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Review Article

Adenosine A_{2A} Receptor as a Target of Treatment for Pulmonary Arterial Hypertension

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Abstract

Pulmonary arterial hypertension (PAH) is a rare condition characterized by small pulmonary artery remodeling that leads to chronic precapillary pulmonary hypertension, elevated pulmonary vascular resistance, and right heart failure. Therapeutic options for PAH remain limited despite the introduction of prostacyclin analogues, endothelin receptor antagonists, and phosphodiesterase 5 inhibitors within the last 15 years. Predominantly, these interventions address the endothelial and vascular dysfunctions associated with PAH, and simply delay progression of the disease rather than offer a cure. To improve treatment efficacy, emerging approaches are focusing on the pro-proliferative phenotype as the target. This phenotype underpins pulmonary vascular remodeling in the lung and contributes to impaired circulation and right heart failure. Several new targets have been investigated and validated in experimental PAH models. Further, the adenosinergic system, specifically the adenosine A2A receptor, is potentially a novel and efficient approach for PAH treatment. Herein, we provide a review of the effects of adenosine on the cardiopulmonary system, focusing on the contribution of the A2A receptor as a pharmacological target that induces pulmonary vasodilatation and cardioprotection in experimental PAH models.

ABBREVIATIONS

PAH: Pulmonary Arterial Hypertension; RV: Right Ventricle; EC: Endothelial Cell; SMC: Smooth Muscle Cell; MCT: Monocrotaline; HF: Heart Failure; $A_{2A}R$: Adenosine A_{2A} Receptor; ATP: Adenosine Triphosphate; cAMP: Cyclic Adenosine Monophosphate; SERCA2: Sarco/Endoplasmic Reticulum Ca^{2+}-Atpase; MCT: Monocrotaline

INTRODUCTION

Pulmonary arterial hypertension (PAH) is characterized by deregulated pulmonary vascular remodeling that leads subsequently to increased pulmonary vascular resistance, right ventricular (RV) hypertrophy, RV dysfunction, uncompensated right heart failure, and premature death [1]. Therefore, PAH is associated with a poor prognosis. In its variety of presentations, this disease is estimated to affect up to 100 million people worldwide [2]. It is defined as an increase in mean pulmonary arterial pressure ≥ 25 mmHg at rest measured on right heart catheterization [3]. There are different hemodynamic definitions of PAH according to the pulmonary capillary wedge pressure, pulmonary vascular resistance, and cardiac output [4]. However, the current classification of PAH was agreed upon at the 4th World Symposium on Pulmonary Hypertension in 2008, in which PAH is separated into five groups (Table 1)[5,6].

Group 1 includes a variety of diseases that share several pathophysiological, histological, and prognostic characteristics. Idiopathic PAH defines group 1.1, in which patients of lack family history or a clearly identified risk factor for PAH. In hereditary PAH (group 1.2), loss-of-function mutations of the transforming growth factor β/bone morphogenetic protein (TGF-β/BMP) receptor superfamily, and more rarely, in activin receptor-like kinase type 1 have been identified as underlying mechanisms [6]. Drug- and toxin-induced forms of PAH are included in groups 1.3, and 1.4, as well as PAH associated with identified diseases (e.g., HIV). Persistent PAH of the newborn is included in group 1.5[6], and patients with pulmonary veno-oclusive disease and/or pulmonary capillary hemangiomatosis are classified in this group as well [1,5,6]. Group 2 includes patients with PAH secondary to left heart disease. Group 3 consists of all forms of PAH associated with disorders of the respiratory system, group 4, with all PAH

Table 1: Current classification of pulmonary arterial hypertension[5,6].

Group 1 - Pulmonary arterial hypertension
• Group 1.1 - Idiopathic pulmonary arterial hypertension
• Group 1.2 - Heritable pulmonary arterial hypertension
• Group 1.3 - Drug-induced and toxin-induced forms of pulmonary arterial hypertension
• Group 1.4 - Pulmonary arterial hypertension associated with identified diseases (for example, HIV and schistosomiasis infections)
• Group 1.5 - Persistent pulmonary hypertension of the newborn
Group 1' - Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
Group 2 - Pulmonary hypertension resulting from left heart disease; this group represents the large group of patients with pulmonary venous hypertension
Group 3 - All forms of pulmonary hypertension associated with alveolar hypoxia and/or disorders of the respiratory system
Group 4 - All (thrombo)embolic diseases leading to pulmonary hypertension
Group 5 - Pulmonary hypertension with unclear multifactorial mechanisms (a group of diseases directly affecting the pulmonary vessels)

caused by thromboembolic diseases, and group 5, with PAH caused by unclear multifactorial mechanisms [6].

