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Targeting of the Adenosine Receptors as A Novel Strategy for the Treatment of Arterial Hypertension

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Abstract

Hypertension is the most common risk factor for cardiovascular disease, which is the leading cause of death in industrialized societies. More than 25% of the adult population had hypertension in 2000, and almost 30% are projected to have this condition by 2025. Prevention, detection, and treatment of hypertension should be a high priority. The treatment reduces the risk of stroke and myocardial infarction by about 40 and 15%, respectively, but cardiovascular disease risks in hypertensive subjects remain increased despite apparently adequate blood pressure control with conventional antihypertensive drugs. To improve treatment efficacy, several new targets have been investigated and validated in experimental hypertension models. Further, the adenosinergic system, specifically the adenosine A2A receptor, is potentially a novel and efficient approach for hypertension treatment. Herein, we provide a review of the effects of adenosine on the cardiovascular system, focusing on the contribution of the A2A receptor as a pharmacological target that induces blood pressure regulation by its actions on the central, vascular and renal systems.

Keywords: Adenosine; Blood pressure regulation; Cardiovascular disease; Adenosinergic system; A2A receptor; Hypertension; Pharmacological target

Introduction

Hypertension is one of the major risk factors for cardiovascular diseases, in addition to high cholesterol, diabetes, obesity, smoking and stress. There are at least 970 million people affected by hypertension worldwide and it is estimated that this number will increase approximately 60%, reaching 1.56 billion hypertensive subjects in 2025 [1]. Hypertension is a public health problem throughout the world, and preventive actions need to be taken to reduce the chance of becoming more widespread. The blood pressure homeostasis depends on the activity of the sympathetic nervous system, the renin-angiotensin-aldosterone system and the vascular endothelium. Hypertension is caused by increasing peripheral vascular resistance if untreated, can lead to complications such as atherosclerosis, stroke and heart attack.

Hypertension is associated with vascular changes, including functional and structural endothelial dysfunction and vascular remodeling. One of the most obvious factors related to the development and progression of hypertension is redox signaling. The metabolism of oxygen by cells generates reactive oxygen species (ROS) potentially deleterious. An abnormal redox signaling, commonly induced by excess of ROS production and/or decrease in antioxidant activity, generates oxidative stress triggering changes in vascular function [2]. The ROS are important intracellular second messengers which modulate activity of many molecules as tyrosine protein phosphatases, protein tyrosine kinases, transcription factors, protein kinases activated by mitogen and ion channels. The induction of these pathways lead to the migration of smooth muscle cells, apoptosis,

expression of pro-inflammatory mediators and alteration of the extracellular matrix. In addition, increased vascular tone occurs by changing the regulatory role of the endothelium and through direct effects on vascular smooth muscle contractility. In physiological conditions, at low concentrations, the intracellular ROS play an important role in redox signaling involved in maintaining function and vascular integrity. Under pathological conditions, the ROS contribute to vascular dysfunction and remodeling via oxidative damage [3,4]. The increased production of superoxide anion and hydrogen peroxide and decreased bioavailability of antioxidants have been demonstrated in experimental and human hypertension [5]. Endothelial dysfunction observed in hypertension is consequent of an imbalance between production and availability of endothelial factors which promotes vascular constriction or relaxation. Prostacyclin (PGI2) and nitric oxide (NO) are among the factors that could promote relaxation of vascular smooth muscle whereas endothelin-1 is considered the most potent endogenous vasoconstrictor [6]. The imbalance occurs due to increased production and release of ROS by the impaired vascular endothelium [7]. Superoxide anion stimulates the synthesis and release of vasoconstrictors [6,7] which will reduce vasodilator response mediated by endothelium and increase vasoconstrictor response, which will contribute to increased peripheral vascular resistance and hypertension. In addition, the increased production of superoxide anion leads to increased concentration of intracellular Ca2+ in vascular smooth muscle, because ROS can inactivate SERCA and induce Ca2+ release from sarcoplasmic reticulum through IP3 channel [8]. Hypertension is also associated with sympathetic hyperactivity due to an increased activation of the renin-angiotensin-aldosterone system which leads to an increase in the concentration of norepinephrine. Angiotensin II increases the release of noradrenaline from sympathetic peripheral terminals, regulates activity of baroreceptors, controls renal blood flow and urinary

excretion of Na+ which could regulate the blood pressure for long term. The sustained elevation of blood pressure tends to cause left ventricular hypertrophy, increased wall thickness and vascular remodeling.

