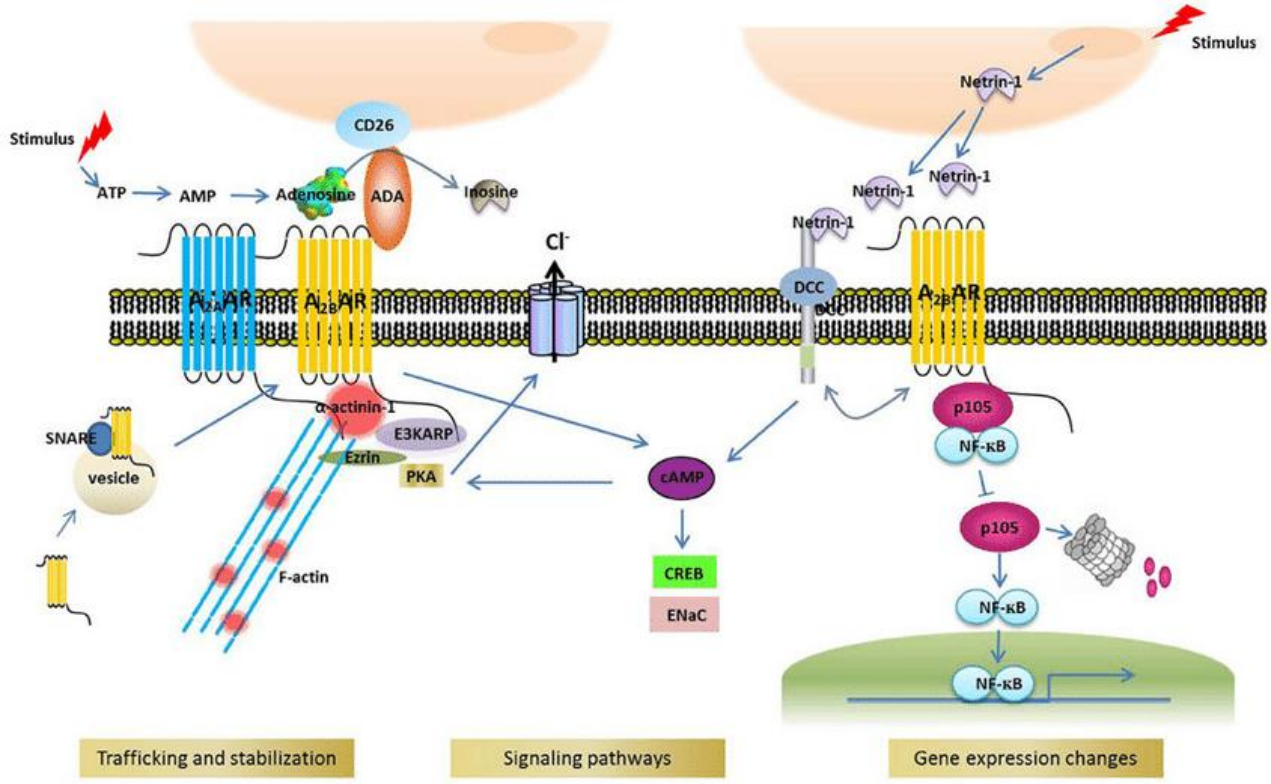
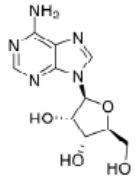


Figure: Overview of A2BAR intracellular signaling pathways.

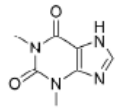
In addition, A2BARs have multiple binding mates that modulate A2BAR responses and functions; these include netrin- 1, E3KARPP- EZRIN- PKA, SNARE, NF- B1/ P105, and- actinin- 1. Netrin- 1, the neuronal guidance Patch, convinced during hypoxia, reduces inflammation by cranking A2BAR, which inhibit neutrophils migration. SNARE protein interacting with A2BAR, substantially that located inside the cell, recruits the receptor to the tube membrane following agonist list. After this commerce, a multiprotein complex with E3KARP(NHERF2) and ezrin stabilizes A2BAR in the tube membrane. Interestingly, list of A2BAR to P105 inhibits NF- B exertion, thereby explaining its anti-inflammatory goods. likewise,- actinin- might favor A2AAR and A2BAR dimerization, therefore converting A2BAR expression on the cell face [38-41].

Therapeutic Potentials

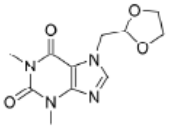
ARs are distributed nowhere throughout the body in the form of homomers, heteromers or oligomers, and are being delved as implicit medicine targets in several pathological conditions for the treatment of colorful conditions. expansive exploration sweats from pharmaceutical diligence and academia lead to the design and discovery of multitudinous promising agonists partial agonists, antagonists and allosteric modulators of ARs with wide diapason of remedial operations. still, only limited number of medicines targeting ARs could reach the request [42,43]. This is substantially due to the complexity of signaling as well as ubiquitous distribution of ARs in both the healthy organs and in diseased apkins, which has assessed a great challenge to the experimenters for the development of medicines with specific remedial action, while climaxing side goods. Adenosine itself has been used for the treatment of ferocious 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 complaint. The A1 AR antagonists like Theophylline, Doxofylline and Bamifylline are available in the request for the treatment of asthma. A list of clinically available medicines targeting ARs for colorful remedial interventions is presented [44,45].



