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Adenosine Receptors and the Heart: Role in Regulation of Coronary Blood Flow and Cardiac Electrophysiology

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Abstract

Adenosine is an autacoid that plays a critical role in regulating cardiac function, including heart rate, contractility, and coronary flow. In this chapter, current knowledge of the functions and mechanisms of action of coronary flow regulation and electrophysiology will be discussed. Currently, there are four known adenosine receptor (AR) subtypes, namely A_1, A_{2A}, A_{2B}, and A_3. All four subtypes are known to regulate coronary flow. In general, A_{2A}AR is the predominant receptor subtype responsible for coronary blood flow regulation, which dilates coronary arteries in both an endothelial-dependent and -independent manner. The roles of other ARs and their mechanisms of action will also be discussed. The increasing popularity of gene-modified models with targeted deletion or overexpression of a single AR subtype has helped to elucidate the roles of each receptor subtype. Combining pharmacologic tools with targeted gene deletion of individual AR subtypes has proven invaluable for discriminating the vascular effects unique to the activation of each AR subtype.

Adenosine exerts its cardiac electrophysiologic effects mainly through the activation of A_1AR. This receptor mediates direct as well as indirect effects of adenosine (i.e., anti-β-adrenergic effects). In supraventricular tissues (atrial myocytes, sinua-trial node and atriovetricular node), adenosine exerts both direct and indirect effects, while it exerts only indirect effects in the ventricle. Adenosine exerts a negative chronotropic effect by suppressing the automaticity of cardiac pacemakers, and a negative dromotropic effect through inhibition of AV-nodal conduction. These effects of adenosine constitute the rationale for its use as a diagnostic and therapeutic agent. In recent years, efforts have been made to develop A_1R-selective agonists as drug candidates that do not induce vasodilation, which is considered an undesirable effect in the clinical setting.

Keywords

A_1 adenosine receptor; A_{2A} adenosine receptor; A_{2B} adenosine receptor; A_3 adenosine receptor; Endothelium; Coronary artery; Smooth muscle; Adenosine receptor knockout; Phospholipase C; MAPK; Adenosine receptor agonist; Adenosine receptor antagonist; Sinus node; AV node; Cardiac electrophysiology; PSVT; Anti-beta adrenergic action

1 General Background: The Adenosine Hypothesis

The heart is an astounding organ, capable of pumping over 8,000 liters of blood through the efficient operation of ~100,000 heartbeats per day. To place this in perspective, the total

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volume of blood ejected by the heart in a single day weighs over nine tons, and over one's lifetime the volume of blood pumped by the heart could fill the Empire State Building! The energy required to perform work of this magnitude is almost exclusively derived from aerobic oxidation of various substrates in the form of adenosine 5′-triphosphate (ATP) (Ingwall 2007; Knaapen et al. 2007). Cycling through up to 30 times its own weight in ATP per day (Ingwall and Weiss 2004; Neubauer 2007), the heart consumes more oxygen than any other organ (Taegtmeyer et al. 2005). Yet, because the myocardial ATP content is relatively small (4–6 μmol g^{-1}) compared to the rapid basal rate of ATP expenditure (30 μmol g^{-1} per minute), it is absolutely crucial that ATP production, and therefore oxygen supply, is closely matched across a broad range of cardiac work loads (Deussen et al. 2006). This inextricable link between myocardial function and metabolic demand is the basis of the "adenosine hypothesis" for the metabolic regulation of coronary flow (Berne 1963; Gerlach and Deuticke 1966).

Using an anesthetized open-chest working dog heart model, Berne demonstrated that myocardial hypoxia results in coronary venous efflux of adenine nucleotides, and that adenosine induces coronary dilation (Berne 1963). Together, these findings led to the following hypothesis:

> Reduction in myocardial oxygen tension by hypoxemia, decreased coronary blood flow, or increased oxygen utilization by the myocardial cell leads to the breakdown of adenine nucleotides to adenosine. The adenosine diffuses out of the cell and reaches the coronary arterioles via the interstitial fluid and produces arteriolar dilation. The resultant increase in coronary blood flow elevates myocardial oxygen tension, thereby reducing the rate of degradation of adenine nucleotides, and decreases the interstitial fluid concentration of adenosine by washout and enzymatic destruction. This feedback mechanism serves to adjust coronary blood flow to meet the new metabolic requirements and a new steady state is achieved. (Berne 1963)

Soon afterward, it was demonstrated that adenosine levels increase almost threefold within as little as 5 s of myocardial ischemia in vivo (Olsson 1970), and the incremental increase in coronary flow correlates highly with this rapid release of endogenous adenosine (Rubio et al. 1974). In the 45 years since the adenosine hypothesis was proposed, extensive investigation has established that adenosine serves as both a "sensor" of imbalances in energetic supply and demand and as a local metabolic regulator of coronary flow (Berne 1980; Deussen et al. 2006; Hori and Kitakaze 1991; Morrison et al. 2007; Tune et al. 2004). Although other effectors confer built-in redundancy for control of the coronary circulation (nitric oxide, ATP-sensitive potassium channels, acidosis, carbon dioxide, pO2, etc.; Deussen et al. 2006), it is clear that under conditions of impaired oxygen supply-to-demand ratio, rapid local production of adenosine leads to marked coronary dilation.

2 Adenosine and Coronary Regulation

Adenosine is an autacoid that plays a critical role in regulating coronary circulation. Adenosine is produced by the action of ecto-5′-nucleotidase on extracellular ATP released from the parenchymal tissue (including endothelium). Extracellular adenosine interacts with specific cell-surface receptors located on the smooth muscle and endothelial cells of the coronary artery to produce relaxation. Currently, there are four known adenosine receptor (AR) subtypes, namely A_1, A_{2A}, A_{2B}, and A_3. Although all four AR subtypes are found in coronary smooth muscle cells, only A_{2A}AR and A_{2B}AR have been shown to be present on coronary endothelial cells (Olanrewaju et al. 2002, 2000). Recently, A_3AR has been localized on endothelial cells in mouse aorta, leading to contraction of smooth muscle through cyclooxygenase I (Cox-I) (Ansari et al. 2007).

To date, pharmacological interventions using adenosine or its analogs are mostly directed toward adenosine-mediated effects on the cardiovascular system, such as the treatment of supraventricular arrhythmia, pharmacological stress myocardial perfusion imaging, congestive heart failure, controlling blood pressure, attenuating reperfusion injury following regional myocardial infarction, reducing infarct size, reducing incidence of arrhythmias, and improving postischemic cardiac function (Geraets and Kienzle 1992; Neubauer 2007; Peart and Headrick 2007; Smits et al. 1998). In the coronary circulation, A_{2A}AR plays a pivotal role in controlling vasodilation, while other receptors play a lesser role (Frobert et al. 2006; Hodgson et al. 2007; Morrison et al. 2002; Talukder et al. 2003). For instance, A_{2B}AR also mediates coronary vasodilation, while both A_1AR and A_3AR have been found to negatively modulate coronary vasodilation induced by A_{2A}AR and/or A_{2B}AR activation (Morrison et al. 2002; Talukder et al. 2002a; Tawfik et al. 2006). However, the significance of A_1, A_{2B}, and A_3ARs in coronary flow regulation remains to be fully elucidated.