The treatment of hypertension is important to reduce cardiovascular events, such as myocardial infarction, heart and kidney failures. Lifestyle changes are essential for the prevention or delay the appearance of hypertension and could increase the effectiveness of pharmacological treatment and reduce cardiovascular risks [9]. Several antihypertensive drugs, with distinct pharmacological targets are currently available for clinical use. Diuretics, angiotensin-converting enzyme inhibitors, beta-blockers, antagonists of α1-adrenergic receptors, antagonists of AT1 receptor and Ca2+ channel blockers are the drugs most widely used for the treatment of hypertension [9]. Despite adequate control of the blood pressure using conventional antihypertensive drugs, cardiovascular risks in hypertensive subjects remain superior in relation to normotensive [10]. This fact must be due to the inability of these drugs in reducing cardiovascular structural changes, such as cardiac hypertrophy, vascular remodeling and renal injury, despite the reduction in blood pressure. There is therefore the need for the development of new drugs that not only reduce blood pressure, but also could improve those structural changes arising from arterial hypertension.

One approach for controlling blood pressure in hypertensive patients is the administration of multiple classes of antihypertensive agents. However, dihydropyridine calcium channel blockers, ACE inhibitors and diuretic agents associated with beta-blockers have a risk of side effects [11]. Moreover, although the incidence of resistance hypertension remains controversial, more than 1.9 % of hypertensive patients experience uncontrolled high blood pressure despite taking three or more antihypertensive medications [12]. Resistant hypertension can also lead to an increased cardiovascular risk for myocardial infarction, congestive heart failure, stroke, and chronic kidney disease or in some cases death [12]. Diuretic therapy and the administration of mineralocorticoid receptor antagonists represent another treatment strategy for patients with resistant hypertension [13]. However, due to the difficulty associated with treating resistant hypertension, new antihypertensive agents are needed. One promising approach is the targeting of adenosine receptors which activation not only reduces blood pressure but also interferes with cardiac and vascular remodeling.

Adenosine and its physiological effects

Adenosine is a purine nucleoside composed of an adenine molecule attached to a ribose sugar molecule via a β-N9 glycosidic bond. It is present both inside and outside of cells, and represents a nexus for different metabolic pathways [14]. In particular, adenosine plays an important role in energy transfer and in signal transduction, via cyclic AMP (cAMP), which regulates many physiological and pathological processes. Under physiological conditions, adenosine levels in cells and tissue fluids are in the nanomolar range, however, they rise substantially in response to different forms of cellular distress, such as ischemia, hypoxia, trauma and inflammation [15]. The rapid release of adenosine in response to abnormal cellular conditions induce a range of tissue responses that are organ-specific for the restoration of homeostasis [16,14]. These responses include control of cardiac rhythm and circulation [17,18], lipolysis [19], renal blood flow [20,21], immune function [22], sleep regulation [23,24], angiogenesis [25] and vasodilatation, as well as inflammatory diseases [26-28].

Adenosine is mainly present in the cytoplasm in its phosphorylated forms, which include adenosine monophosphate (AMP), adenosine diphosphate (ADP), and adenosine triphosphate (ATP). These forms are generated through ATP hydrolysis by the ecto-5-nucleotidase enzyme, an integral part of energy regulation at the cellular level [29]. In response to cellular stress and damage, ATP is released into the extracellular space and is rapidly dephosphorylated by extracellular nucleotidases [30], thereby leading to a substantial increase in the levels of adenosine. Adenosine can interact with G protein-coupled receptors (GPCR), which are coupled to various secondary messenger systems. Extracellular and intracellular adenosine molecules are also susceptible to deamination by adenosine deaminase to form inosine, while intracellular adenosine can be secreted to the extracellular fluid or rephosphorylated to form ATP, with the latter reaction catalyzed by adenosine kinase [31,32].

