

Chapter 18

Adenosine Receptors in the Lungs



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Abstract The ubiquitous adenine nucleoside adenosine (Ado), which plays an important role in cellular energetics, is released from cells under physiologic and pathophysiologic conditions. Another source of extracellular Ado is rapid degradation of extracellular adenosine 5'-triphosphate (ATP) by ectoenzymes. Extracellular Ado acts as an autocrine and paracrine agent by the activation of G protein-coupled cell surface receptors (GPCRs), designated as A₁, A_{2A}, A_{2B}, and A₃. Almost four decades ago, published data have indicated that Ado could play a role in immune-mediated histamine release from pulmonary mast cells. Since then, numerous studies have indicated that Ado's signal transductions are involved in various pulmonary pathologies including asthma and COPD. This chapter is a succinct review of recent studies in this field.

Keywords Adenosine · Adenosine receptors · Lungs · Pulmonary mast cells · Asthma · COPD

18.1 Introduction

The ubiquitous adenine nucleoside adenosine (Ado) plays a major role in cellular metabolism and energetics. The levels of extracellular Ado are determined by its release from cells under physiologic and pathophysiologic conditions as well as the degradation of extracellular adenosine 5'-triphosphate (ATP) by ectoenzymes, CD39 and CD73 in particular (Zimmermann 2000; Zimmermann et al. 2012). Extracellular Ado is eliminated from the extracellular space by ecto-adenosine deaminase (ADA) (Franco et al. 1997) and active Ado transporters that transport Ado into cells (Thorn and Jarvis 1996). Extracellular Ado acts as an autocrine and

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paracrine agent, the effects of which are mediated by four different G protein-coupled receptors: A_1 , A_{2a} , A_{2b} , and A_3 (A_1 AdoR, A_{2a} AdoR, A_{2b} AdoR, and A_3 AdoR, respectively). These receptors, which are expressed to various degrees by different cell types throughout the body including the lungs (Burnstock et al. 2012; Zhou et al. 2009), manifest variable affinity to Ado (Fredholm et al. 2001). AdoR are coupled to cascades of intracellular cellular-response pathways, mainly through the activation or inhibition of adenylate cyclase and the subsequent alteration of intracellular cyclic adenosine monophosphate (cAMP) levels (Karmouty-Quintana et al. 2013). The activation of AdoR can lead to both pro-inflammatory and anti-inflammatory effects, depending on the type of receptor and the experimental setting (Schepp and Reutershan 2008).

In the early 1980s, Holgate and his colleagues have shown for the first time that inhaled Ado induces bronchoconstriction in asthmatic but not healthy human subjects and that this action was mediated mainly by histamine released from lung mast cells and not by a pulmonary-pulmonary central vagal reflex triggered by Ado (Cushley et al. 1983; Mann et al. 1985; Church and Holgate 1993). Since then, data obtained in numerous studies have shown that Ado plays important roles in pulmonary physiology and pathophysiology (Caruso et al. 2006; Polosa and Blackburn 2009; Caruso et al. 2009). One characteristic of acute lung injury (ALI) is elevated Ado levels in the lung, which activate anti-inflammatory and tissue-protective mechanisms (Zhou et al. 2009; Karmouty-Quintana et al. 2013; Gonzales et al. 2014). Specifically, initial activation of AdoR blunts the production of multiple cytokines, decreases inflammatory cell infiltration, and preserves pulmonary vascular barrier function (Eckle et al. 2009). Similarly, Ado exerted a protective anti-inflammatory effect in an in vitro model of lung transplantation/ischemia-reperfusion model (Smail et al. 2016). In contrast, sustained AdoR activation results in pro-inflammatory effects, e.g., increased cytokine production and inflammatory cell infiltration (Zhou et al. 2009). This conundrum of the Ado's dual nature has stymied the development of new drugs aimed at the modulation of AdoR signal transductions.

This chapter is a succinct review of recent studies in this field. The large number of relevant publications and the limited scope of this review inevitably impose selective articles' citation. We thus apologize if our selection of articles does not include article(s) that others may feel should have been cited.

18.2 A_1 AdoR

A_1 AdoR, which has the highest affinity to Ado, is expressed at low levels in the lung; relatively higher levels were detected in the newborn mice (Metsola et al. 2014). The activation of A_1 AdoR reduces adenylate cyclase's activity via the activation of pertussis toxin-sensitive G_i and G_o proteins, stimulates phospholipase C via $G_{\beta\gamma}$ subunits, and activates pertussis toxin-sensitive K^+ channels (Pelleg et al. 1996)

and K_{ATP} channels (Schepp and Reutershan 2008). Activation of the A_1 AdoR could be pro- or anti-inflammatory depending on the specific pathophysiologic conditions and the levels of extracellular Ado.