The distribution of ARs along the branches of coronary arteries also varies. In the porcine heart, expression of A_1 and A_{2A}AR proteins has been documented in the left anterior descending artery (LAD), but only A_{2A}ARs are expressed coronary arterioles (Hein et al. 2001). Another study found that A_1, A_{2A}, and A_{2B}ARs are also expressed in coronary arterioles and venules (Wang et al. 2005). Functional studies in A_{2A}AR knockout (KO) mice suggested that A_{2B}AR may be more important in regulating larger coronary arteries (e.g., the LAD) than previously thought (Teng et al. 2008).

3 Endothelium-Dependent and Endothelium-Independent Regulation

It has been suggested that both A_{2A}AR and A_{2B}AR mediate hyperpolarization of smooth muscle and nitric oxide (NO) release from coronary artery endothelium (Hasan et al. 2000; Olanrewaju et al. 2002; Watts et al. 1998). Cell culture studies have demonstrated the involvement of A_{2A}AR- and A_{2B}AR-mediated NO release in porcine and human coronary endothelial cells (Li et al. 1998; Olanrewaju and Mustafa 2000). However, very few functional studies demonstrated that NO release is responsible for A_{2A}AR- or A_{2B}AR-mediated coronary vasodilation. Inhibition of NO synthase has been found to limit basal coronary flow (CF) in various species (Flood et al. 2002; Zatta and Headrick 2005). It has been shown in porcine coronary arterial rings that N^G-methyl-L-arginine (L-NMA, 30 μM), an NO synthase inhibitor, attenuated the relaxations of endothelium-intact but not endothelium-denuded rings induced by adenosine-5′-*N*-ethylcarboxamide (NECA), a nonselective adenosine agonist, and 2-[*p*-(2-carboxyethyl)]phenylethyl- amino-5′-*N*-ethylcarboxamidoadenosine (CGS-21680), a selective A_{2A}AR agonist (Abebe et al. 1995). It has been speculated that endogenously released adenosine and prostanoids induce NO- and/or K_{ATP} channel-dependent vasodilation and thereby modulate basal coronary tone (Flood et al. 2002; Hein et al. 2001; Talukder et al. 2002b; Zatta and Headrick 2005). Using two different NO synthase inhibitors in isolated hearts from wild-type and A_{2A}AR KO mice, it was found that A_{2A}AR plays a significant role in background NO release, thus affecting basal coronary tone (Teng et al. 2008). The role of A_{2B}AR in NO release remains to be determined, however.

The ARs responsible for endothelial-independent relaxation of coronary artery smooth muscle have not been conclusively determined; however, both A_{2A}AR and A_{2B}AR have been implicated (Morrison et al. 2002; Talukder et al. 2003, 2002b). A study with denuded porcine coronary arteries clearly demonstrated that A_{2A}AR plays a predominant role in endothelial-independent vasodilation, while A_{2B}AR may play a minor role (Teng et al. 2005).

4 Baseline Coronary Flow Control

It has been shown that both A_{2A}AR and A_{2B}AR mediate endogenous and exogenous adenosine-induced dilation of mouse coronary arteries (Morrison et al. 2002; Talukder et al. 2003). A_{2A}AR activation also contributes significantly to basal NO release and basal tone in coronary circulation (Flood et al. 2002; Teng et al. 2008; Zatta and Headrick 2005).

The cardiovascular effects of A_{2B}AR activation are similar to those mediated by A_{2A}AR; however, the affinity of adenosine to the latter is lower (Feoktistov and Biaggioni 1997; Hack and Christie 2003; Schulte and Fredholm 2003). The role of A_{2A}AR in basal vascular tone remains to be determined. However, it has been speculated that under pathological conditions such as ischemia, A_{2B}AR may be upregulated to compensate for the downregulation of A_{2A}AR-mediated responses. Indeed, an upregulation of A_{2B}AR gene expression has been found in ischemic mouse hearts (Ashton et al. 2003; Morrison et al. 2007). A more recent study has also demonstrated upregulation of A_{2B}AR in coronary arteries of A_{2A}AR gene KO mice, suggesting that A_{2B}AR provides a supportive role to the predominantly A_{2A}- mediated control of the coronary circulation (Teng et al. 2008).

5 Second-Messenger Systems

It has been well recognized that A_1 and A_3 ARs are coupled to $G_i/G_o/G_q$ proteins and inhibit the activity of adenylate cyclase (AC), while A_{2A} and A_{2B}ARs are coupled to G_s and activate AC, leading to cyclic adenosine 5′-monophosphate (cAMP) accumulation and subsequent activation of protein kinase A (PKA) (Fredholm et al. 2000). Indeed, in coronary arteries, where A_{2A}AR is predominant, A_{2A}AR-induced vasodilation is mediated mainly by the cAMP-dependent pathway (Hussain and Mustafa 1993; Rekik and Mustafa 2003). However, other second-messenger systems, such as phosphatidylinositol 3-kinase, tyrosine kinase and phospholipase C (PLC), may also be activated by ARs (Ansari et al. 2008; Peart and Headrick 2007; Tawfik et al. 2005), but their roles in mediating the effects of adenosine on the coronary vasculature have not been clearly defined. In addition, crosstalk between the cAMP/PKA pathway and the PLC/PKC pathway has also been reported (Germack and Dickenson 2004). Currently, the tangled web of these two second-messenger systems has garnered the most attention in studies of AR mechanism of action in cardiovascular tissue.

5.1 cAMP–MAPK

Following the activation of G_s protein by A_{2A}AR and A_{2B}AR, various second messenger signaling pathways including mitogen-activated protein kinases (MAPK) are initiated. The signal transduction pathway from G-protein-coupled receptors to MAPK is not fully understood, and may vary in different cell types (Fredholm et al. 2000). There are three well-characterized MAPKs: extracellular regulated kinase (ERK), or p42/44, p38, and jun *N*-terminal kinase (JNK). They seem to play a role in ischemic preconditioning, postconditioning (Morrison et al. 2007), smooth muscle cell growth, vascular smooth muscle migration, and vascular contraction (Haq et al. 1998; Kalyankrishna and Malik 2003; Wilden et al. 1998). Adenosine is reported to stimulate all MAPKs in the perfused rat heart (Haq et al. 1998). Agonist binding to A_{2A}AR can result in both activation and inhibition of ERK phosphorylation, depending on the type of cell expressing these receptors, and so can the second messenger pathway controlled by A_{2A}AR (Fredholm et al. 2000). A_{2B}AR is the only subtype capable of activating all three types of MAPKs (ERK1/2, p38, and JNK). It has also been shown that the same concentration of NECA and adenosine induces ERK1/2 phosphorylation to a greater extent than cAMP production (Fredholm et al. 2000). The involvement of p38 MAPK in adenosine-induced vasodilation has been recently reported (Teng et al. 2005); however, the role of MAPKs in the regulation of vascular tone requires more complete characterization.