Adenosine mediates a wide variety of physiological functions by interacting with transmembrane adenosine receptors, namely A1, A2A, A2B and A3 receptors (A1R, A2AR, A2BR and A3R, respectively). These receptors have distinct localization profiles, they are associated with specific signal transduction pathways, and they are subject to various types of regulation upon exposure to agonists. These receptors are also considered potential targets for the treatment of acute and chronic diseases based on their involvement in cellular processes responsible for tissue injury [33]. Each adenosine receptor subtype has been characterized according to an adenylate cyclase effector system which utilizes cAMP as a secondary messenger. A1R and A3R are coupled to Gi proteins and inhibit adenylate cyclase, thereby leading to a decrease in cellular cAMP levels. Morever, A1R are linked to various kinase signaling pathways, including those mediated by protein kinase C, phosphoinositide 3 (PI3) kinase, mitogen-activated protein (MAP) kinase and they also directly activate K+ channels and inhibit Ca2+ channels [34]. A3R also utilize PI3 kinase and MAP kinase, pathways, as well as phospholipase D, RhoA and Wnt pathways, to control cell functions [34]. Both A2AR and A2BR are positively coupled to adenylyl cyclase through Gs proteins, and their activation causes an increase in intracellular cAMP [34]. Furthermore, stimulation of A2BR can trigger adenylyl cyclase activation via Gs proteins or PLC activation via Gq proteins. Classification, body distribution and function of adenosine receptors are shown in Table 1.

Receptor	Coupling to effector system	Body distribution	Physiological function
A1	G Protein-coupled: Gi Adenylate cyclase: ↓cAMP Kinase pathways: PKC, MAPK, PI3K Ion channels: ↑K+, ↓Ca2+	Broad distribution: high in nerves, heart, kidney and adipose tissue	Decreased renal blood flow, inhibition of renin release, inhibition of lipolysis, increased systemic blood pressure, vasoconstriction, bronchoconstriction, inhibition of neurotransmitter release, inhibition of insulin and glucagon release, reduced heart rate, sleep, analgesia, cardiac preconditioning

A2A	G Protein-coupled: Gs Adenylate cyclase: ↑cAMP	Broad distribution: very high in basal ganglia; high in nerves, blood vessels, kidney and immune cells	Wakefulness and locomotion, increased renal flow, immunosuppression, vasodilation and hypotension, coronary vasodilation, angiogenesis, cardioprotection, baroreflex control
A2B	G Protein-coupled: Gs, Gq/11 Adenylate cyclase: ↑cAMP Phospholipase C: ↑↓IP3, ↑Ca2+	Broad distribution, but generally low abundance	Vascular integrity, cardiac preconditioning, pro-inflammation (acute injury) and anti-inflammation (some chronic disease states), fibrosis
A3	G Protein-coupled: Gi Adenylate cyclase: ↓cAMP kinase pathways: MAPK, PI3K Phospholipase D, RhoA and Wnt pathways	Restricted distribution, varying in different species: high in mast cells	Increased mast cell activation, airway contraction, inflammatory pain, white cell chemotaxis, chronic neuropathic pain relief, anticancer (melanoma)

Table 1: Classification, distribution and physiological function of the adenosine receptors [34,35,57,96,97,114,120]. cAMP, cyclic adenosine monophosphate; PKC, protein kinase C, MAPK, mitogen-activated protein kinase; PI3K, phosphoinositide 3 kinase; IP3, inositol triphosphate; RhoA, Ras homolog gene family member A.

Adenosine has long been described as a molecule that mediates functions of the central and cardiovascular systems, inducing hypotensive/vasodilatation or hypertensive/vasoconstriction effects depending on the specific receptor subtypes and body systems involved. It can regulate blood flow either by acting directly on vascular cells or indirectly because of its effects on the central/ peripheral nervous systems or renal system [35]. Figure 1 summarizes adenosine signaling pathways which play important role to regulate blood pressure. Pharmacological manipulation of these pathways is of great interest and is currently being investigated as a therapeutic target for a number of cardiovascular diseases. These studies are being conducted in conjunction with several molecules, that exhibit both agonist and antagonist activities against known adenosine receptors involved in different cardiovascular conditions including hypertension.
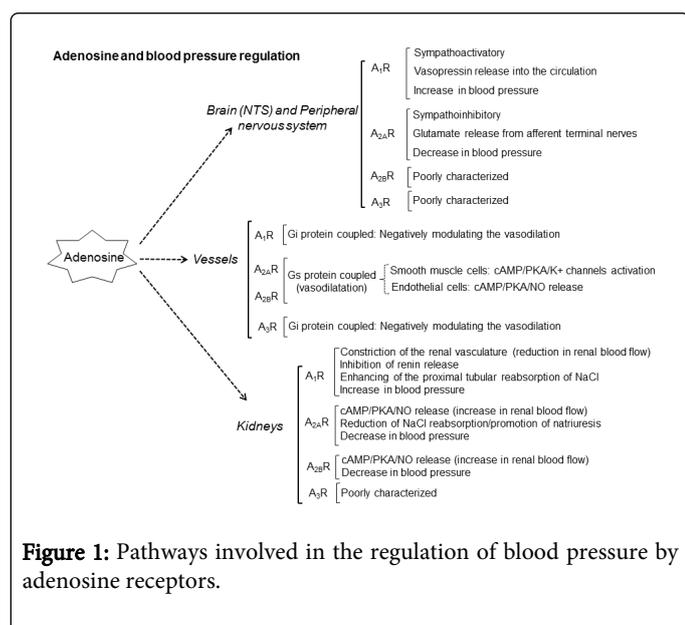