The pathological characteristics of PAH include pulmonary arterial endothelial cell (EC) dysfunction, pulmonary artery EC and smooth muscle cell (SMC) proliferation, vasoconstriction, and in situ thrombosis. Furthermore, because sub-groups of PAH have common clinical characteristics, they are managed similarly [7]. However, despite the development of many new therapies over the last two decades, PAH remains an incurable disease process. If it is not interrupted, it will eventually become life threatening [8].

Many factors have been identified or proposed as contributing to vasoconstriction and vascular remodeling. These fall into several key, but somewhat interrelated and overlapping categories as follows: vasoactive factors, calcium signaling molecules, inflammatory mediators, growth factors, bone morphogenetic protein receptor 2 mutations, and metabolic dysfunction [6]. Over the past two decades, three major pathways (prostacyclin, endothelin, and nitric oxide [NO] pathways) have been established as being key elements in the development and progression of PAH [9-11]. These pathways have been targeted by PAH-specific therapies that fall into tree drug classes: prostacyclin (PGI_2) analogues, endothelin receptor antagonists, and phosphodiesterase-5 inhibitors (iPDE5) [12]. Additionally, some of these drugs were shown to improve symptoms, survival, functional class, and time to clinical worsening. Further, the use of these agents in clinical practice has been associated with outcome improvements among patients with PAH compared with historical data; however, there is still room for improvement [11,13-15].

Pulmonary arterial vessel relaxation is one of the main goals of PAH treatment. Thus, new therapeutic approaches, which induce NO release and relaxation through different pathways, such as iPDE5 and PGI_2 analogues, are emerging nowadays to improve the life quality of patients with PAH [12]. Moreover, stronger evidence suggesting that the adenosine A_{2A} receptor ($A_{2A}R$) could be a new target to treat PAH has been reported recently [16-18]. Therefore, in this review we focus on molecular mechanisms of relaxation induced by the activation of $A_{2A}R$, and we comment on the newest findings of the literature concerning the aforementioned affirmation.

ADENOSINE AND ITS ENDOGENOUS ACTIONS

Adenosine is a purine nucleoside comprised of adenine and ribose joined by a glycosidic bond. It is a both a precursor and a metabolite of adenine nucleotides. Because all cells can use free energy derived from the catabolism of adenosine triphosphate (ATP) to perform various functions (e.g., synthesis, secretion, contraction, and ion transport), all cells are possible sources of adenosine. Many of the cells that "produce" adenosine also express adenosine receptors on their surface [19]. Activation of these receptors often leads to an overall reduction of work performed and oxygen consumed by cells and organs. For example, adenosine reduces the pacemaking rate of the cardiac sinoatrial (SA) cells, thereby reducing the heart rate and cardiac load [20].

Adenosine is mainly present in the cytoplasm in its phosphorylated forms, adenosine monophosphate (AMP), adenosine diphosphate (ADP), and ATP. All these forms are generated through AMP hydrolysis by ecto-5-nucleotidase enzyme, an integral part of energy regulation at the cellular level. Under physiological conditions adenosine is maintained at a low intracellular concentration (estimates range between ten and a few hundred nanomolar) by both S-adenosylhomocysteine and S-adenosylhomocysteine hydrolases [21]. In response to cellular stress and damage, ATP is released into the extracellular space and is rapidly dephosphorylated by extracellular nucleotidases [22], with the subsequent substantial increase of adenosine levels. Extracellular adenosine can then interact with G protein-coupled receptors, which are coupled to various second messenger systems (Figure 1). Alternatively, extracellular adenosine can be transported into cells by passive diffusion through a specific bi-directional transport system [23]. Both extra and intracellular adenosine particles can be deamined to inosine by the actions of the adenosine deaminase. Intracellular adenosine can be secreted to the extracellular fluid or phosphorylated back to ATP, reaction that is catalyzed by adenosine kinase [23-25].

