Adenosine and its Receptors in the Heart: Regulation, Retaliation and Adaptation

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***Short Title*:** Roles of adenosine receptors in the heart

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Abstract

The purine nucleoside adenosine is an important regulator within the cardiovascular system, and throughout the body. Released in response to perturbations in energy state, among other stimuli, local adenosine interacts with 4 adenosine receptor (AR) sub-types on constituent cardiac and vascular cells: A_1, A_{2A}, A_{2B}, and A_3ARs. These G-protein coupled receptors (GPCRs) mediate varied responses, from modulation of coronary flow, heart rate and contraction, to cardioprotection, inflammatory regulation, and control of cell growth and tissue remodeling. Research also unveils an increasingly complex interplay between members of the AR family, and with other receptor groups. Given generally favorable effects of AR activity (*eg.* improving the balance between myocardial energy utilization and supply, limiting injury and adverse remodeling, suppressing inflammation), the AR system is an attractive target for therapeutic manipulation. Cardiovascular AR-based therapies are already in place, and trials of new treatments underway. Although the complex interplay between ARs and other receptors, and their wide distribution and functions, pose challenges to implementation of site/target specific cardiovascular therapy, the potential of adenosinergic pharmacotherapy can be more fully realized with greater understanding of the roles of ARs under physiological and pathological conditions. This review addresses some of the major known and proposed actions of adenosine and ARs in the heart and vessels, focusing on the ability of the AR system to regulate cell function, retaliate against injurious stressors, and mediate longer-term adaptive responses.

Author Keywords: Adenosine; Adenosine Receptors; Angiogenesis; Atherosclerosis; Cardioprotection; Contractility; Glycolysis; Heart Rate; Hypertrophy; Inflammation; Infarction; Ischemia-Reperfusion; Preconditioning; Postconditioning; Remodeling; Vasculogenesis

Abbreviations: AR, adenosine receptor; ANP, atrial natriuretic peptide; AV, atrioventricular; ECM, extracellular matrix; E_{pac}, exchange protein directly activated by cAMP; FFA, free fatty acid; GPCR, G-protein coupled receptor; HIF, hypoxia inducible factor; HSP, heat shock protein; IFN, interferon; IL-, interleukin; K_{ATP}, ATP-gated K^+ channel; MAPK, mitogen-activated protein kinase; MMP, matrix metalloproteinase; NHE, Na^+/H^+ exchanger; NO, nitric oxide; PI3K, phosphoinositide 3-kinase; P_i, inorganic phosphate; PKC, protein kinase C; PLC, phospholipase C; PostC, postconditioning; PreC, preconditioning; ROS, reactive oxygen species; SA, sinoatrial; 8-PT, 8-phenyltheophylline; STEMI, ST-segment elevation myocardial infarction; TNF-α, tumor necrosis factor α; VEGF, vascular endothelial growth factor.

1. Introduction

Adenosine exerts a range of generally beneficial effects in the heart and vessels (1,2), and has been described as a 'retaliatory metabolite' (3). This nucleoside is released from metabolically compromised cells to mediate responses that appear directed at optimizing the balance between energy utilization and generation (**Fig. 1**), thus linking physiological control (via ARs) to cellular energy state. From evolutionary and teleological viewpoints, emergence of adenosine sensitivity is an effective way for cells to sense and respond to acute or prolonged shifts in energy balance. Adenosine is also released in response to physiological and pathological stimuli not necessarily linked to energy state. In this review select roles of cardiovascular ARs are considered within a hierarchy of regulation, retaliation and adaptation. Under physiological conditions or mild perturbations, 'regulatory' effects of adenosine may optimize myocardial energy supply and demand, enhancing O_2 and substrate delivery and modulating energy use through fine-tuning of adrenergic sensitivity, heart rate and conduction (**Fig. 1**). There is experimental evidence that endogenous adenosine can optimize the balance between myocardial energy generation and expenditure, improving the efficiency of O_2 utilization (4,5). With more severe insult such as ischemia or hypoxia, cells may in a sense 'retaliate' via receptor-mediated effects of greatly enhanced adenosine release, which triggers cytoprotective responses that induce short- and longer-term resistance to stress (**Fig. 1**). Finally, ARs play a role in more sustained 'adaptive' changes in myocardial/vascular structure and function. These differing responses are beneficial, yet AR responses may be modified in different pathologies, a dysfunction that can potentially contribute to shifts in resistance to and progression of disease. However, the roles of adenosine and ARs in healthy and diseased humans are yet to be fully delineated, with the bulk of research evidencing important regulatory roles for ARs in a variety of animal models.