Figure 1: Pathways involved in the regulation of blood pressure by adenosine receptors.

Adenosine receptors in the central nervous system (CNS)

In the CNS, A1R are widely expressed by neurons in the cortex, hippocampus and cerebellum [36]. These receptors are also expressed by astrocytes [37], oligodendrocytes [38] and microglia [39]. In neurons, A1R localize to synaptic regions where they modulate the release of neurotransmitters such as glutamate, acetylcholine, serotonin and gamma-aminobutyric acid (GABA) [40]. A2AR exhibit a more restricted localization to the striatum and olfactory bulb [27]. However, these receptors are also expressed by neurons, microglia oligodendrocytes and possibly astrocytes [41,42]. Furthermore, A2AR have been described association with dendritic spines and postsynaptic regions of the basal ganglia [43]. It has been demonstrated that these receptors localize to the presynaptic regions (in the hippocampus), and they modulate the release of neurotransmitters such as glutamate, acetylcholine, GABA and noradrenaline [44-47]. A2BR are expressed at low levels on neuronal and glial cells, such as microglia and astrocytes [48,49] while low levels of A3R have been detected in the hippocampus, cortex, cerebellum and striatum [46]. Cellular localization of A3R has also been observed for neurons, astrocytes and microglia [50-52].

One of the most well-established effects of adenosine on the CNS is its capacity to increase intracellular cAMP in several areas of the brain. The intensity of this effect has been found to be species-dependent. Accumulating evidence also supports a modulatory role for central adenosine receptors on baroreflex activity. Briefly, since adenosine can bind A1R and A2AR that are located in the nucleus of the solitary tract (NTS), which is an important center for cardiovascular control and other autonomic functions, adenosine can differentially modulate cardiovascular control of arterial pressure, heart rate, regional sympathetic activity and vascular conductance [53]. Adenosine may also directly inhibit central neurons via postsynaptic A1R, and activate neurons via A2AR. In the NTS, adenosine may exert inhibitory effects via A1R located on post- and presynaptic sites of neurons and vagal afferents, respectively [54,55].

In the NTS, there are two sources of adenosine: extracellular ATP that is released by synapses under physiological conditions as a neurotransmitter and is degraded to adenosine by ectonucleotidases [29], and intracellular ATP which is catabolized to adenosine under

pathological conditions such as hypoxia, ischemia, and severe hemorrhage [56].

Activation of A1R that are located in the caudal, subpostremal division of the NTS, results in an increase in mean arterial pressure. After bilateral sinoaortic denervation and vagotomy, and after the blockade of inotropic glutamatergic transmission in the NTS, pressor and sympathoactivatory responses to stimulation of NTS A1R are abolished/attenuated [57]. It is hypothesized that stimulation of A1R facilitates release of vasopressin into the circulation, and this would be consistent with the inhibition of tonic baroreflex restrain that is subsequently observed.

Conversely, stimulation of A2AR in the NTS evokes a distinct pattern of regional sympathetic responses, as well as a decrease in mean arterial pressure and heart rate [58]. Specifically, activation of A2AR in the NTS decreases renal sympathetic nerve activity and post-adrenal sympathetic nerve activity. Several studies have also shown that the hypotensive effects of activating A2AR in the NTS are mediated by a release of glutamate from afferent terminals, and/or from intrinsic NTS interneurons involved in barorreflex transmission [59-61].