There are a few reports linking ARs to p38 MAPK that provide clues as to which mediators are involved in the activation of p38 MAPK. A recent report demonstrated that cAMP inhibits p38 MAPK activation in endothelial cells derived from human umbilical vein (Rahman et al. 2004). In contrast, PKA was found to activate p38 MAPK in macrophages (Chio et al. 2004). Furthermore, the signaling pathways both up- and downstream of the p38 MAPK pathway are diverse, which may explain why p38 can be activated and create crosstalk among various stimuli (Eckle et al. 2007; Ono and Han 2000). For instance, it has been reported that p38 MAPK plays a significant role in angiotensin II-induced contraction (Meloche et al. 2000; Watts et al. 1998), while others have found that p38 MAPK is involved in adenosine-induced vasodilation (Teng et al. 2005). It is also possible that different p38 MAPK subtypes ($p38_{\alpha}$, $p38_{\beta}$, and $p38_{\gamma}$) are responsible for signaling via different pathways. Further investigation is needed to clarify the relationship between ARs and MAPKs vis-à-vis coronary regulation.

5.2 PLC–PKC

By virtue of differential coupling to either G_s (A_{2A} and A_{2B}ARs) or G_i proteins (A_1AR and A_3AR), along with variable tissue distribution of AR subtypes, adenosine elicits both relaxation (A_{2A}- and A_{2B}-mediated) and constriction (A_1- and A_3-mediated) in the peripheral and coronary vasculature. While this is discussed in further detail below with regard to coronary regulation, recent evidence supports a role for the phospholipase C (PLC)–protein kinase C (PKC) system in A_1AR-mediated contraction of aortic vascular smooth muscle (Tawfik et al. 2005). Specifically, isolated aortic rings from wild-type and A_1AR-KO mice were treated with adenosine, NECA, a nonselective AR agonist or 2-chloro-N^6-cyclopentyl- adenosine (CCPA), an A_1AR selective agonist, demonstrating uniform contractile responses in the 100 nM to 1 μM range in wild-type aortas only. Adenosine-induced vasoconstriction was not observed in aortas from A_1AR knockout mice with either nonselective (adenosine, NECA) or A_1-selective (CCPA) agonists, and the contractile response in wild-type aortas was eliminated by an A_1AR-selective antagonist, 1,3-dipropyl-8-cyclopentylxanthine (DPCPX). CCPA-mediated contraction in wild-type aortic rings was also eliminated by the PLC inhibitor U-73122, indicating a role for the PLC–PKC pathway in adenosine-mediated vasoconstriction (Tawfik et al. 2005). Other studies have shown that A_1AR enhances PKC expression in porcine coronary arteries (Marala and Mustafa 1995a, b, c). Moreover, a PKC inhibitor, GO-6893, was able to inhibit ENBA-induced contraction in mouse aorta (Ansari et al. 2008). Taken together, these findings suggest that the PLC–PKC path- way has a major role in A_1AR-mediated vascular tone (i.e., contraction of coronary arteries and the aorta).

5.3 Other Second Messengers

Phosphatidylinositol 3-kinase (PI_3 kinase) activates protein kinase B (PKB, also known as Akt), which phosphorylates and activates a cyclic nucleotide phosphodiesterase, 3B. Increases in cyclic nucleotide concentrations inhibit agonist- induced contraction of vascular smooth muscle. A PI_3-kinase inhibitor, LY 294002, has been shown to inhibit KCl, phorbol 12,13-dibutyrate (PDBu), and serotonin-induced contraction in bovine carotid artery smooth muscle strips, suggesting that the PI_3-kinase pathway plays a role in vascular smooth muscle tone (Komalavilas et al. 2001). A recent study provided the first evidence that A_{2B}AR-mediated cAMP formation activates ERK1/2 via a pathway dependent on PI_3 kinase, tyrosine kinases and Rap1 in CHO cells (Schulte and Fredholm 2002).

Tyrosine kinase and PKC are also found to trigger the MAPK system (Fredholm et al. 2000; Lowes et al. 2002; Robinson and Dickenson 2001; Yang et al. 2000; Zhao et al. 2001). Studies in A_1AR-induced delayed preconditioning in rabbits have suggested an important

role for tyrosine kinase and PKC. These studies also speculate that the p38 MAPK/Hsp27 pathway may be a distal effector of this protection (Dana et al. 2000).

5.4 K^+ Channels

All four major types of K^+ channels (K_{ATP}, K_v, K_{IR} and K_{Ca}) are present in both coronary endothelial and smooth muscle cells (Frieden et al. 1999; Glavind-Kristensen et al. 2004; Kim et al. 2003; Li et al. 1999; Liu et al. 2001; Quayle et al. 1997; Rogers et al. 2007; Sun Park et al. 2006). However, the involvement of K^+ channels in adenosine-induced responses remains unclear. Activation of A_{2B}AR activates K_{ATP} channels in human and guinea pig coronary arteries independent of NO (Kemp and Cocks 1999; Mutafova-Yambolieva and Keef 1997; Niiya et al. 1994). K_{ATP} channels have been shown to mediate A_{2A}AR-induced vasodilation in systemic artery circulation and afferent arterioles of rat kidney and porcine coronary arterioles (Bryan and Marshall 1999; Hein et al. 2001; Tang et al. 1999). A study of cultured porcine coronary endothelial cells demonstrated the involvement of both K_{ATP} and K_{ca} in A_{2A} and A_{2B}AR-mediated hyperpolarization (Olanrewaju et al. 2002), which also leads to NO release (Olanrewaju and Mustafa 2000). Another study also suggested that activation of A_1AR on endothelial cells leads to K_{ATP} channel opening and subsequent Ca^{2+} influx, and an increase in $[Ca^{2+}]_{i,}$, which may lead to direct activation of eNOS via the Ca^{2+}–calmodulin pathway and NO release (Ray and Marshall 2006). In guinea pig coronary artery smooth muscle cells, the A_{2A}AR selective agonists CGS-21680 and N^6-[2-(3,5-dimethoxyphenyl)-2-(2-methoxyphenyl] ethyl adenosine (DPMA) failed to induce hyperpolarization, while the nonselective agonist NECA induced glibenclamide-sensitive hyperpolarization, suggesting that A_{2B}AR may be the only AR subtype involved in K_{ATP}-induced hyperpolarization in coronary smooth muscle (Mutafova-Yambolieva and Keef 1997). Further studies using patch clamp techniques will be valuable in clarifying the role of K^+ channels in adenosine-mediated vasoregulation.