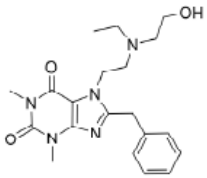
Name: Adenosine
1. MoA: A_1 AR agonist
Application: Paroxysmal supraventricular tachycardia (PSVT)
2. MoA: A_{2A} AR agonist
Application: Myocardial perfusion imaging



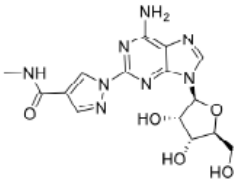
Name: Theophylline
MoA: A_1 AR antagonist
Application: Asthma



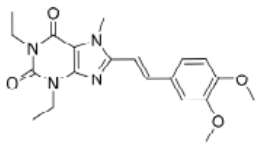
Name: Doxofylline
MoA: A_1 AR antagonist
Application: Asthma



Name: Bamifylline
MoA: A_1 AR antagonist
Application: Asthma



Name: Regadenoson
MoA: A_{2A} AR agonist
Application: Myocardial perfusion imaging



Name: Istradefylline
MoA: A_{2A} AR antagonist
Application: Parkinson's disease

This thematic issue highlights the current state of the art in the development of implicit agonists partial agonists, antagonists and allosteric modulators of ARs in different stages of preclinical and clinical trials, substantially fastening on their essential places in cancer, central nervous system(CNS) diseases, pain, inflammation, rheumatoid arthritis, and other autoimmune conditions [46]. Borah etal., bandied the progress and probable future of P1 receptor ligands that are under clinical trials as promising new remedial agents. Choudhry etal., compactly stressed the pathophysiological places of adenosine on ARs in the modulation of different CNS diseases. In particular, modulation of A1 and A2A ARs has shown to affect different CNS diseases similar as cognitive diseases, psychiatric conditions, and neurodegenerative conditions [47]. Gorain etal., and Pratap etal., bandied the natural medium of ARs in interceding colorful types of cancers and stressed the progress in the development of both agonists and antagonists as implicit anticancer chemotherapeutic agents. Authors further emphasized that A2A and A3 ARs are the most promising targets as compared to other subtypes for the cancer chemotherapy. Pal etal., exfoliate light on the remedial eventuality of A2A and A3 ARs as promising targets for the treatment of rheumatoid arthritis(RA), as these two receptors have been set up to be overexpressed in the seditious towel and lymphocytes of RA cases. motes that are under development in colorful phases of clinical trials have been also bandied. Particularly A3 AR agonists like CF502,CF101 and A2A AR agonists like CGS 21680 and LASS Bio- 1359 have been set up to be promising for the treatment of RA. Shakya etal., bandied the development of colorful new chemical realities targeting ARs for the treatment of conditions like Inflammation, neuroinflammation, autoimmune and affiliated diseases [48,49,50].

Conclusion

Adenosine is an endogenous modulator with several implicit remedial operations, due to its ubiquitous presence and capability to interact with major physiological processes. In the CNS, for illustration, activation of A1ARs could be Salutary in different pathologies similar as epilepsy and acute, habitual, and neuropathic pain. likewise, although data regarding the part of A3ARs in cerebral ischemia, the inhibitory effect of A1ARs on glutamate release is abecedarian for protection from ischemic damage. also, A2AAR antagonists are promising remedial agents for PD, due to their commerce with D2R. Istradefylline has been accepted in combination with levodopa and is accessible in Japan. Other remedial targets for A2AAR in the CNS include announcement, HD, epilepsy, acute and habitual stress, and sweat memory. Interestingly, caffeine, the most extensively medicine used in the world, seems to be defensive in a number of neurological and psychiatric pathologies that involve ARs. In the cardiovascular system, otherwise adenosine via A1ARs is formerly commercially available as Adenocard, a remedial agent for supraventricular tachycardia. Partial agonists of A1ARs are also witnessing clinical trials prepared to access their cardioprotective action and lack of side

goods. As of A2AARs, they are involved in vasodilation, through their expression in smooth muscle and endothelial cells, while A2BARs and A3ARs have remedial implicit in the heart, for cardiac fibrosis and infarct, independently. In addition, substantiation from several sources indicates that adenosine and its receptors are targets for cancer remedy. In particular, A2AAR antagonists may represent a new approach to adding the vulnerable response against Excrescences by neutralizing adenosine- intermediated immunosuppression, especially in hypoxic conditions, in which the attention of adenosine rises dramatically**.**

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