Accumulating evidence indicates that essential hypertension can be triggered by central mechanisms. For example, inappropriate modifications of synaptic functions within networks can contribute to the development of hypertension, which is a multifactorial disorder that can affect several aspects of human health [62]. Increased sympathetic nerve activity is also often observed concomitantly with hypertension, whereas, activation of A2AR has been shown to evoke a decrease in blood pressure due to a decrease in sympathetic nerve activity [62].

Adenosine receptors and their actions on peripheral vascular beds

Adenosine can also regulate the blood pressure by acting directly on vascular cells [63] because it has been shown to induce a potent vasodilation effect [64]. Correspondingly, adenosine and its analogues have been shown to induce the vasodilatation of canine basilar arteries [65], porcine coronary arteries [66], rat aorta [67], and dog carotid arteries [68]. The most extensively evaluated function mediated by the postsynaptic adenosine receptors is vasodilatation. In particular, A2A and A2B receptor-mediated vasodilation has been reported in association with several vessels, namely muscular arteries (mesenteric [69], renal [70], and coronary arteries [71]), elastic arteries and the aorta of several species (guinea pig [72], rat [73], and hamster [74]). Adenosine has also been shown to relax pre-contracted isolated pulmonary arterial rings. It is hypothesized that these effects are mediated by activation of A2AR and A2BR [75] with A1R and A3R negatively modulating the vasodilation induced by these receptors [76-78]. Meanwhile, A1R appear to be involved in lowering the heart rate and negatively regulating blood pressure, with the latter involving an induction of vascular smooth muscle contraction [78]. In the coronary arteries, vasodilatation is primarily caused by activation of A2AR [79-83]. A2AR also have an important protective role in the kidneys, lungs, and heart during ischemia/reperfusion injury. Activation of A2AR has been shown to promote beneficial effects against lung ischemia/reperfusion injury when the A2AR agonist, CGS21680, was administered prior to ischemia and during reperfusion [84]. Furthermore, these protective effects were associated with signaling by extracellular-signal-regulated kinases (ERK) and cAMP.

Endogenous A2AR expressed by PC12 cells were found to activate the ERK phosphorylation cascade, possibly due to an increase in cAMP levels [85,86].

In an A2A receptor knockout mouse model, a decrease in adenosine-mediated aortic relaxation has been observed [78], and this supports the importance of A2AR in maintaining vascular tone. Further support is provided by experiments conducted in our laboratory using a newly synthesized compound, LASSBio-1027, which exhibits vasodilator and antihypertensive actions that are mediated by activation of A2AR [88]. LASSBio-1027 induced concentration-dependent relaxation of the aorta via the activation of A2AR and the release of nitric oxide (NO). Molecular docking studies confirmed these results by identifying potential interactions between LASSBio-1027 and the A2A receptor [87]. In a spontaneous hypertensive rat (SHR) model, this new compound induced hypotension and produced an antihypertensive effect with prolonged treatment, yet had no effect on the blood pressure of normotensive rats [87].

Some investigators have suggested that vascular relaxation in response to activation of A2AR may be independent of endothelial cells [88], while other investigators have shown that relaxation mediated by A2AR includes a significant role for endothelial cells [89]. These controversial results may be resolved by the findings that A2AR are located not only in the vascular endothelium, but also in vascular smooth cells [90]. Furthermore, a role for activated A2AR in vasodilation has been confirmed [91,92]. The activation of endothelial A2AR, which are coupled to Gs proteins, induces the release of NO via activation of the adenylate cyclase-protein kinase A pathway [93,94]. In vascular smooth cells, activation of A2AR increases activation of cAMP and protein kinase A, thereby, leading to phosphorylation and opening of K+ channels [95]. As a result, hyperpolarization and vasodilatation occur [96].

Renal adenosine receptors and the blood pressure regulation

While the renal localization of the adenosine receptors is well-documented, the reported distribution of adenosine receptors in the kidney vasculature and tubular segments varies depending on the detection technique employed. A1R have a high affinity for adenosine and are expressed in preglomerular microvessels, (including afferent arterioles), in glomeruli (including mesagial cells), juxtaglomerular cells and vasa recta [96,97]. A2AR and A2BR have been detected in whole kidney preparations [96] in the glomeruli of rat and mouse kidneys, in the medullary descending vasa recta and in the papilla [98]. A3R and their mRNA have been detected in whole kidney preparations of various species [98].