Adenosine is present in several body tissues and is produced by different cell types. It is an important modulator of the central and peripheral nervous systems, and it is involved in the homeostasis of the cardiovascular, renal, respiratory, and immune systems [26]. Additionally, it plays an important role in energy transfer (during the transition from ATP to ADP)

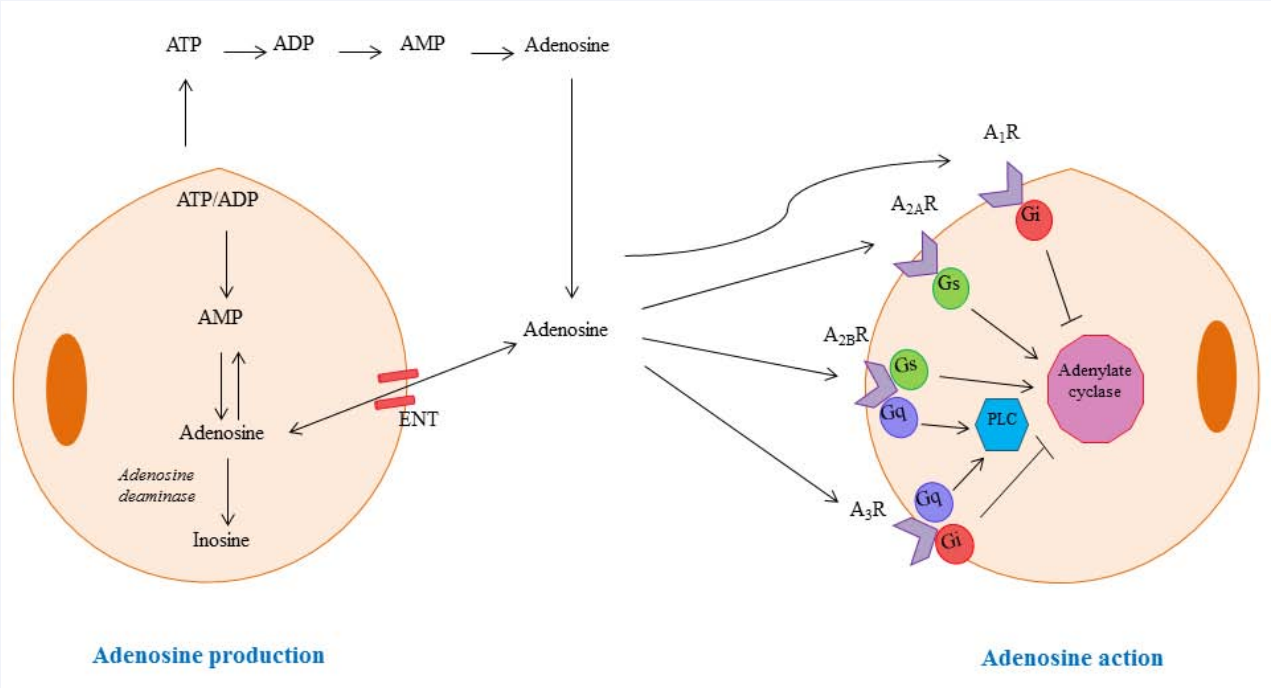

Figure 1 Adenosine mechanism of action. It can be formed in both the intracellular and extracellular compartments. It is mainly released into the extracellular space via equilibrative nucleoside transporters (ENTs). After released adenosine mediates its action through activation of four different membrane-spanning GPCRs subtypes: A_1R, $A_{2A}R$, $A_{2B}R$ and A_3R.

and signal transduction, through cyclic AMP (cAMP), which regulates many physiological and pathological processes. Thus, its rapid release in response to abnormal cellular conditions has two roles: initially, extracellular adenosine represents a "danger" signal and it is released rapidly upon tissue injury; as a consequence, increased extracellular levels of this nucleoside lead to a range of tissue responses for homeostasis restoration that can be considered organ-specific [26]. Evidence indicates that the adenosinergic system is essential in the mediation of intrinsic protection and in determining myocardial resistance to insult; therefore, adenosine may be considered as a potential cardioprotective molecule and its receptors could represent potential therapeutic targets in the setting of heart failure [25].

