Adenosine: Newer Therapeutic Perspectives.

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ABSTRACT

Adenosine receptors are major targets. There is growing evidence that they could also be appropriate targets in a wide range of conditions, including cerebral and cardiac ischaemic diseases, sleep disorders, immune disorders and cancer. After more than three decades of medicinal chemistry research, a considerable number of selective agonists and antagonists of adenosine receptors have been discovered, and some have been clinically evaluated, although none has yet received regulatory approval. Discussed in this review article are the therapeutic application of adenosine receptor modulators.

Keywords: adenosine, receptor modulators, disorders

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INTRODUCTION

The simplest of the purines, adenosine, first recognised by Albert Szent Györgyu in (1929) as a Physiologic regulator of coronary vascular tone, is an endogenous nucleoside composed of adenosine attached to a ribose molecule. It is found in biological fluids throughout the body and exists free in the cytosol of all cells and is transported in and out mainly by a membrane transporter. Adenosine is a metabolite of adenosine triphosphate (ATP), having a very short half-life of 1.5 sec due to its rapid metabolism. Both adenosine and ATP act as transmitters or modulators in CNS but their mapping is difficult, because purinergic neurons are not identifiable histochemically. Adenosine metabolism serves mainly as a safety mechanism and is known to increase dramatically under metabolically stressful conditions. Adenosine plays a vital role in modulation and protection of nervous system, cardiac system and homeostatic mechanisms. Adenosine is an intermediate metabolite in many biochemical pathways and has been shown to play a role in the regulation of coronary and systemic vascular tone, platelet function and lipolysis in adipocytes. In addition, it mediates other important functions like induction of sleep, antioxidant and antiseizure effects, neuroprotection etc [1-5].

Adenosine Metabolism and Release

It exists free in the cytosol of all cells and is transported in and out mainly by a membrane transporter. Little is known about the way in which this is controlled but the extracellular concentrations are usually quite low compared with intracellular levels. Adenosine in tissues comes partly from this intracellular source and partly from extracellular hydrolysis of released ATP or ADP. ATP is packaged into vesicles and released by exocytosis, as a conventional transmitter. It can also leak out of cells, in large amounts, in condition of tissue damage. In high concentrations, ATP itself acts as an excitotoxin (like glutamate), and produces further neuronal damage. In such cases of tissue damage, ATP undergoes hydrolysis and rapidly converted to Adenosine by Adenosine kinase. Adenosine produced intracellularly from ATP, is not packaged into vesicles and is released mainly by carrier mediated transport. Adenosine serves mainly as a safety mechanism, protecting neurons from damage, ishaemia or seizure activity.

After intracellular reuptake, Adenosine undergoes rapid phosphorylation to AMP by Adenosine kinase or deamination to inosine by Adenosine deaminase.

Adenosine Receptors

Adenosine exerts its effects via purinergic receptors which are A1, A2 (A2a, A2b), A3. They are seven spanning proteins, coupled to various G-proteins, coupled to inhibition or stimulation of adenylyl cyclase. A1 and A3 receptors stimulate, while A2 receptors are inhibitory in action. The overall effects of Adenosine are inhibitory.

A1 Receptors

- Most abundant adenosine receptor.
- A1 receptors acts through the inhibition of adenylate cyclase.
- It also inhibit G-protein-coupled activation.
- Mainly present in brain (hippocampus, neocortex, cerebellum), dorsal horn of spinal cord, adipose tissue, heart muscle, kidney, liver, pancreas, eye.
- The effects of A1 receptors are inhibitory in action leading to sedation, motor incoordination, drowsiness, cerebral vasodilatation, anticonvulsant action.

A2 Receptors

- Widely distributed than A1 receptors.
- These receptors acts through the activation of adenylate cyclase resulting in the elevation of intracellular cAMP.

Divided into: 1) A2a 2) A2B.
A2A Adenosine Receptors

- are mainly present in striate neurons, pre and post synaptic nerve terminals, mast cells, airway smooth muscles, circulating leukocytes, and olfactory tubercle and their stimulation is anti-inflammatory in action.
- Hence these receptors are used to sense excessive tissue inflammation, enhance neural communication, promote coronary vasodilatation, and have anti-platelet effects.
- CNS effects may be favourable in patients with Huntington’s chorea, and agonists may also inhibit psychosis.
- A2A agonists cause profound vasodilatation, with a corresponding increase in plasma renin activity.