The kidney plays an integral role in the maintenance of extracellular fluid volume and electrolyte balance, and thus, contributes to long-term control of arterial pressure [99]. Adenosine plays a critical role in the regulation of renal vascular tone and reactivity, and additionally affects tubular transport [100,101]. Correspondingly, activation of A1R has been shown to constrict the renal vasculature, inhibit renin release and enhance the proximal tubular reabsorption of NaCl [102,103]. The vasoconstrictor effects of A1R activation in the afferent arteriole is currently a major focus since adenosine is a primary mediator of tubular glomerular feedback [103]. When A2R are stimulated an endothelium–dependent relaxation effect is achieved via stimulation of adenylyl cyclase, thereby leading to an increase in renal

blood flow [104] and a decrease in blood pressure [105]. Stimulation of A2AR also promotes natriuresis by reducing NaCl reabsorption in the thick ascending loop of Henle and the collecting duct [106-108] and attenuates tubular glomerular feedback responses by stimulating NO synthase [109]. In afferent arterioles, activation of A2AR has been shown to counteract restriction induced by A1R that lead to dilation and decreased autoregulation [104]. Functional expression of both A2AR and A2BR has been detected, although the opposing vasodilator effect during adenosine-mediated afferent arteriolar vasoconstriction was predominantly associated with activation of A2BR [109]. In contrast, the renal function of A3R remains poorly characterized. They may play a role in sodium and fluid balance by regulating the Na+/H+ exchange [110] or may exacerbate renal ischemia-reperfusion injury [111]. Interestingly, however, expression of A3R has been found to increase with age and their expression is upregulated in response to high salt intake [109].

Carroll et al. (2012) demonstrated that stimulation of adenosine levels with salt loading and down-regulation of A1R via increased adenylyl cyclase activity related to stimulation of A2AR may play an important role in enhanced salt excretion of the kidney, and thus, the regulation of blood pressure [109]. Salt-sensitivity is an important characteristic of individuals that exhibit essential hypertension as well as other forms of salt-dependent hypertension that affect African-Americans, diabetics, and the aged. Thus, the identification of potential targets for the management of salt-sensitive hypertension may be of therapeutic benefit, and the A2A receptor pathway may represent an important therapeutic target [110].

Adenosine receptors as drug targets

The knowledge of the physiological functions of adenosine and its receptors was important to identify the therapeutic potential of it [112]. However, the successful development of a targeted therapeutic for adenosine was not reached yet. Many promising ligands have been identified but side effects such as tachycardia and tolerance [113] due to low selectivity have precluded their clinical development. The identification of differences in receptor subtype structure at the molecular level may facilitate the design of not only potent ligands but also subtype selective ligands. Preclinical and clinical studies of adenosine receptors ligands are described in Table 2. Regadenoson, an A2A receptor agonist, has been approved by the US Food and Drug Administration (FDA) for clinical use in case of myocardial perfusion imaging in patients with suspected coronary artery disease.