6 Insight from Adenosine Receptor Gene-Modified Models

Most of what is known about adenosine-mediated coronary regulation is derived from pharmacologic studies using a broad spectrum of experimental models (Abebe et al. 1994; Belardinelli et al. 1998; Berne 1980; Deussen et al. 2006; Flood et al. 2002; Hasan et al. 2000; Hori and Kitakaze 1991; Makujina et al. 1992; Mustafa and Abebe 1996). Applying an ever-expanding collection of highly selective AR analogs (both agonists and antagonists) in such a variety of models has confirmed that the A_{2A}AR is the predominant subtype mediating adenosine-induced coronary vasodilation (Belardinelli et al. 1998; Shryock et al. 1998). However, the pharmacologic approach is limited by the selectivity of the ligands and/or potency, and frequently results in only indirect evidence that activation of other AR subtypes modifies adenosine-mediated coronary responses (Kemp and Cocks 1999; Makujina et al. 1992; Talukder et al. 2002b). The adventage of gene-modified models with targeted deletion or overexpression of a single AR subtype has allowed a more complete evaluation of adenosine-mediated responses than previously possible through agonist/antagonist studies alone. The cardiovascular phenotypes of several AR KO/overexpression models are reviewed by Ashton et al. (2007); Table 1 summarizes available data on the vascular phenotypes of A_1, A_{2A}, A_{2B}, and A_3AR KO models.

6.1 A_{2A}AR KO Mouse

The A_{2A}AR KO mouse model was developed and characterized by Ledent et al. 1997. Although the model was developed primarily as a tool for Parkinson's disease research, A_{2A} knockout mice were noted to be hypertensive, suggesting a direct vascular/cardiovascular effect of this targeted deletion. Subsequent studies combined the specificity of A_{2A}AR deletion with the traditional pharmacologic approach to demonstrate that although basal

coronary flow was unchanged by A_{2A}AR deletion (Morrison et al. 2002, 2007; Talukder et al. 2003), adenosine-induced coronary dilation was significantly impaired in isolated hearts (Morrison et al. 2002; Talukder et al. 2003) and in isolated coronary arteries (Teng et al. 2008). During recovery from global ischemia, isolated A_{2A}AR KO hearts also demonstrated reduced coronary flow compared to wild-type littermate controls (Morrison et al. 2007). Together, these studies indicate that A_{2A}AR plays a primary role in murine coronary regulation. Importantly, the observation that a nonselective adenosine analog, NECA, induced coronary dilation in hearts lacking A_{2A}ARs documented for the first time that other AR subtypes modulate adenosine-induced coronary regulation (Morrison et al. 2002). This NECA-induced coronary dilation in A_{2A} knockout hearts was attenuated by alloxazine, a putatively selective A_{2B}AR antagonist, indicating that A_{2B}ARs act in concert with A_{2A}ARs to elicit murine coronary dilation (Morrison et al. 2002; Talukder et al. 2003).

6.2 A_{2B} AR KO Mouse

Limited data exist regarding the vascular phenotype of A_{2B} KO mice, as this is the latest of the AR KO models to be developed. Most recent reports on studies with A_{2B} KO mice demonstrate a critical role for the A_{2B}AR in protecting against excessive vascular adhesion and injury (Yang et al. 2008, 2006), hypoxia-induced vascular leak (Eckle et al. 2008), and infarct size associated with regional ischemia- reperfusion (Eckle et al. 2007). In two distinct A_{2B}AR KO in vivo models, tail-cuff measurements showed no differences in resting blood pressure (Hua et al. 2007; Yang et al. 2006). The effects of A_{2B}AR deletion on coronary flow are not yet reported. However, using the A_{2B} KO model recently characterized by Hua et al. (2007), preliminary data have indicated that targeted deletion of A_{2B}ARs has no effect on either basal or postischemic coronary flow compared to wild-type hearts (Morrison et al., unpublished observations). While prior studies have shown that A_{2B}ARs plays a role in adenosine-induced coronary dilation (Morrison et al. 2002), it is not clear whether the absence of A_{2B}ARs would result in the attenuation of this effect.

6.3 A_{1A}R and A_3AR KO Mouse

Based on data obtained in earlier pharmacologic studies, along with more recent data from studies using A_{2A} and A_{2B}AR knockout mice, it can be concluded that adenosine-induced coronary dilation is predominantly mediated by A_{2A}AR and to a smaller extent by A_{2B}AR. As noted above, the vasodilatory effect of both A_{2A} and A_{2B}AR activation is largely due to their coupling to G_s proteins and the resultant activation of AC and production of cAMP (Hussain and Mustafa 1993; Rekik and Mustafa 2003). Since both A_1AR and A_3AR are G_i coupled, and their activation attenuates cAMP production by AC inhibition, it is not unreasonable to expect that A_1AR and/or A_3AR activation would negatively modulate A_{2A}AR- and A_{2B}AR-mediated vasodilation. Early evidence of A_1AR-mediated coronary vasoconstriction is derived from pharmacologic studies (Hussain and Mustafa 1995), but more recently this phenomenon has been confirmed in both coronary (Tawfik et al. 2006) and aortic (Tawfik et al. 2005) vasculature using A_1AR KO mouse. Similarly, early attempts to clarify the relative roles of each AR subtype in aortic and coronary vasoregulation using pharmacologic agents (Talukder et al. 2002b) have been followed by direct and convincing evidence from A_3AR KO mice demonstrating that A_3 activation causes vasoconstriction in both the coronary (Talukder et al. 2003) and aortic vasculatures (Ansari et al. 2007). Thus, while activation of A_{2A} and A_{2B} ARs leads to coronary dilation, A_1 and A_3AR activation negatively modulates this effect through vasoconstriction.

Using functional studies with even more selective and potent pharmacologic ligands, targeted gene deletion of individual AR subtypes has proven invaluable for discriminating the vascular effects unique to the activation of each AR subtype. Coming full circle, it seems fitting that information gained from these models is now being harnessed to improve our

pharmacologic approach to both diagnostic and therapeutic interventions in the clinical management of heart disease.