1.1 Signal generation

Adenosine can be considered a metabolic signal, released from cells to activate ARs in

response to energy perturbations or imbalances in O_2 supply *vs*. demand. This adenosine signal can be linked simply to net hydrolysis of adenine nucleotides, however loss of purine moieties is a costly approach to cell signaling. Cells thus possess systems for maintaining essential adenine nucleotide pools, permitting controlled release of low regulatory quantities of adenosine whilst ensuring rapid recapture (thus localizing effects to sites of stress or injury).

Adenosine is generated through 2 primary paths - hydrolysis of 5'-AMP or metabolism of s-adenosylhomocysteine. The pathway involving 5-AMP, which is derived primarily from adenine nucleotides but also potentially from cAMP, is highly regulated, coupled to bioenergetic state, and is the most important in generating regulatory adenosine (6,7). The hydrolysis of 5'-AMP can occur either intracellularly or via ecto-nucleotidases. Several studies identify the intracellular 5'-AMP pool as the major source of adenosine release under baseline conditions and during ischemia or hypoxia (8-10). Nonetheless, studies of ecto-nucleotidase inhibition or knockout highlight the physiological importance of this external source of adenosine.

Within the cell the myokinase (adenylate kinase) equilibrium facilitates elevations in substrate for adenosine (5'-AMP) as a function of $[ADP]^2$ (which rises with reductions in the Gibbs free energy of ATP hydrolysis). In addition, regulation of 5'-nucleotidases during de-energization (via shifts in ATP, ADP, P_i, Mg^{2+}) may further promote activity. The adenosine kinase reaction, in turn, effectively and rapidly re-captures adenosine into the nucleotide pool, and its inhibition is key to adenosine release during de-energization, an effect potentially mediated by P_i (7,11,12). Through these mechanisms, adenosine formation is sensitized to perturbations in energy state, yet can be independently regulated through control of enzymatic pathway activity.

As noted above, while the majority of adenosine derives from intracellular paths, ecto-nucleotidase dependent formation appears particularly important in cardiovascular regulation. CD73 activity has been shown to be critical to cardioprotection (13,14), thromboregulation and inflammation (15,16), neointima formation (17), and inhibition of inflammatory/immune

sequelae of cardiac transplantation (18). Interestingly, these responses all involve modulation of inflammatory or vascular cells, perhaps reflecting a specific role for extracellular adenosine generation in endothelial/inflammatory control. Intra- and extracellular sources may be relevant in different cell types under different conditions, generating threshold adenosine levels required for local AR activation. The ecto-nucleotidase pathway will specifically generate adenosine within the extracellular compartment, in close proximity to surface receptors and local inflammatory cell types.

Adenosine not recaptured via cellular re-uptake and the kinase reaction is deaminated to inosine, which is additionally generated in IMP hydrolysis. Inosine also interacts with A_1 and A_3AR, whereas analysis of human A_{2A} and A_{2B} sub-types reveals no substantial agonism. Since extracellular inosine accumulates to much higher levels than adenosine during ischemia or hypoxia, intrinsic A_1 and A_3AR activity under these conditions should involve a major inosine-dependent component. Differing metabolism patterns for 5'-AMP and IMP also leads to potentially distinct patterns of AR agonism by inosine *vs*. adenosine. Olsson and Pearson suggest that IMP catabolism is dominant in cells that primarily generate ATP via anaerobic glycolysis (1), and studies reveal significant generation of inosine from IMP rather than 5'-AMP in ischemic or hypoxic hearts. Inosine and adenosine also compete for nucleoside transport, thereby enhancing each other's extracellular levels (and thus signaling capacity). The roles and importance of inosine-dependent AR activation warrant further investigation.

1.2. Mediation of adenosine responses - the ARs

Adenosine modifies cellular function via membrane-bound A_1, A_{2A}, A_{2B}, and A_3ARs (19). It may also impact via energy substrate effects. Although generally considered as independent functional 'monomers', recent work reveals that these receptors can heterodimerize with other GPCRs, and there is evidence of significant receptor cross-talk in AR responses. The A_1AR can heterodimerize with P2Y1 or D1 dopamine receptors (20,21), and the A_{2A}AR with P2Y, D2

dopamine and mGLU5 receptors (22-24). While these studies assess interactions in recombinant expression models other work does confirm existence of oligomers *in vivo*, albeit in non-cardiac tissue (25). Although of considerable interest, the expression and roles of endogenous receptor complexes in cardiovascular cells remains poorly defined.