Adenosine receptors and their differential pattern of expression modulate a series of pleiotropic activities that are known to contribute to the control of inflammation, remodeling, and tissue repair [24]. Consequently, pharmacological manipulation of the adenosine signaling pathway is of great interest. This signaling pathway is currently under study as a therapeutic target for a number of respiratory diseases in conjunction with several molecules, with both agonist and antagonist activities, against known adenosine receptors involved in different conditions of the respiratory system, including PAH [24].

ADENOSINE RECEPTORS AND THEIR EFFECT ON THE CARDIOVASCULAR SYSTEM

For many years, adenosine has been known for its potent vasodilation effect, particularly in the coronary circulation [27]. Adenosine and its analogues have been shown to produce vasodilatation in canine basilar arteries [28], porcine coronary arteries [29], rat aorta [30], and dog carotid arteries [31]. Adenosine is released by several types of cells and activates four different membrane-spanning G protein-coupled receptors: A_1R, $A_{2A}R$, $A_{2B}R$, and A_3R. It can be released from the parenchymal tissue (including the endothelium) and after it interacts with specific extracellular receptors located on SMCs and ECs of the blood vessels to produce relaxation [5] (Figure 1). The release of adenosine increases under physiological stressful conditions, when it activates a homeostatic response (e.g., relaxation) to promote balance between the normal cells and tissue functions [32].

Both A_1R and A_3R are coupled negatively to adenylate cyclase through the Gi/o protein subunits; their activation causes a decrease in intracellular cAMP, and A_1R is linked to various kinase pathways such as protein kinase C, phosphoinositide 3 (PI3) kinase, and mitogen-activated protein (MAP) kinases. Furthermore, A_1R can directly activate K^+ channels and inhibit Q-, P-, and N-type Ca^{2+} channels [33]. The A_3R is coupled both to Gi and Gq proteins, inhibits adenylyl cyclase, and stimulates phospholipase C (PLC). This receptor can also utilize phospholipase D, RhoA, Wnt, MAP kinase, and PI3 kinase pathways to control cell function [33]. Both $A_{2A}R$ and $A_{2B}R$ are coupled positively to adenylyl cyclase through the Gs protein, and their activation causes an increase in intracellular cAMP [34]. Stimulation of $A_{2B}R$ can trigger adenylyl cyclase activation via Gs and PLC activation via the Gq protein [33] (Figure 1).

The most extensively studied and accepted function mediated by the postsynaptic adenosine receptors is vasodilatation. In fact, the involvement of A_{2A} and A_{2B} receptor-mediated vasodilation in

several vessels has been reported, namely in muscular arteries (mesenteric [35], renal [36], and coronary arteries [37]) and in elastic arteries, including the aorta of several species: guinea pigs [38], rats[39], and hamsters[40]. Adenosine relaxes precontracted isolated pulmonary arterial rings and its effects probably occur via A_{2A} and A_{2B} receptor activation [41]. In contrast, A_1R and A_3R, modulate negatively the A_{2A-B} R-induced vasodilation [43-45]. A_1R appears to be involved in lowering the heart rate. Additionally, it plays a negative role in regulating blood pressure, causes contraction of vascular smooth muscle, and decreases coronary blood flow [45]. Thus, adenosine can act as a vasoconstrictor besides being a vasodilator. However, this depends on the interaction with specific subtypes and tissue localization. The number of actions after adenosine receptor activation, the large base of current knowledge, and the rapid pace of adenosine research suggest that additional clinical applications of adenosine receptor research are quite promising [19].

SIGNALING PATHWAYS OF THE A_{2A} RECEPTOR-INDUCING RELAXATION AND ITS CARDIOPROTECTIVE EFFECTS

In the coronary arteries, vasodilatation is primarily caused by the activation of the $A_{2A}R$ [46-50]. Additionally, some studies demonstrated that the $A_{2A}R$ had an important protective role in the kidneys, lungs, and heart during ischemia/reperfusion injury. Further, the activation of $A_{2A}R$ promoted beneficial effects against lung ischemia/reperfusion injury when the $A_{2A}R$ agonist CGS21680 was administered before ischemia and during reperfusion [51]. These protective effects during ischemia/reperfusion injury were closely related to extracellular-signal-regulated kinases (ERK) and cAMP. The endogenous $A_{2A}R$ expressed in PC12 cells activated the ERK phosphorylation cascade, probably triggered by a rise in cAMP [52,53].