A2B Adenosine Receptors

- Similar to A2A but not identical.
- Perhaps the most poorly characterised of the adenosine receptors.
- Acts by inhibiting the formation of cAMP.
- A2B is found on the human mast cell - this may be particularly relevant to the management of asthma, caecum, colon, bladder, lung, mast cells.
- Like A2A receptors, A2B promote vasodilatation.

A3 Adenosine Receptors

- Key receptor in both stimulation and inhibition of cell growth (stimulates many normal cells in micromolar concentrations)
- Induces apoptosis at higher concentrations in both normal and tumour cells.
- Low concentrations have antiproliferative effects on tumour cells.
- A3 receptors are mainly present in normal and tumour cells, testis, thyroid, cerebellum and hippocampus.
- Acts by the stimulation of cAMP.
- Main action of A3 receptor is bronchoconstriction.

Newer Therapeutic Aspects of Adenosine and Its Receptors

Cardiovascular System – Adenosine is the drug of choice for AV nodal re-entrant tachycardia due to the inhibitory effect of adenosine on the AV node. A1 receptors are responsible for the important process of “pre-conditioning”.

Ischemia/reperfusion (I/R) Injury - Interstitial adenosine concentration doubles after five min of cardiac ischemia. Adenosine antagonists reduce the effect of cardiac IPC. Adenoreceptor stimulation reduces myocardial damage following ischemia/reperfusion and during cardiopulmonary bypass. Adenosine may attenuate ischemia/reperfusion injury by a number of possible mechanisms, including purine salvaging, improved tissue perfusion, anti-inflammatory action and a direct intracellular initiator/effect mechanism.

Refractory primary pulmonary hypertension (RPPH) - In RPPH, pulmonary vasodilation is achieved by two known pathways. Nitric oxide acts by elevating intracellular cyclic guanosine monophosphate levels resulting in smooth muscle relaxation with a specific potent vasodilator effect. On the other hand, adenosine causes potent selective pulmonary vasodilation by acting at adenosine receptors (A2) on vascular smooth muscle to increase intracellular cyclic adenosine 3’5’ monophosphate (AMP), resulting in smooth muscle relaxation and improvement in systemic and myocardial oxygen delivery.

Central Nervous System

Parkinsonism - Continued neuronal degeneration can lead to the emergence of dementia or imbalance, substantial disability. There is a need for medications that can slow the underlying progression of degeneration, improve PD symptoms in early disease without inducing dyskinesia and improve motor fluctuations and ‘off’ time in advanced disease. Expression of A2A receptors in the brain is predominantly in the basal ganglia, especially the striatum. At a receptor level, there appears to be antagonism between A2A and D2.
dopaminergic receptors, and also between A1 and D1 receptors. This is important, because dopamine’s effect seems to be in allowing initiation of movement. Adenosine receptor stimulation antagonises this effect.

Epilepsy- Epileptogenesis is the process that leads to epilepsy and spontaneous seizures is thought to be triggered by an initial acute brain injury, e.g. status epilepticus, followed by progressive neuronal cell loss, mossy fibre sprouting and formation of an astrogliotic scar. Adenosine is an inhibitory modulator of brain activity. By acting on its receptors, mainly by activation of A1 receptors in hippocampus, it exerts predominant inhibitory effects. These inhibitory actions of adenosine can be used therapeutically to suppress seizures and are considered important for maintaining postictal depression and for restoring the metabolic equilibrium following seizures.

Anaesthesia and Intensive care medicine – Several double blind, placebo controlled, cross over studies in healthy human subjects have shown pain reducing effects of adenosine infusion at doses of 50-70 mg/kg/min. Adenosine, given in combination with morphine or ketamine, has an additive effect on pain reduction. Adenosine infusion 50-500 mg/kg/min during general anaesthesia for surgery, provided good recovery from anaesthesia and sustained post operative pain relief.

Pain management - Intrathecal adenosine is a potential treatment for neuropathic pain (adenosine 0.5 or 2.0mg).

Respiratory System

Bronchial Asthma

Adenosine levels are increased in broncho-alveolar-lavage fluid exhaled breath of patients with allergic asthma and in the plasma of patients with exercise-induced asthma. Adenosine induces hyper responsiveness in the airways of asthmatics, in vivo following inhalation and in vitro in small airways. Theophylline, a non-selective adenosine receptor antagonist and bamiphylline, a selective A1 adenosine receptor antagonist (which does not bind to human A 2 b and A 3 receptors), improve lung function and symptoms in humans with asthma.