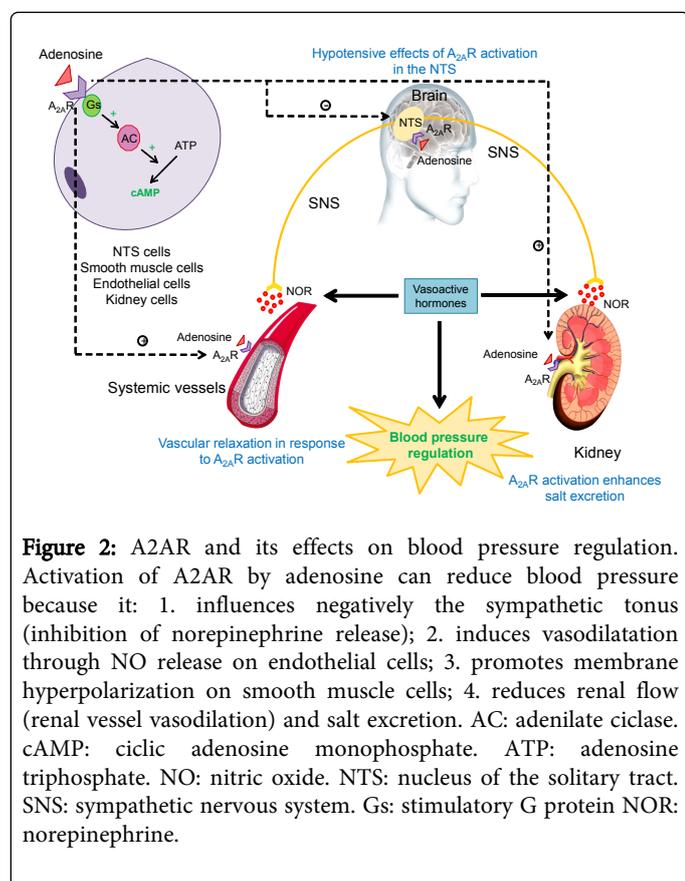| Compound	Receptor selectivity	Indication or use (phase)
Agonists		
Adenosine (Adenocard, Adenoscan)	A1, A2A	Paroxysmal supraventricular tachycardia (approved), myocardial perfusion imaging (approved), other uses in testing
Apadenoson	A2A	Myocardial perfusion imaging (III)
Regadenoson	A2A	Myocardial perfusion imaging (completed)
BAY 60-6583	A2B	Atherosclerosis (preclinical)
Binodenoson	A2A	Myocardial perfusion imaging (III)
BVT.115959	A2A	Diabetic neuropathic pain (II)
Capadenoson	A1	Atrial fibrillation, chronic treatment (II)
LASSBio-1027	A2A/A3	Systemic hypertension (preclinical)
LASSBio-1386	A2A	Pulmonary hypertension (preclinical)
LASSBio-1359	A2A	Pulmonary hypertension (preclinical)
LASSBio-1366	A2A	Pulmonary hypertension (preclinical)
MRS3558	A3	Autoimmune inflammatory diseases (preclinical)
Cl-IB-MECA	A3	Liver cancer (I-II)
CP608,039	A3	Cardiac ischemia (discontinued)
Antagonists		
Caffeine	A1/A2A/A2B/A3	Motor manifestations of Parkinson's disease and excessive daytime somnolence in Parkinson's disease (completed)
ATL 844	A2B	Asthma and/or diabetes (preclinical)
Naxifylline	A1	Heart failure (renal function) (discontinued)
FK-453	A1	Acute renal failure (preclinical)

Rolofylline	A1	Heart failure (renal function) (discontinued)
Toponafylline	A1	Heart failure (renal function) (IIb)
Vipadenant	A2A	Parkinson's disease (II)

Table 2: Therapeutic use for agonists and antagonists of adenosine receptors. [16, 87,114, 118-120].

Over the past 20 years, medicinal chemistry efforts have generated agonists and antagonists of adenosine that exhibit high affinity and high selectivity for the human variants of the four adenosine receptors. Ongoing research is directed towards the development of novel adenosine ligands with refined structure-activity relationships to improve their in vivo biodistribution and tissue selectivity [113]. However, a significant issue is the widespread expression of adenosine receptors.

A2AR as a novel drug target to treat hypertension

A2AR appears to be the main subtype of adenosine receptor which could reduce blood pressure through the effects in the NTS, peripheral vessels and kidneys (Figure 2). Recently, we have described the design and pharmacological profile of new N-acylhydrazones (NAH) LASSBio-1359 [114], LASSBio-1366 [115], LASSBio-1386 [116] and LASSBio-1027 [88]. All exhibited vasodilator activity through the activation of adenosinergic A2AR. Long-term administration of these compounds in SHR [88] did not induce tolerance to the antihypertensive effect suggesting that NAH could represent new candidates for the treatment of arterial hypertension.

Figure 2: A2AR and its effects on blood pressure regulation. Activation of A2AR by adenosine can reduce blood pressure because it: 1. influences negatively the sympathetic tonus (inhibition of norepinephrine release); 2. induces vasodilatation through NO release on endothelial cells; 3. promotes membrane hyperpolarization on smooth muscle cells; 4. reduces renal flow (renal vessel vasodilation) and salt excretion. AC: adenilate ciclase. cAMP: ciclic adenosine monophosphate. ATP: adenosine triphosphate. NO: nitric oxide. NTS: nucleus of the solitary tract. SNS: sympathetic nervous system. Gs: stimulatory G protein NOR: norepinephrine.

Based on the central, vascular and renal control of blood pressure that activation of A2AR mediate, we hypothesize that additional applications for A2AR as targets for the treatment of arterial hypertension in the clinical setting will be identified. Further clinical studies also need to carefully monitor individual differences in treatment and the potential for combining the direct actions of A2AR agonists with drugs targeting other pathways and/or targets.

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