7 Clinical Application of Selective A_{2A}AR Agonists for the Detection of Coronary Artery Disease

Adenosine (Adenoscan) has been used as a pharmacological stress agent in conjunction with radionuclide myocardial perfusion imaging (MPI) in patients unable to undergo adequate exercise stress. Dipyridamole, an adenosine uptake blocker, was also used for this purpose for several years prior to the approval of Adenoscan by the US Food and Drug Administration (Cerqueira 2006). Due to frequent side effects (e.g., bronchospasm, AV nodal conduction block) of these two agents, there was a need for better selective drugs for myocardial stress testing. In the late 1980s to early 1990s (Abebe et al. 1994; Mustafa and Askar 1985), it was discovered that adenosine-induced vasodilation of coronary arteries of several species, including humans, was mediated predominately by A_{2A}AR (Ramagopal et al. 1988; Shryock et al. 1998). This discovery led to the development of more selective agonists for the A_{2A}AR subtype, including the Ciba–Geigy (Novartis) compound CGS-21680 (Francis et al. 1991; Hutchison et al. 1989). CGS-21680 was later discovered to be a very selective agonist for the A_{2A}AR subtype in a number of species, including humans (Abebe et al. 1994; Makujina et al. 1992). It was shown that CGS-21680 and another A_{2A}-selective compound from Ciba–Geigy (2-[(2-cyclohexylethyl)amino]-adenosine, CGS-22492) produced significant relaxation in isolated human coronary arteries from organ donors (Makujina et al. 1992). However, it was also discovered that the nonselective analog NECA produced greater relaxation than the A_{2A}-selective CGS-21680 and CGS-22492, suggesting that there was another AR subtype (possibly A_{2B}AR) causing this additional relaxation (Makujina et al. 1992).

Since ARs were not cloned at the time of the study described above, and little was known about A_{2B}ARs, the possibility was left open that another AR subtype contributes to relaxation of human coronary arteries. It was not until the availability of A_{2A}AR KO mouse that an unequivocal demonstration of the role that the A_{2B}AR plays in the regulation of coronary flow became possible (Morrison et al. 2002). Using A_{2A}AR KO mice, Mustafa and his coworkers showed that NECA increased coronary flow, whereas CGS-21680 did not have an effect (Morrison et al. 2002). Moreover, it has recently been reported that there is a compensatory upregulation of the A_{2B}AR receptor in A_{2A}AR KO mice (Teng et al. 2008), further lending support to the theory that most likely the A_{2B}AR is responsible for NECA-induced vasorelaxation of coronary arteries in the A_{2A}AR KO mouse model and perhaps in human coronary arteries. Validation of the role of A_{2B}ARs in functional responses in coronary arteries will be determined in A_{2B}AR KO mouse hearts, as the A_{2B}AR KO mouse model has just recently become available. This is an area of active investigation in Mustafa's group.

These data strongly suggest that, in addition to the A_{2A}AR, the A_{2B}AR also plays a role in the regulation of coronary flow in humans and animals. Therefore, complete dilation of the coronary vascular bed to determine coronary reserve in patients with suspected coronary artery disease may require the use of a combination of A_{2A}AR and A_{2B}AR agonists. These observations are supported by a recent report (Nitenberg et al. 2007) showing that intracoronary infusion of adenosine (60 μg) elicits a lower hyperemic response than postocclusion hyperemia (30 s). These authors concluded that the use of an adenosine infusion represents a potential source of error in determination of coronary reserve, and may result in an underestimation of the physiological significance of coronary stenosis. It is true that adenosine, being the natural endogenous nonselective AR agonist, will activate all four AR subtypes, including A_{2A} and A_{2B}. However, adenosine is a less potent and nonselective

agonist that will also activate A_1 and A_3 ARs, causing a reduction in coronary flow (Talukder et al. 2002a; Tawfik et al. 2006), which serves to counter the increase in flow due to A_{2A} and A_{2B} AR activation.

If A_{2B}ARs play an important role in human coronary vasodilation, as suggested by earlier studies (Makujina et al. 1992), then re-evaluating the sole use of A_{2A}AR- selective agonists in myocardial perfusion stress testing may be warranted. It is possible that adjunctive use of selective A_{2B}AR agonists in concert with currently employed highly selective A_{2A} agonists may lead to a more complete evaluation of both coronary artery disease and coronary reserve. This becomes important in light of the fact that two A_{2A}-selective AR agonists are in Phase III clinical trials (binodenoson, MRE-0470/WRC-0470, Aderis Pharmaceuticals; apadenoson, ATL-146e, Adenosine Therapeutics) and another, Lexiscan™ (regadenoson, CVT-3146, CV Therapeutics), has recently received FDA approval for use in pharmacological stress myocardial perfusion imaging. Newly available and highly selective A_{2B}AR analogs are beginning to advance our understanding of the role of A_{2B}ARs in the heart, and it is plausible to envision their adjunctive use for coronary dilation in this clinical setting.

8 Cardiac Electrophysiology of Adenosine: Recent Developments

8.1 Introduction

This section focuses on several aspects of the cardiac electrophysiology of adenosine and gives an update on clinical applications of second-generation AR ligands. For a broader discussion of the cardiac electrophysiology of adenosine, the reader is referred to several previously published reviews (Belardinelli et al. 1995; Dhalla et al. 2003; Pelleg and Belardinelli 1993; Pelleg et al. 2002; Shen and Kurachi 1995; Zablocki et al. 2004).

Adenosine is a ubiquitous adenine nucleoside found in every cell of the human body; it is released into the extracellular space under physiologic and pathophysiologic conditions. The actions of extracellular adenosine are mediated by four subtypes of AR coupled to G proteins: A_1, A_{2A}, A_{2B} and A_3. In the heart, the electrophysiologic effects of adenosine are mediated mainly by A_1AR. The latter receptor mediates the direct effects as well as the indirect effects; i.e., the anti-β-adrenergic effects of adenosine (Dobson et al. 1987; Schrader et al. 1977).

8.2 Basic Aspects

8.2.1 Negative Chronotropic Action—Adenosine suppresses the activity of cardiac pacemakers including the sinus node (SN), atrio–ventricular (AV) junction, and His–Purkinje system; an inverse relationship between pacemaker hierarchy and sensitivity to adenosine was observed. Specifically, the following sensitivity cascade has been observed: Purkinje fibers > His bundle > AV junction > SN (for references, see Pelleg et al. 1990a). This action is mediated by A_1AR and the activation of a potassium outward current ($I_{KAdo,Ach}$), as well as the suppression of inward calcium current (I_{Ca}) and the hyperpolarization-activated current ("funny" current) (I_f) (Belardinelli et al. 1988; Zaza et al. 1996). Since norepinephrine shifts the activation curve of I_f to the right (DiFrancesco and Borer 2007) and enhances I_{Ca}, the antiadrenergic action of adenosine can also play an important role in its negative chronotropic effects. Data obtained in vitro were interpreted to suggest that the suppression of I_f is more relevant than the activation of $I_{KAdoAch}$ to the modulation of SN automaticity by adenosine (Zaza et al. 1996). However, data obtained in vivo suggest that I_f plays a larger role in the pacemaker activity of His–Purkinje fibers vs. SN (Pelleg et al. 1990a). Specifically, in dogs with complete AV nodal conduction block where SN and ventricular pacemakers were operating concurrently but independently,