Organ-specific vascular hyporesponsiveness (thoracic aorta and left femoral, superior mesenteric, right renal, pulmonary, and middle cerebral arteries) following shock is closely related to the differential expression of A_{2A}Rs in the corresponding vasculatures under normal and shock conditions [54]. The participation of $A_{2A}R$ in regulating and protecting vascular reactivity following shock and its activation has a beneficial effect on hemorrhagic shock by improving vascular reactivity and hemodynamic parameters [54].

In an $A_{2A}R$ knockout mice model, a decreased adenosine-mediated aortic relaxation was shown[45], and this fact can provide additional support to confirm the importance of $A_{2A}R$ on maintenance of the vascular tone. In further support of this concept, our research group synthetized a new compound that exhibited vasodilator and antihypertensive actions that were mediated by activation of the $A_{2A}R$ [55]. Some investigators have suggested that vascular relaxation in response to $A_{2A}R$ activation may be independent of ECs [56]. Others have shown a significant involvement of the ECs in $A_{2A}R$-mediated relaxation [57]. This controversy, however, may be resolved by the findings of recent studies, which showed that the $A_{2A}R$ is located not only in the vascular endothelium but also in the vascular smooth cells [58], and confirmed that its activation is involved in vasodilation [59,60]. Activation of endothelial $A_{2A}R$, which is coupled to a Gs protein, induces NO release by activating the adenylate cyclase-protein kinase A pathway [61,62]. Moreover, activation of $A_{2A}R$ in vascular smooth cells increases activation of cAMP and protein kinase A, which leads to phosphorylation and opening of K^+ channels. This effect, in turn, causes hyperpolarization and results in vasodilatation [63] (Figure 2).

Along with vascular cells, $A_{2A}R$ is expressed in other myocardial cells types. Additionally, $A_{2A}R$ gene is expressed in mast cells [64], neutrophils [65], and CD4+ T cells [66]. Evidence of $A_{2A}R$ expression on myocytes has also been demonstrated in adult rat ventricular myocytes through the detection of $A_{2A}R$ messenger RNA (mRNA) [67] and by immunoblotting of ventricular cells of mice [68]. Although the numerous in vivo studies on $A_{2A}R$ implicate anti-inflammatory effects, the results of additional studies suggest that this protection could be caused in part because of direct myocardial effects [68-72].

The constitutive overexpression of $A_{2A}R$ in young mice was associated with increased cardiac contractility, higher heart rates, and a small increase in left ventricular mass. Viewed in terms of excitation-contraction coupling, the major alterations induced by $A_{2A}R$ overexpression were increased Sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA2) expression and Ca^{2+} uptake by the sarcoplasmic reticulum [73]. Thus, these findings suggest the beneficial effects of $A_{2A}R$-mediated signaling on cardiac function and cardiac hemodynamics [74]. Moreover, adenosine inhibits collagen synthesis and hypertrophy of vascular smooth cells and cardiac fibroblasts via the cAMP pathway ($A_{2A}R$ and $A_{2B}R$ activation) [75].

As previously mentioned, PAH is characterized by excessive pulmonary vasoconstriction and abnormal vascular remodeling processes that usually affect all vessel layers (intima, media, and adventitia) and result in a severe loss of cross-sectional area, and therefore, increased RV after load [6]. Large pulmonary artery compliance is also decreased, contributing to strain on the RV [6]. Although the pathogenesis of PAH is incompletely understood, evidence suggests that PAH is associated with activation of inflammatory processes, endothelial damage and dysfunction, and abnormal coagulation [76]. Thus, the modification of pulmonary vascular structures causes an increased resistance on the RV load that induces RV dysfunction [77].

In this review, added to the beneficial actions of $A_{2A}R$ activation (vasodilatation and cardioprotective effects) reported to date, we also will describe the significance of $A_{2A}R$ agonist use during the pathogenesis of PAH and the potential of such a drug as a possible treatment of the disease.