Early studies have shown that ischemia-induced constriction of the pulmonary vasculature is mediated by the activation of A_1 AdoR, which results in thromboxane release (Neely et al. 1991) as well as pulmonary ischemia-reperfusion injury (Neely and Keith 1995). Subsequent *in vivo* studies using a mouse model have shown that physiologic doses of Ado decrease alveolar fluid clearance (AFC), probably by means of an A_1 AdoR-dependent mechanism that causes Cl^- efflux through CFTR, whereas lower doses increased AFC via the A_2aR and/or A_3R (Factor et al. 2007). Similarly, alcohol decreases alveolar fluid clearance and impairs survival from acute lung injury. Alcohol induced increases Ado levels in the lung, which may be responsible for reduction in AFC and associated worsening of lung injury (Dada et al. 2012).

A_1 AdoR expression is increased significantly during LPS-induced injury thereby suggesting that extracellular Ado levels and Ado receptors may play a role in LPS-induced toxicity (Metsola et al. 2014). Indeed, A_1 AdoR has been implicated in polymorphonuclear cell trafficking and alterations in microvascular permeability in lipopolysaccharide (LPS)-induced lung injury model (Ngamsri et al. 2010). A more recent study in a mouse model has shown that A_1 AdoR activation improves lung function and decreases inflammation, edema, and neutrophil chemotaxis after ischemia-reperfusion (Fernandez et al. 2013a). This protective effect of A_1 AdoR's activation agrees with the finding that pulmonary injury was exacerbated in ADA double-knockout mice, which is also deficient in the expression of A_1 AdoR (Sun et al. 2005). Similarly, an A_1 AdoR agonist significantly increased lung compliance and oxygenation and decreased pulmonary artery pressure, decreased neutrophil infiltration by myeloperoxidase activity and edema, and reduced tumor necrosis factor-alpha production in an isolated, ventilated, blood-perfused rabbit lung model of ischemia-reperfusion (Gazoni et al. 2010).

The expression of A_1 AdoR in the airways of asthmatic subjects is upregulated (Wilson et al. 2009). Ado-induced bronchoconstriction in human subjects is indirect (see above); however, in rodents this action is mediated by A_1 AdoR and a central vagal reflex (Wilson et al. 2009). Although A_1 AdoR activation affects "different cell types to produce bronchoconstriction, inflammation, mucous gland hyperplasia, angiogenesis, and fibrosis, all of which are important in the pathophysiology of human asthma" (Wilson et al. 2009), the exact role of Ado and A_1 AdoR in asthma has not been fully delineated, and accordingly none of the drug candidates targeting A_1 AdoR signal transduction has been approved by the FDA (see, e.g., Gottlieb et al. 2011).

Adenosine activation of leukocyte A_1 AdoR plays a significant role in their recruitment to lungs infected with an influenza virus and thereby contributes to influenza pathogenesis (Aeffner et al. 2014).

18.3 A_{2A}AdoR

A_{2A}AdoR is expressed by various inflammatory cell types, and its activation results in broad anti-inflammatory effects (Hasko and Pacher 2008). A_{2A}AdoR signaling attenuates acute lung injury by enhancing alveolar fluid clearance in mice (Eckle et al. 2008). The expression of A_{2A}AdoR was decreased significantly by an allergen challenge in a mouse model of asthma suggesting that A_{2A}AdoR deficiency leads to airway inflammation and airway hyperresponsiveness in this setting (Nadeem et al. 2007).

A_{2A}AdoR activation stimulates the formation of cAMP (Ongini and Fredholm 1996); the latter can significantly upregulate SOCS-3 protein expression (Sands et al. 2006). *In vitro* and *in vivo* studies have shown that hypoxia can induce pulmonary artery smooth muscle cell A_{2A}AdoR expression (Qian et al. 2013; Fan et al. 2016). A_{2A}AdoR upregulates SOCS-3 protein, which inhibits pulmonary vascular remodeling in lung tissue of hypoxic pulmonary hypertension rats (Fan et al. 2016). In addition, a recent study utilizing a hypoxia-induced pulmonary hypertension (HPH) mouse model has shown that hypoxia enhanced the expression of A_{2A}AdoR, the activation of which attenuated the release of specific inflammatory cytokines in the lung (Huang et al. 2017). The latter was associated with reduced thickening of pulmonary arterioles and improved hypoxemia (Huang et al. 2017).