adenosine suppressed the activities of both pacemakers in a dose-dependent manner through the activation of A_1AR; however, in the presence of isoproterenol, the dose–response to adenosine in the SN and in the ventricular pacemaker shifted to the left and right, respectively (Pelleg et al. 1990a). Thus, the accentuation of the adenosine's action in the SN seemed to be the result of its suppression of isoproterenol-enhanced I_f and I_{Ca} (indirect, anti-β-adrenergic action), which was added to its induced $I_{KAdoAch}$ (i.e., direct action), while in the ventricular pace- makers, the action of adenosine was mediated mainly by its suppression of I_f, an action which was attenuated in the presence of isoproterenol due the rightward shift of the I_f activation curve induced by the catecholamine (DiFrancesco and Borer 2007). This interpretation agrees well with the maximal diastolic potentials of approximately −65 mV and −90 mV in the SN and His–Purkinje pacemaker cells, respectively, as well as the I_f activation curve, which indicates fractional activation (i.e., activated channel probability of 0.33) and full activation (i.e., activated channel probability of 1.0) of this current at membrane potentials of −65 mV and −90 mV, respectively (DiFrancesco and Borer 2007). The limited yet significant role of I_f in the pacemaking mechanism in the SN is indicated by the fact that CsCl and ZD7288, which are known blockers of I_f, slowed but did not arrest spontaneous pacemaking in SN cells (Denyer and Brown 1990; Sanders et al. 2006). Further support for this interpretation was given by the fact that in this canine model, quinidine, which suppresses acetylcholine-induced $I_{KAdoAch}$, and probably also adenosine-induced $I_{KAdoAch}$, attenuated the negative chronotropic action of adenosine in the SN but not in ventricular pacemakers (Pelleg et al. 1990a). Thus, data obtained in isolated single cells in vitro should be extrapolated to the in vivo setting with great caution; the lack of electrotonic interactions and constitutive neural input (among other factors) in commonly used in vitro models may affect this process.

Overexpression of A_1AR was associated with (i) a 20-fold increase in the potency of 2-chloroadenosine in slowing heart rate and a 35% reduction in maximal heart rate induced by β-adrenoceptor stimulation (Headrick et al. 2000), (ii) a reduced positive chronotropic response to exercise, and (iii) little effect on the resting heart rate (Kirchhof et al. 2003). Interestingly, overexpression of A_3AR was associated with depressed heart rate preferentially at rest (Fabritz et al. 2004). These data give further support to the notion that A_1AR mediates the negative chronotropic action and anti-β-adrenergic effects of adenosine. The role of A_3AR, if any, in the cardiac electrophysiology of adenosine remains to be determined.

8.2.2 Negative Dromotropic Action—The negative dromotropic action of adenosine is manifested in the prolongation of the PR and AH intervals as well as complete AV nodal (AVN) conduction block. Adenosine does not alter the HV interval; therefore, its dromotropic action is mainly due to its effects on the AVN. The seminal work of Belardinelli et al. (see (Belardinelli et al. 1987) elucidated the mechanisms of action of adenosine on the AVN; their major findings were: (i) adenosine mediates hypoxia/ischemia-induced AVN conduction block; (ii) adenosine hyperpolarizes cell membrane potential, shortens action potential duration, slows the recovery of I_{Ca}, and prolongs postrepolarization refractoriness in isolated single AVN cells; (iii) these actions of adenosine are mediated by A_1AR, and; (iv) the degree of amplification of A_1AR occupancy as determined by the negative dromotropic response to adenosine is relatively minimal, indicating "tight" coupling between receptor occupancy and its physiologic outcome (Belardinelli et al. 1981; Clemo and Belardinelli 1986; Clemo et al. 1987; Dennis et al. 1992). A subsequent study confirmed that A_1AR and a pertussis toxin-sensitive G protein mediate the AVN conduction block associated with global myocardial ischemia in vivo (Xu et al. 1993).

8.2.3 Adenosine's Effects on Atrial and Ventricular Myocardium—In the atria, adenosine exerts direct and indirect anti-β-adrenergic effects. The activation of $I_{KAdoAch}$ in

atrial myocytes, which is mediated by A_1AR and pertussis toxin-sensitive G protein, results in shortened action potential duration and refractoriness (Pelleg et al. 1996), thereby facilitating re-entry. Indeed, a common side effect of adenosine is the induction of transient atrial fibrillation (Pelleg et al. 2002). Recently, Hove-Madsen et al. (Hove-Madsen et al. 2006) have demonstrated that A_{2A}AR is expressed in the human right atrium and distributed in a banded pattern along the Z lines, overlapping with the ryanodine receptor. In this study, an A_{2A}AR- selective agonist did not affect the L-type inward Ca^{2+} current (I_{CaL}) amplitude, but it did increase spontaneous calcium release from the sarcoplasmic reticulum (SR) and reduce the fast time constant for I_{Ca} inactivation (Hove-Madsen et al. 2006). These data were interpreted to suggest that activation of the A_{2A}AR stimulates the ryanodine receptor itself (Hove-Madsen et al. 2006).

In general, adenosine does not directly affect ventricular myocytes; although direct activation by adenosine of the ATP-dependent potassium outward current ($I_{K, ATP}$) in isolated rat ventricular myocytes has been proposed (Kirsch et al. 1990), subsequent studies in vitro and in vivo failed to support this hypothesis (Song et al. 2002; Xu et al. 1994). Adenosine exerts pronounced anti-β-adrenergic effects in the ventricular myocardium, which are mediated by A_1AR and reduced intracellular levels of cAMP (Belardinelli and Isenberg 1983). Adenosine attenuates the catecholamine-dependent increase in inward L-type Ca^{2+} current (I_{CaL}), the delayed rectifier potassium current and chloride current (I_{Cl}). In addition, adenosine attenuates I_{CaL}- and transient inward current (I_{Ti})-dependent afterdepolarizations and triggered activity (Song et al. 1992). Interestingly, adenosine terminated episodes of ventricular tachycardia (VT) and abolished the delayed afterdepolarizations (DAD) associated with digoxin toxicity in the perfused guinea-pig heart in vitro and guinea-pig and canine hearts in vivo (Fogaça and Leal-Cardoso 1985; Xu et al. 1995). Because catecholamines play a mechanistic role in digoxin-induced DAD and triggered activity, it was concluded that this antiarrhythmic effect of adenosine was mediated by its anti-β-adrenergic action (Xu et al. 1995). Indeed, several studies have indicated that adenosine can exert an antiarrhythmic effect in the setting of other catecholamine/cAMP-dependent ventricular tachycardias (see below).