A_{2A} RECEPTOR AS A NEW TARGET FOR PAH TREATMENT

The development of PAH involves a complex interplay of multiple genetic, environmental, and hormonal abnormalities that lead to abnormal pulmonary vascular remodeling involving ECs, SMCs, and fibroblasts. Endogenous adenosine levels vary in different tissues, with adenosine levels being higher in the pulmonary than in the systemic circulation [78], for example, SMCs synthetize a substantial amount of adenosine [79], and

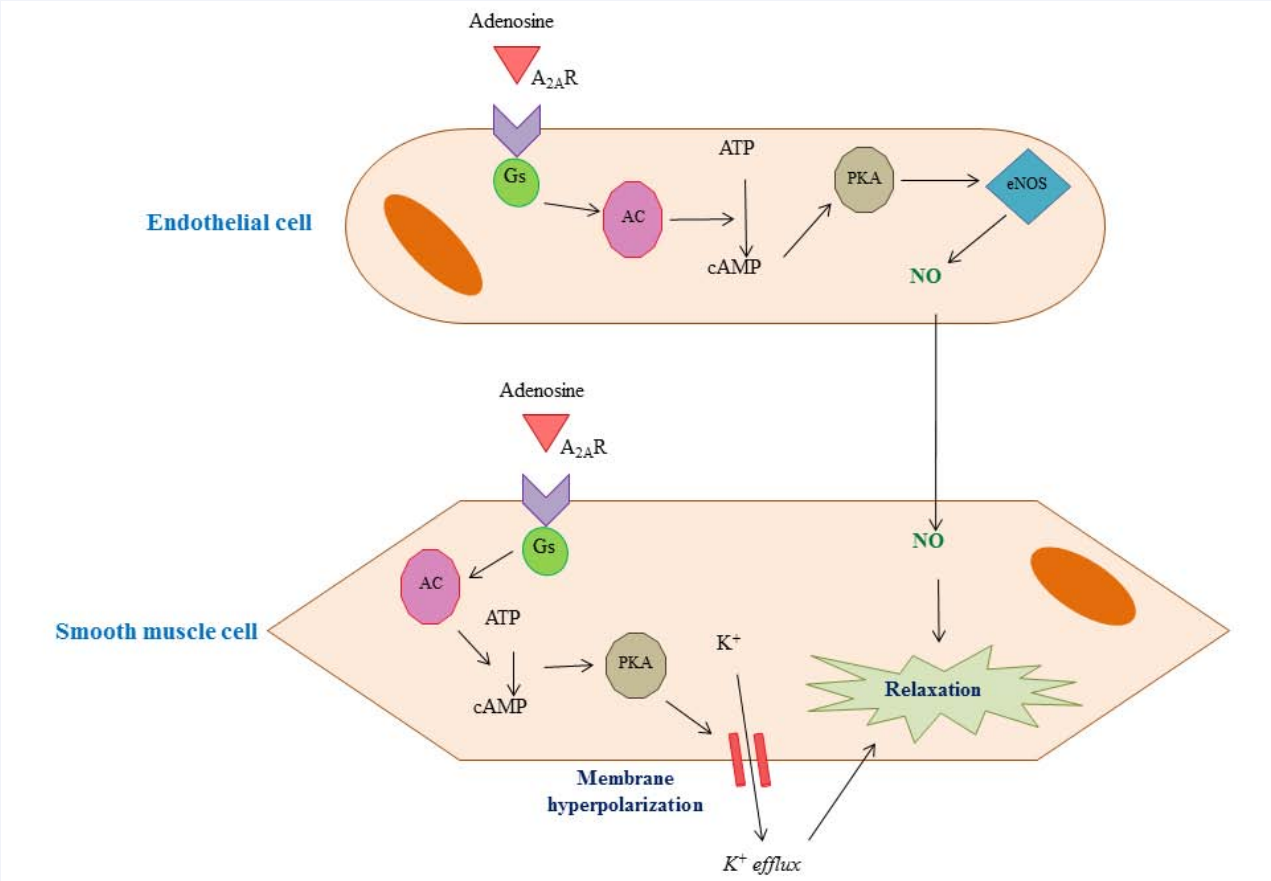

Figure 2 A_{2A} receptor mechanism of relaxation on vascular smooth cells. After its activation $A_{2A}R$ mediates the relaxation both NO release on endothelial cells or membrane hyperpolarization on smooth muscle cells. PKA: Protein kinase A. eNOS: Endothelial nitric oxide synthase. AC: Adenilate ciclase.

extracellular adenosine levels increase markedly in response to hypoxia [80]. However, patients with PAH have lower plasma adenosine levels in their pulmonary circulation compared to control subjects, which indicates a possible deficiency in adenosine signaling in PAH [78]. Immunohistochemical analyses of lung parenchyma demonstrated $A_{2A}R$ expression in bronchiolar and alveolar epithelial cells, SMCs localized in bronchiolar and vessels walls, and ECs in pulmonary arteries [81]. Further, the $A_{2B}R$ receptor was expressed mainly in mast cells and macrophages, and the A_1R was expressed only in a few alveolar macrophages [81].