An A_{2A}AdoR agonist significantly increased lung compliance and oxygenation and decreased pulmonary artery pressure, decreased neutrophil infiltration by myeloperoxidase activity and edema, and reduced tumor necrosis factor- α production in an isolated, ventilated, blood-perfused rabbit lung model of ischemia-reperfusion (Gazoni et al. 2010).

In contrast, it was recently shown that the activation of A_{2A}AdoR modulated the activation of fresh human alveolar inflammatory cells in patients with interstitial lung disease (Alfaro et al. 2017). A_{2A}AdoR plays a role in the regulation of different stages of immune responses, including antigen presentation, T-cell activation, expansion, survival, and memory (Ohta and Sitkovsky 2001). Specifically, Ado suppresses the immune response by activation of A_{2A}AdoR expressed by T-cells. Indeed, a selective antagonist of A_{2A}AdoR reduced the tumor burden in a mouse lung cancer *in vivo* model and restored immune responsiveness *ex vivo* (Mediavilla-Varela et al. 2017).

Chronic lung inflammation is associated with fibroblasts proliferation, beginning to proliferate, the formation of new blood vessels, and the increase in extracellular matrix resulting in the development of pulmonary fibrosis (Della Latta et al. 2013). Genetic knockout of A_{2A}AdoR in mice significantly exacerbates, while activation of A_{2A}AdoR attenuates the progression of pulmonary fibrosis induced by bleomycin (a chemotherapeutic agent used to treat several neoplastic diseases and widely used ones for the induction of lung fibrosis (Della Latta et al. 2015; Chen et al. 2017). The beneficial effects of A_{2A}AdoR activation in this setting are mediated at least partially via the stromal cell-derived factor-1 (SDF-1)/C-X-C chemokine receptor type 4 (CXCR4) pathway, the inhibition of which protects the lungs from fibrogenesis in BLM-exposed mice (Chen et al. 2017).

18.4 A_{2B}AdoR

Ado and its cell surface receptors play an important role in the regulation of inflammation following acute lung injury (Karmouty-Quintana et al. 2013). A_{2B}AdoR are expressed by mast cells, bronchial smooth muscle cells, and lung fibroblasts; their activation increases the release of various inflammatory cytokines and promotes differentiation of lung fibroblasts into myofibroblasts, typical of the fibrotic events (Della Latta et al. 2013).

A_{2B}AdoR mediates the relaxing effects of Ado on guinea pig airways (Breschi et al. 2007). Hypoxia is associated with increased soluble CD73 activity, which contributed to hypoxia-induced increase in Ado's plasma level and Ado-mediated erythrocyte A_{2B}AdoR activation inducing 2,3-BPG production and triggering O₂ release that prevents multiple tissue hypoxia, inflammation, and pulmonary vascular leakage (Liu et al. 2016). Extracellular Ado promote dermal fibrosis (Fernandez et al. 2013b), and the activation of A_{2B}AdoR promoted renal fibrosis in both mice infused with angiotensin II and mice subjected to unilateral ureteral obstruction (Dai et al. 2011). A study in a mouse model of bleomycin-induced injury and whole-lung lysate from patients without and with idiopathic pulmonary fibrosis has shown that inhibition of hypoxia-inducible factor 1- α (HIF1 α) attenuated pulmonary fibrosis in association with reductions in A_{2B}AdoR expression in alternatively activated macrophages (Philip et al. 2017). These data were interpreted to suggest that hypoxia, through HIF1 α , contributes to the development and progression of pulmonary fibrosis through its regulation of A_{2B}AdoR expression on alternatively activated macrophages (AAMs), cell differentiation, and production of profibrotic mediators (Philip et al. 2017).

In contrast, oxygenation may weaken local tissue hypoxia-dependent Ado and A_{2A}AdoR-mediated anti-inflammatory mechanism and thereby further exacerbating lung injury in the setting of acute respiratory distress syndrome (ARDS) (Thiel et al. 2005; Aggarwal et al. 2013). That notwithstanding, exposure to a hyperoxic environment causes lung injury associated with an increase of Ado levels, which protects vascular barrier function in hyperoxic lung injury through the A_{2B}AdoR-dependent preservation of the endothelial cellular adhesion protein occluding (Davies et al. 2014). In addition, the activation of A_{2B}AdoR reduced endotoxin-induced acute lung injury in a murine model (Schingnitz et al. 2010).