8.3 Clinical Aspects

8.3.1 Supraventricular Tachycardias—The seminal work of Belardinelli et al. in the late 1970s and early 1980s led in 1989 to the introduction of adenosine as an effective and safe antiarrhythmic drug for the acute termination of paroxysmal supraventricular tachycardia (PSVT) involving the AVN (Adenocard) (DiMarco et al. 1983; for reviews, see Pelleg and Kutalek 1997; Pelleg et al. 2002). The rationale for the use of adenosine as an antiarrhythmic drug in this setting is derived from its potent suppression of AVN conduction; the latter breaks or slows down re-entrant circuits involving the AVN. However, it has also led to several “off label” uses of adenosine as a diagnostic drug, including the differential diagnosis of broad QRS complex tachycardia (i.e., SVT with aberrant ventricular conduction vs. VT), and assessment of accessory AV pathway ablation (Conti et al. 1995; Keim et al. 1992).

In recent years, a second generation of adenosine receptor-related drug candidates has been developed (Hutchinson and Scammells 2004). For example, tecadenoson (CVT-510; CV Therapeutics, Inc.) is a novel selective A_1AR agonist that is being evaluated as a drug candidate for the acute suppression of PSVT (Cheung and Lerman 2003; Peterman and Sanoski 2005). Clinical trials have shown that the drug effectively terminates PSVT without the side effects caused by the activation of ARs other than the A_1AR, which is associated with the use of adenosine in this setting.

Focal atrial tachycardias are a group of SVTs characterized by the concentric spread of a wave of depolarization from a specific localized source, the mechanism of which includes abnormal automaticity, triggered activity and microreentry (Lindsay 2007). The response to programmed atrial stimulation as well as several pharmacologic agents including adenosine has been used to differentiate these mechanisms. Regarding adenosine, data obtained in recent years support the hypothesis that adenosine-induced suppression or termination of a focal atrial tachycardia is indicative of a microreentry mechanism rather than abnormal automaticity or triggered activity (Iwai et al. 2002; Markowitz et al. 2007, 1999).

8.3.2 Ventricular Tachycardia/Fibrillation—Due to its anti-β-adrenergic actions in the ventricular myocardium, adenosine can affect catecholamine-dependent ventricular arrhythmias. In an early study, adenosine terminated sustained, exercise-triggered VT in four patients with structurally normal hearts (Lerman et al. 1986). Observations in this study have led to the hypothesis that the mechanism of the adenosine-sensitive VT is cAMP-mediated triggered activity (Lerman et al. 1986). Data obtained in subsequent studies in similar patients have supported this hypothesis and indicated that the action of adenosine is mediated by A_1AR (Lerman 1993). Idiopathic repetitive nonsustained monomorphic VT, which is characterized by frequent ectopic beats and salvos of VT, and typically occurs at rest, can also be sensitive to adenosine (Lerman et al. 1995). Among the idiopathic VT, the right outflow tract VT, which is the most common form (and presents as repetitive monomorphic VT or exercise-induced VT) and the left outflow tract VT (Nogami 2002) are both adenosine sensitive (Iwai et al. 2006; Lerman et al. 1997). Thus, the responsiveness to adenosine suggests that the mechanism of these tachycardias is probably cAMP-mediated triggered activity (Lerman et al. 2000).

In a swine model of prolonged ventricular fibrillation (VF), a selective A_1AR antagonist accelerated the deterioration in the VF waveform; this finding was interpreted to suggest that endogenous adenosine exerts cardioprotective effects during sudden cardiac arrest associated with VF (Mader et al. 2006). However, data obtained in human subjects raise doubts regarding the use of an A_1AR antagonist in this setting. Specifically, because endogenous adenosine (which accumulates during hypoxia and ischemia) may perpetuate asystole, the use of aminophylline, a nonselective AR antagonist, in the setting of cardiac arrest has been proposed as an acute pharmacologic intervention to improve resuscitation outcome (Viskin et al. 1993). However, subsequent studies have shown that aminophylline offers no benefits in this situation (Hayward et al. 2007).

8.4 Adenosine as a Diagnostic Tool

Several diagnostic applications of adenosine, in addition to the diagnosis of broad QRS complex tachycardia mention above, have been proposed. Viskin et al. (Viskin et al. 2006) have shown that by provoking transient bradycardia followed by sinus tachycardia, adenosine challenge induces changes in QT interval that could be useful in distinguishing patients with long QT syndrome (LQTS) from healthy subjects. Specifically, adenosine challenge resulted in dissimilar responses in patients with LQTS and healthy subjects; the largest difference was recorded during maximal bradycardia, where the difference between the mean QT and QTc values of the two groups was 121 ms (vs. a 59 ms difference at baseline) and 125 ms (vs. a 55 ms difference at baseline), respectively (Viskin et al. 2006). These observations by Viskin et al. (2006) explain the several cases of adenosine-induced polymorphic ventricular tachycardia (i.e., Torsade-de-Pointe; see review by Pelleg et al. 2002).

Several studies have indicated that adenosine can also identify patients with sick sinus syndrome (SSS). For example, Fragakis et al. (2007) found that, when a cutoff value of 525

ms for sinus recovery time (i.e., the time elapsed from sinus arrest until the emergence of the first sinus beat) was used as an indicator of sinus node dysfunction, sinus node recovery time (corrected for baseline rate) had 74% and a specificity of 100% for diagnosis of SSS, while the recovery time following adenosine had a sensitivity of 94 and a specificity of 84%, respectively (Fragakis et al. 2007). Earlier studies reported similar values; i.e., 80% sensitivity and 97% specificity (Burnett et al. 1999), and 67% and 100%, respectively (Resh et al. 1992).

Adenosine has been used in the diagnosis of patients with neurally mediated syncope; i.e., vasovagal syncope and syncope of unknown origin. Based on its sympathomimetic action (direct via activation of chemoreceptors and indirect via the baroreflex), adenosine has been proposed as an adjuvant provocative agent in the protocol of head-up tilt table test (HUT) (Mittal et al. 2004; Shen et al. 1996). The fact that adenosine plasma levels (Carrega et al. 2007; Saadjian et al. 2002) and the number of A_{2A}AR, which were upregulated (Carrega et al. 2007), were higher in patients with a positive HUT was interpreted to suggest that endogenous adenosine mediates syncope in a specific cohort of syncopal patients. However, prolonged adenosine induced AV block in conjunction with HUT in patients with unexplained syncope failed to predict recurrent syncopal episodes (Cheung et al. 2004).