Several lines of experimental evidence suggest that adenosine may be a potential endogenous regulator of PAH development by balancing SMC growth and collagen synthesis and by maintaining vascular homeostasis in the systemic circulation. Adenosine can act at $A_{2A}R$, induce powerful vasodilatation, and affect systemic blood pressure. It can exert a similar effect on pulmonary arteries [81]. Thus, adenosine action on $A_{2A}R$ regulates the pulmonary vascular remodeling and reduces exacerbated vasoconstriction.

Using an $A_{2A}R$ knockout mice model, Xu et al. provided the first evidence of the critical contribution of $A_{2A}R$ to the development of PAH. At the postnatal age of 14–16 weeks, $A_{2A}R$ KO mice exhibited characteristics of hemodynamic, histological, and ultrastructural changes of PAH: increased RV systolic pressure (RVSP) and increased RV mass, increased wall area and thickness, increased cellular proliferation in pulmonary resistance vessels, activation and hypertrophy of the SMCs and ECs, as well as collagen deposition in the adventitia of pulmonary arterial walls [17].

These investigators explained that spontaneous PAH and altered remodeling of pulmonary arteries at hemodynamic, histological, and ultrastructural levels are supported by the anatomical localization of $A_{2A}R$ in the vasculature primarily (where vasodilatation is mediated), added to the demonstration of the functional activation of $A_{2A}R$ in ECs (where adenosine-induced vasodilatation is mediated)[17]. Therefore, adenosine has been shown to cause vascular smooth muscle relaxation in the pulmonary circulation, and thus, it has been proposed for the therapy of clinical and experimental pulmonary hypertension. These findings suggest that the adenosine effect is likely to be mediated by $A_{2A}R$ in pulmonary vessels [17].

Curiously, our research group also investigated the $A_{2A}R$ involvement on regulation of cardiopulmonary physiology in rats with PAH induced by monocrotaline (MCT). Our results showed that after 14–28 days of MCT injection the animals exhibited a reduction in exercise capacity. This result corresponds well with the time course of the development of PAH [18]. When we treated the MCT-rats with a specific $A_{2A}R$ agonist (LASSBio-1386), the exercise capacity significantly improved compared with the control animals [18].