A_{2B}AdoR was found to play an important role in mediating lung inflammation after an ischemia-reperfusion challenge by stimulating cytokine production and neutrophil chemotaxis in a mouse model *in vivo* (Anvari et al. 2010). In contrast, several studies have shown that Ado and A_{2B}AdoR play an important role in the resolution of pulmonary edema and inflammation during ALI (Eckle et al. 2009). For example, in a mouse model of ALI (intratracheal LPS treatment followed by injurious mechanical ventilation), it was found that alveolar epithelial A_{2B}AdoR signaling contributes to lung protection (Hoegl et al. 2015).

Stromal cell-derived factor (SDF)-1 is a chemokine that regulates the release of neutrophils from the bone marrow into the circulation; during inflammation, the

concentration of SDF-1 in the bone marrow decreases, and polymorphonuclear neutrophils enter the circulation from where they can migrate to the lungs during ALI (Konrad et al. 2017). SDF-1 is expressed in the human lung during acute lung injury (Petty et al. 2007). The effects of SDF-1 are mediated by two receptors: CXCR4 and CXCR7 (Rath et al. 2014), the inhibition of which results in an anti-inflammatory effect during ALI (Konrad et al. 2017). Using a mouse model of ALI and an *in vitro* preparation of human epithelium/endothelium, it was found that the anti-inflammatory effects of CXCR4 and CXCR7 antagonism in terms of PMN migration, chemokine release, and microvascular permeability are linked to adenosine A_{2B} AdoR signaling in hematopoietic cells (Konrad et al. 2017).

18.5 A_3 AdoR

Significant amounts of A_3 AdoR are expressed in the rat lung (Haeusler et al. 2015). A_3 AdoR levels have been found to be elevated in subjects with chronic lung disease and in different pulmonary pathological conditions (Della Latta et al. 2013). The selective Ado A_3 AdoR agonist 2-chloro-N⁶-(3-iodobenzyl)adenosine-5'-N-methylcarboxamide (2-Cl-IB-MECA) significantly increased lung compliance and oxygenation and decreased pulmonary artery pressure, decreased neutrophil infiltration by myeloperoxidase activity and edema, and reduced tumor necrosis factor- α production in an isolated, ventilated, blood-perfused rabbit lung model of ischemia-reperfusion (Gazoni et al. 2010). Similarly, 2-Cl-IB-MECA attenuated lung dysfunction, inflammation, and neutrophil infiltration in a mouse model of lung ischemia-reperfusion (Mulloy et al. 2013).

Previous studies have shown that extracellular purine nucleosides and nucleotides are potent modulators of human lung mast cell (HLMC) degranulation and histamine release (Pelleg and Schulman 2002; Polosa et al. 1995). Low and high concentrations of Ado enhanced and suppressed, respectively, the release of histamine from Fc ϵ RI-stimulated HLMC; this action was mediated by A_3 AdoR (Gomez et al. 2011). The dose-dependent contrasting effects of Ado on histamine release associated with an allergic reaction were confirmed in a subsequent study using cultured HLMC (Nishi et al. 2016). Rudich et al. examined whether the activation of A_3 AdoR modulates rather than mediates the effects of Ado in human mast cells, presumably at a transcriptional level (Rudich et al. 2015). Using the HMC-1 cell line, Rudich et al. found that A_3 AdoR activation represses the expression of genes involved in tissue remodeling and that is coupled to downregulation of the receptor expression, both at protein and mRNA levels (Rudich et al. 2015). Furthermore, since in this study, dexamethasone, a commonly prescribed asthma medication, exerted a synergistic signal that increased Cl-IB-MECA induced gene upregulation and facilitated cytokine secretion, it was speculated that this interaction might underlie the resistance to corticosteroids that is experienced in severe refractory asthma (Rudich et al. 2015).

18.6 Conclusions

Although the prevailing school of thought is that the production of Ado and its activation of AdoR play largely beneficial roles in acute pathophysiologic condition and sustained elevated Ado levels can become detrimental by activating pathways that promote tissue injury and fibrosis (Karmouty-Quintana et al. 2013), many studies challenge this concept. Specifically, it seems that even in the acute phase of injury, the resulting effects of elevated extracellular Ado levels critically depend on the targeted cell type and the localized Ado level at the receptors' sites. This could explain why, until now, neither selective agonists nor antagonists of AdoR subtypes have been approved by the FDA for the treatment of either acute or chronic lung injury and inflammation (Borea et al. 2016).

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