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Cardiovascular adenosine receptors: Expression, actions and interactions

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ABSTRACT

Intra- and extracellular adenosine levels rise in response to physiological stimuli and with metabolic/energetic perturbations, inflammatory challenge and tissue injury. Extracellular adenosine engages members of the G-protein coupled adenosine receptor (AR) family to mediate generally beneficial acute and adaptive responses within all constituent cells of the heart. In this way the four AR sub-types—A_1, A_{2A}, A_{2B}, and A_3Rs—regulate myocardial contraction, heart rate and conduction, adrenergic control, coronary vascular tone, cardiac and vascular growth, inflammatory–vascular cell interactions, and cellular stress-resistance, injury and death. The AR sub-types exert both distinct and overlapping effects, and may interact in mediating these cardiovascular responses. The roles of the ARs in beneficial modulation of cardiac and vascular function, growth and stress-resistance render them attractive therapeutic targets. However, interactions between ARs and with other receptors, and their ubiquitous distribution throughout the body, can pose a challenge to the implementation of site- and target-specific AR based pharmacotherapy. This review outlines cardiovascular control by adenosine and the AR family in health and disease, including interactions between AR sub-types within the heart and vessels.

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Contents

1. Introduction

The purine nucleoside adenosine is generated in both intra- and extracellular compartments, and levels rise in response to physiological and pathological stimuli. Through activation of cell surface (and potentially intracellular) ARs, adenosine mediates a variety of actions, fine-tuning cardiovascular function, improving the cellular energy balance, and promoting cellular resistance to stress or injury (Olsson & Pearson, 1990; Shryock & Belardinelli, 1997). Indeed, adenosine was described in 1985 as a 'retaliatory metabolite' (Newby et al.,

Abbreviations: ADP, adenosine diphosphate; AMP, adenosine monophosphate; ANP, atrial natriuretic peptide; AR, adenosine receptor; ATP, adenosine triphosphate; AV, atrioventricular; CRE, cAMP response element; ECM, extracellular matrix; GPCR, G-protein coupled receptor; HIF, hypoxia inducible factor; IFN, interferon; IL-, interleukin; IMP, inosine monophosphate; K_{ATP}, ATP-gated K^+ channel; MMP, matrix metalloproteinase; NO, nitric oxide; PI3K, phosphoinositide 3-kinase; P_i, inorganic phosphate; PKC, protein kinase C; PostCon, postconditioning; PreCon, preconditioning; SA, sinoatrial; TNFα, tumor necrosis factor α; UTR, untranslated region; VEGF, vascular endothelial growth factor.

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1985), released to protect cells of the heart against excessive external stimulation. However, adenosine release (thus AR activation) is not restricted to conditions of stress or injury, being sensitive to even mild perturbations in energy state, and to varied regulatory molecules (e.g. catecholamines, histamine, NO) and cell signaling pathways (e.g. PKC signaling), and also deriving from cAMP pools. Resultant shifts in adenosine levels impact all major aspects of cardiovascular function, including the rate and strength of beating, conduction of the cardiac impulse, autonomic control of the heart, coronary perfusion, cardiovascular growth/remodeling, and cardiac and vascular resistance to injurious insult. The AR system is also critical to the development of a healthy heart, and protects against embryonic stress (Rivkees & Wendler, 2012). Thus, the adenosinergic system underpins the formation, development, physiological regulation and stress or disease resistance of the mammalian heart. Such effects render the AR system an attractive target for new pharmacotherapeutics. Ongoing research continues to unmask new cardiovascular actions of the ARs, underlying signaling mechanisms, AR interactions, and effects of ARs in different disease states.

2. The AR family

2.1. AR gene expression

Adenosine regulates cell function via four structurally related G-protein coupled receptors (GPCRs)—A_1, A_{2A}, A_{2B}, and A_3Rs (Fredholm et al., 2011). The ARs were initially classified based on pharmacologic responses to adenosine analogues and methylxanthine antagonists—the A_1 and A_3Rs inhibiting and the A_2R sub-type activating adenylate cyclase. The A_2 was subsequently sub-divided according to the existence of distinct high- (A_{2A}) vs. low-affinity (A_{2B}) binding sites. All four AR sub-types are expressed throughout the heart (Yang et al., 2007; Chandrasekera et al., 2010), with differing mRNA (*Adora*) levels inferring substantial differences in patterns of sub-type expression (Fig. 1). Intact heart and HL-1 atrial myocytes both express highest levels of *Adora1*, followed by *Adora2a* and much lower expression of *Adora2b* and *Adora3*. In contrast, analysis of cardiac fibroblasts (Epperson et al., 2009) reveals high expression of *Adora2b* and *Adora2a*, with very low levels of *Adora1* and *Adora3* (Fig. 1). Differing expression patterns across cells reflect in part differential transcriptional control, which also contributes to inducibility of specific ARs with hypoxia or inflammation. In addition, expression is subject to control by miRNAs, short intron/intergenic RNAs targeting genes that possess complementary sites in their 3′- or 5′-untranslated regions (UTRs). Recent work reveals inflammatory cytokines induce A_{2B}R expression in epithelial cells independently of gene promoter activity, involving post-transcriptional control by *miR-27b* and *miR-128a* (Kolachala et al., 2010). Neutrophil and T cell A_{2A}R expression is controlled by *miR-214*, *miR-15*, and *miR-16* (Heyn et al., 2012), for example. The precise mechanisms regulating myocardial AR expression remain to be defined. Given emerging data on the efficacy of anti-miRNAs as a new class of drug, an understanding of miRNA control of AR expression may ultimately permit control of AR expression via select miRNA targeting. Since much information regarding AR transcription stems from analysis of non-cardiac cells, the following discussion entails a brief description of AR transcription in varied cell types.