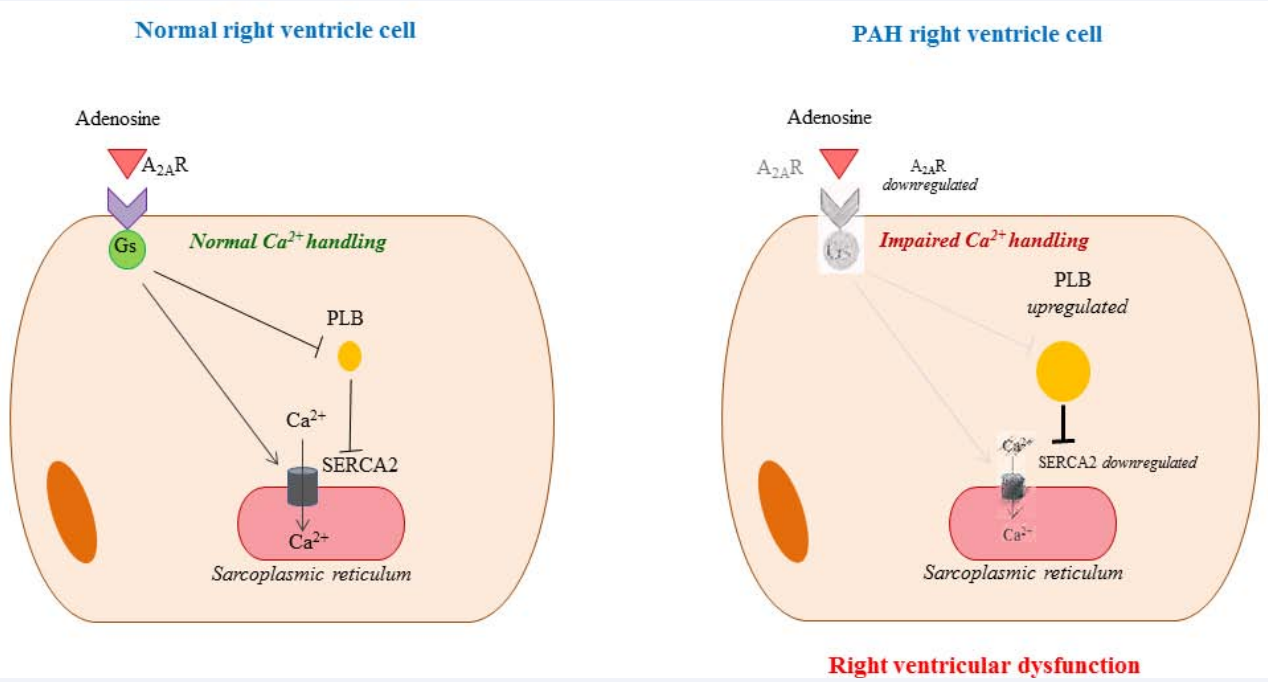

Figure 3 $A_{2A}R$ induces a homeostatic state on Ca^{2+} handling through modulation of SERCA2/PLB expression and activity. Right ventricular myocytes during pulmonary hypertension show a downregulation of $A_{2A}R$ and SERCA2, and an upregulation of phospholamban culminating on impaired Ca^{2+} handling. SERCA2: Sarco/endoplasmic reticulum Ca^{2+}-ATPase. PLB: Phospholambam.

In a second study, we showed that another $A_{2A}R$ agonist synthetized by our laboratory (LASSBio-1359) was also capable of inducing pulmonary vascular relaxation and promoting the recovery of endothelial dysfunction of the pulmonary artery rings in rats with PAH [16]. MCT injection also induced fibromuscular hypertrophy and hyperplasia in the arteriole walls of rats with PAH. This condition increased the RVSP and led to RV hypertrophy. However, daily oral treatment with the $A_{2A}R$ agonists, which were administered to the rats with PAH in both studies, abolished the increase in RVSP and reduced RV hypertrophy, after the disease was established [16,18].

Another observation of our experimental data was a reduction of $A_{2A}R$ expression both on pulmonary tissue and on RV tissue from rats with PAH [18]. We were able to demonstrate for the first time that $A_{2A}R$ levels were altered on PAH. These data supported previous reports cited in this review that showed a downregulation of this receptor in different experimental models of cardiovascular disease. Further, in our MCT model of PAH, we also observed a decrease in RV SERCA2 protein expression and in Ca^{2+}-ATPase activity at 28 days after MCT injection, in combination with the increased protein expression of total phospholamban that inhibits SERCA2 activity. Thus, it can be postulated that the upregulation of phospholamban inhibits SERCA2 activity and may be associated with the reduced $A_{2A}R$ expression and cardiac dysfunction [18] (Figure 3).

CONCLUDING REMARKS

Advances in our understanding of the pathogenetic role of adenosine in PAH may be translated into effective treatment options soon [24-26]. Considering the complex interplay driven by the different patterns of receptor distribution and/or affinity of the four known adenosine receptor subtypes in specific cell types at different stages of the disease, it is likely that combination of selective antagonist/agonists for different adenosine receptors subtypes will be required to obtain reasonable clinical efficacy. Alternatively, controlling the factors involved in driving adenosine concentrations in tissue may be also of great significance.

Thus, the data discussed herein indicate a role for $A_{2A}R$ in mediating beneficial effects during established PAH in rats as pulmonary vascular relaxation, reduction of pulmonary vessel and RV hypertrophy, amelioration of RV dysfunction, and exercise capacity. We provide a brief review of the importance of the adenosinergic system, specifically the $A_{2A}R$, as new target for the treatment of PAH. Further, we consider that of new therapeutic strategies and careful attention to patients with PAH is need currently.

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