Unfortunately, many studies as well as reviews of those mentioned above (and other similar studies) have treated the cardiovascular effects of adenosine and ATP as being identical. While ATP mimics adenosine due to its rapid degradation to the nucleoside by ectoenzymes, the reverse does not hold; specifically, before its degradation, ATP triggers a cardio-cardiac central vagal reflex mediated by the activation of $P2X_{2/3}$ receptors localized on vagal sensory nerve terminals in the left ventricle; adenosine is devoid of this action (Xu et al. 2005). Thus, the negative chronotropic and dromotropic actions of ATP are mediated by adenosine and the vagus nerve (Pelleg et al. 1997); a mechanism found in cat, dog and man, but not in rodents (Pelleg et al. 1990b). Brignole et al. (Brignole et al. 2003) and Flammang et al. (2006) used bolus intravenous injections of ATP as a diagnostic tool in patients with syncope of unknown cause (for references, see Parry et al. 2006). The former group has used a maximal RR interval >6 s while the latter group has used complete AVN block duration >10 s as an indication of a positive test. In view of the fact the both ATP and adenosine suppress ventricular escape rhythms (Lerman et al. 1988; Pelleg et al. 1986), it is difficult to interpret the RR interval data as the rate of ATP degradation, and hemodynamic factors can directly affect this parameter. Using the RR interval >10 s criterion, it seems that ATP can identify a cohort of elderly patients in whom the mechanism of syncope is bradycardia and who may benefit from pacemaker therapy (see Flammang and AMS Investigators 2006; Flammang et al. 2005; Parry et al. 2006). In these patients, the bradycardia can be due to SN dysfunction, AVN dysfunction, abnormal vagal input to the heart, and any combination of these three causes.

8.5 Future Prospects

In view of the current efforts by the pharmaceutical industry, one can expect the introduction of AR ligands as new drugs for the treatment and diagnosis of cardiac arrhythmias in the near future. This would constitute a quantum step forward in the harnessing of adenosine signal transduction for the benefit of patients.

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Abbreviations

AC	Adenylate cyclase
AH	Atrial to His bundle activation time (representative of AV-nodal conduction time)
AR	Adenosine receptor
ATP	Adenosine 5′-triphosphate
AV	Atrioventricular
AVN	AV-nodal
CCPA	2-Chloro-N^6-cyclopentyl-adenosine
CF	Coronary flow
CGS-21680	2-[*p*-(2-carboxyethyl)]-phenylethyl-amino-5′-*N*-ethylcarboxamidoadenosine
CGS-22492	2-[(2-Cyclohexylethyl)amino]-adenosine
Cox-I	Cyclooxygenase I
CPA	N^6-Cyclopentyladenosine
DAD	Delayed afterdepolarizations
DPCPX	1,3-Dipropyl-8-cyclopentylxanthine
DPMA	N^6-[2-(3,5-Dimethoxyphenyl)-2-(2-methoxyphenyl] ethyl adenosine
ECG	Electrocardiogram
ERK	Extracellular regulated kinase
HV	His bundle to ventricular activation time
HUT	Head-up tilt table test
I_{Ca}	Inward calcium current
I_{CaL}	Inward L-type $Ca2^+$ current
I_{Cl}	Chloride current
I_f	Hyperpolarization-activated current (“funny” current)
$I_{KAdo,Ach}$	Outward potassium current
$I_{K,ATP}$	ATP-dependent outward potassium current
I_{Ti}	Transient inward current
JNK	Jun *N*-terminal kinase
KO	Knockout
L-NMA	N^G-Methyl-L-arginine
LAD	Left anterior descending artery
LQTS	Long QT interval syndrome
MAPK	Mitogen-activated protein kinase
NECA	Adenosine-5′-*N*-ethylcarboxamide
NO	Nitric oxide
PDBu	Phorbol 12,13-dibutyrate

PI_3-kinase	Phosphatidylinositol 3-kinase
PLC	Phospholipase C
PKA	Protein kinase A
PKB (Akt)	Protein kinase B
PKC	Protein kinase C
PR	P wave to R wave interval on the ECG
PSVT	Paroxysmal supraventricular tachycardia
QT	Q wave–T wave interval in the ECG
QTc	Corrected QT interval
RR	R wave–R wave interval in the ECG
SN	Sinus node
SR	Sarcoplasmic reticulum
SSS	Sick sinus syndrome
SVT	Supraventricular tachycardia
VF	Ventricular fibrillation
VT	Ventricular tachycardia

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Table 1

Vascular phenotype of AR KO mice

Gene deletion	Experimental model (refs.)	Vascular phenotype (refs.)
A_1AR KO	• Isolated aortic rings (Tawfik et al. 2005) • Isolated hearts (Morrison et al. 2006; Reichelt et al. 2005; Salloum et al. 2007; Tawfik et al. 2006) • Postischemic isolated hearts (Morrison et al. 2006; Salloum et al. 2007)	• Enhanced basal coronary flow (Morrison et al. 2006; Tawfik et al. 2006) • Unchanged basal coronary flow (Reichelt et al. 2005; Salloum et al. 2007) • Enhanced adenosinergic dilation (Tawfik et al. 2005; Tawfik et al. 2006) • Unchanged adenosinergic dilation (Reichelt et al. 2005) • Reduced postischemic coronary flow (Morrison et al. 2006) • Unchanged postischemic coronary flow (Salloum et al. 2007)
A_{2A}AR KO	• In vivo tail cuff pressure (Ledent et al. 1997) • Isolated hearts (Morrison et al. 2002, 2007; Talukder et al. 2003) • Isolated coronary arteries (Teng et al. 2008)	• Hypertension (Ledent et al. 1997) • Unchanged basal coronary flow (Morrison et al. 2002, 2007; Talukder et al. 2003) • Impaired adenosinergic coronary dilation (Morrison et al. 2002, 2007; Talukder et al. 2003; Teng et al. 2008) • Reduced postischemic coronary flow (Morrison et al. 2007)
A_{2B}AR KO	• In vivo tail-cuff pressure (Yang et al. 2006; Hua et al. 2007) • Isolated hearts (unpublished observations from Mustafa's group)	• Normal basal blood pressure (Yang et al. 2006; Hua et al. 2007) • Unchanged basal coronary flow (unpublished observations from Mustafa's group) • Unchanged postischemic coronary flow (unpublished observations from Morrison's group)
A_3AR KO	• In vivo tail-cuff pressure (Ge et al. 2006; Zhao et al. 2000) • Isolated hearts (Cerniway et al. 2001; Ge et al. 2006; Harrison et al. 2002; Talukder et al. 2002a) • Postischemic isolated hearts (Cerniway et al. 2001; Harrison et al. 2002) • Isolated aortic rings (Ansari et al. 2007)	• Normal basal blood pressure (Ge et al. 2006; Zhao et al. 2000) • Enhanced adenosinergic hypotension (Zhao et al. 2000) • Enhanced adenosinergic coronary dilation (Talukder et al. 2002a) • Unchanged basal coronary flow (Cerniway et al. 2001; Ge et al. 2006; Harrison et al. 2002; Talukder et al. 2002a) • Unchanged postischemic coronary flow (Cerniway et al. 2001; Harrison et al. 2002) • Reduced A_3-mediated vasoconstriction (Ansari et al. 2007)