Gastrointestinal System

The stimulation of A2a receptors resulted in amelioration of inflammation in the intestinal mucosa, with a reduction of leucocyte infiltration and inhibition of proinflammatory cytokine levels (TNF-α, IFN-γ and IL-4). However, it has been recently observed that the selective A2a receptor agonist CGS21680 was ineffective in ameliorating various inflammatory parameters of colitis induced by dextran sodium sulphate (DSS) in mice. Overall, the actual significance of A2a receptors in the pathophysiology of intestinal inflammation remains undetermined, and further investigations are required to establish the therapeutic relevance of A2a agonists in IBD. Adenosine A3 receptors are also emerging as possible targets for treatment of bowel inflammation.

Renal System

A1 antagonists act as potassium-sparing diuretics and may protect against contrast-induced injury. A1 receptors are an absolute requirement for normal tubuloglomerular feedback. It seems that A1 antagonists protect against decline in renal function seen with diuretic therapy. Increased adenosine sensitivity (with increased vasoconstriction) may be important in the pathogenesis of contrast-induced nephrotoxicity.

Blood

Platelet effect – Study of these receptors on platelets is made difficult, due to the presence of adenosin, a non– receptor protein, that binds also binds to A2 agonists.

Immune implications – Adenosine accumulation and stimulation of receptors has been implicated in the immunosuppression seen in critical illness. A3 receptor stimulation may inhibit tumour growth eg, melanomas, lymphomas, prostate cancer etc.
Drugs Acting On Adenosine Receptors

Adenosine, Dipyrdimole, Caffeine, Theophylline, Aminophylline, Theobromine are the various drugs acting through adenosine receptors. Newer drugs acting through adenosine receptors in market are Regadenoson, Pentostatin and Istradefylline.

Adenosine

Adenosine is an Endogenous nucleoside and Normally present in all cells of the body .It acts by stimulating adenosine (A1) receptors. Adenosine is the drug of choice for AV nodal re-entrant tachycardia. It is given as a rapid bolus intravenous injection 3mg dose followed by dose of 6mg , if necessary .It has an ultrashort half life of  10 – 20 sec. It is also used as a pharmacological stress agent, in the name , Adenoscan , to increase coronary blood flow for thallium-201 myocardial perfusion scintigraphy with patients who are unable to exercise sufficiently.Adverse Events are facial flushing,shortness of breath, bronchospasm , nausea, metallic taste.

Regadenoson

Regadenoson was approved by the United States Food and Drug Administration on April 10, 2008. It is A2A adenosine receptor agonist and acts by promoting coronary vasodilation and sympathetic stimulation.It is mainly used as Diagnostic imaging agent with and as a Pharmacological stress agent as it Produces hyperemia quickly and maintains it for a duration that is useful for radionuclide myocardial perfusion imaging in patients unable to undergo adequate exercise stress.Dosage is 0.4mg/5ml. Adverse Effects are Dyspnoea , Rhythm conduction abnormality , Flushing , Chest discomfort.

Pentostatin

Newer adenosine drug , that mimics the adenosine nucleoside and acts by inhibiting the enzyme adenosine deaminase and interferes with the cell's ability to process DNA. It is used mainly as an anti cancer chemotherapeutic agent in Hairy Cell Leukemia , Steroid-refractory acute and chronic graft-versus-host disease , Chronic Lymphocytic Leukemia- relapsed.It is given as intravenous infusion once in every two weeks – for 3 to 6 months .Adverse Effects are mainly Leukopenia , Pruritis , Myalgia ,Abdominal pain , Cough/Chills.

Istradefylline

It is World’s first Antiparkinsonism drug in this new therapeutic area targeting adenosine receptors. It acts as a Selective Adenosine A2a Receptor antagonist.It is used in the treatment of Parkinson’s disease with reduction of dyskinesia from long term treatment with Levodopa. It also improves wearing off phenomena and is well tolerated in Parkinson’s disease.It is currently available only in the Japan market.

Newer Drug Under Trial

Tozadenant

This drug has been found effective in Parkinson’s disease who have motor fluctuations on Levodopa. It has developed positive results in Phase 2 clinical trials and Phase 3 trials begins in the first half of 2015.it has been proved to be well tolerated and efficient in reducing off time without increasing troublesome dyskinesia.

CONCLUSION

Adenosine receptors have got a wide distribution in our body but drugs acting on these receptors are relatively less in number. Growing evidence have proved that Adenosine receptors are promising therapeutic targets on a wide range of conditions such as Parkinsonism , Sleep disorders , Inflammatory disorders and tumours etc . Many drugs on adenosine receptors are under trial and in a short span of time , they are believed to create a turn over in the era of Medicine [5].
REFERENCES