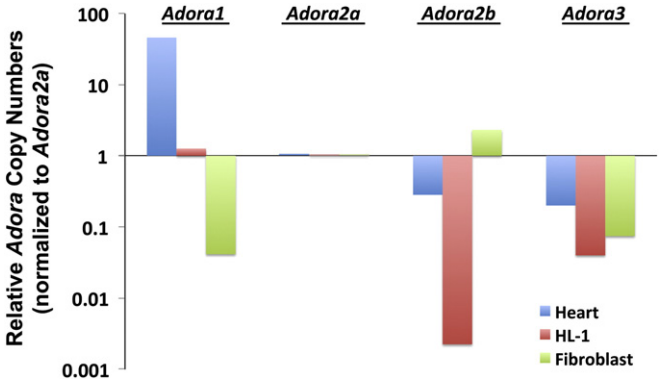

Fig. 1. Expression patterns for AR mRNAs (*Adora1*, *Adora2a*, *Adora2b*, *Adora3*) in murine myocardium, murine HL-1 atrial myocytes (means of 4–6 determinations; *Adora* expression calibrated against 18s rRNA copy numbers), and rat cardiac fibroblasts (data adapted from Epperson et al., 2009). *Adora* sub-type expression in hearts and cells is normalized to *Adora2a* for the purposes of comparison. Intact heart expresses high levels of *Adora1* followed by *Adora2a*, with *Adora2b* and *Adora3* ≥2-orders of magnitude lower; myocytes similarly express high levels of *Adora1* and *Adora2a*, with *Adora2b* and *Adora3* 1- to 2-orders of magnitude lower; fibroblasts express high levels of *Adora2b* and *Adora2a*, with low levels of *Adora1* and *Adora3*.

2.1.1. A_1R transcription

The A_1R gene (*Adora1*) was initially cloned in 1991 from rat brain tissue (Mahan et al., 1991). Putative cAMP response element (CRE), HIF-1 and B-Myb binding sites exist in the human promoter (St Hilaire et al., 2009), and Nkx2.5, NF-κB and GATA4 sites in mice. GATA4 and Nkx2.5 act to synergistically control *Adora1* expression (Rivkees et al., 1999). Exon modifications in the 5′-UTRs appear to play a role in differing basal expression patterns across cell types (Ren & Stiles, 1994). In terms of induction processes, hypoxia can induce A_1Rs in smooth muscle in a NF-κB dependent manner (Hammond et al., 2004), as does oxidative stress (Nie et al., 1998). Adenosine levels themselves may also regulate A_1R expression: in a murine model of left ventricular dysfunction (Funakoshi et al., 2007) low adenosine levels are associated with increased A_1R expression, and reductions in A_1R agonism increase A_1R expression (Hettinger-Smith et al., 1996). Thus, low levels of adenosine and AR engagement may up-regulate A_1R expression in a feedback manner.

2.1.2. A_{2A}R transcription

The A_{2A}R gene (*Adora2a*) was cloned in 1989 from murine thyroid cDNA (Libert et al., 1989), and later from rat brain cDNA (Chern et al., 1992). The human promoter expresses putative CRE, Nkx2.5, B-Myb and NF-κB sites, with CRE, Nkx2.5, HIF-1 and GATA4 sites in the murine promoter (St Hilaire et al., 2009). The expression of *Adora2* is negatively controlled by A_{2A}R activity and cAMP levels (Saitoh et al., 1994). Analysis of the rat gene reveals that the NF-1 transcription factor represses *Adora2a* expression cell-specifically (Lee et al., 2003). Inflammatory induction of A_{2A}Rs in macrophages (Murphree et al., 2005) and epithelium (Morello et al., 2006) is NF-κB dependent, while hypoxic induction in pulmonary endothelium involves HIF-2α (not HIF-1α) binding to a hypoxia-responsive element (Ahmad et al., 2009). Additionally, CO generated from HO-1 activity (itself induced by A_{2A}Rs) can up-regulate *Adora2a* and A_{2A}R expression in macrophages (Haschemi et al., 2007).

2.1.3. A_{2B}R transcription

The A_{2B}R gene (*Adora2b*) was initially cloned from human (Pierce et al., 1992) and rat brain (Stehle et al., 1992). Both human and murine promoters express putative binding sites for B-Myb, Nkx2.5, HIF-1 and NF-κB, with the human promoter also exhibiting GATA4, GATA6, and CRE sites (St Hilaire et al., 2009). Studies in vascular smooth muscle show that A_{2B}R transcription and expression is up-regulated by the proliferation-inducing transcription factor B-Myb (St. Hilaire et al., 2008), while hypoxic A_{2B}R induction in dendritic cells (Yang et al., 2010b) and human endothelium (Kong et al., 2006) is HIF-1α dependent. Regulation of transcription in the heart awaits more detailed investigation.

2.1.4. A_3R transcription

The A_3R gene (*Adora3*) was first cloned in 1992 from rat striatal cDNA (Zhou et al., 1992), with two rat mRNA variants vs. three for the

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