The AR sub-types themselves also interact, which may be important in expression of cardiovascular responses. For example, A_1ARs may counter A_2AR mediated vasodilatation (26), anti-adrenergic actions of A_1ARs are counteracted by A_{2A}ARs (27), and there is evidence of interaction between A_1, A_{2A} and A_{2B}ARs in mediating cardiac protection (28). These effects potentially reflect receptor dimerization, since A_1/A_{2A} heteromers occur in other tissue (29). However, these heteromers have not been studied in cardiovascular cells. In terms of cardiac protection, ARs also interact with opioid receptors to limit injury and cell death during ischemia-reperfusion (30). Thus, the AR system exhibits complex interactions between its own members and with other GPCRs. This might be predicted given that purinergic receptors represent one of the earliest signaling systems (31), allowing protracted evolution and refinement of complex signal linkages between cellular function and energy state.

2. Regulation

Within the heart adenosine is attributed with regulatory functions that include control of cardiac contractility/adrenergic responsiveness, impulse generation and conduction, coronary vascular tone, and cardiac substrate utilization. These are addressed here in more detail. Other regulatory functions may be directed at adaptation (*eg.* regulation of fibroblast activity) or protection, and are addressed in subsequent sections. Adenosine also plays a key role in regulating inflammatory responses in a wide range of cells (32). However, full coverage of the latter is beyond the scope of this review, and thus aspects of inflammatory control relevant to the heart and vessels are addressed within the context of specific AR responses.

2.1. Inotropic and adrenergic control

Adenosine primarily modifies cardiac contractility in an indirect fashion, through the modulation of adrenergic responses (33). The anti-adrenergic effects of adenosine in animal models are mediated via A_1ARs, involve $G\alpha_i$ inhibition of PKA activation by ß-adrenoceptors (33,34), and modulation of ß1-adrenoceptor stimulated G_s cycling (35). Dobson and colleagues also show that the A_1AR can attenuate ß-adrenergic responses in a PKC-dependent process (36, 37) involving Gβγ and PLC activation of PKC-ε (38). Distal targets include p38-MAPK (which may play a role in modifying contractile responses) and HSP27 (implicated in cardioprotective responses). There is also evidence for a modest direct inotropic effect of A_{2A}ARs in mammalian myocytes (39,40), involving Ca^{2+} transient augmentation by cAMP/PKA-dependent and PKC-independent signals (37). The A_{2A}AR may additionally modify contractility by countering the anti-adrenergic actions of A_1ARs (27,35). The relevance of these differing inotropic actions in human myocardium remains to be established.

In addition to effects on cardiomyocyte adrenoceptor responses, adenosine and A_1ARs inhibit release of noradrenaline from cardiac nerves (41), reducing levels during ischemia and reperfusion (42,43). These effects are shown to be protective (42), and will contribute (with the abovementioned responses) to inhibition of cardiac activation during periods of enhanced adenosine release. Differing A_1/A_{2A}-dependent actions of adenosine may act to limit cardiac over-stimulation, matching metabolic capacity of the tissue with the level of adrenergic drive. However, the relevance of modest A_2AR-dependent inotropy remains to be established, and the high (indeed non-selective) µmolar levels of potent A_{2A}AR agonist (CGS21680) required to elicit measurable shifts in Ca^{2+} transient and contractility (37) indicate the response would only be engaged at exceedingly high levels of extracellular adenosine. While speculative, A_{2A}ARs may modestly augment contractility in ischemic or hypoxic hearts (when such levels are achieved). The ability of A_{2A}ARs to counter A_1AR-inhibition of adrenergic responses could also enhance

contractility under such conditions - an effect estimated to represent ~2/3 of the total contractile response to the A_{2A}AR (27). However, again these responses are elicited at high CGS21680 levels, an agonist 50- to 100-fold more potent than adenosine at A_{2A}ARs. One would thus not predict appreciable (direct or indirect) A_{2A}AR effects with <10 µM adenosine - levels rarely achieved except in severe ischemia or hypoxia. On the other hand, the A_1AR-mediated effect is engaged at much lower agonist levels and predominates, limiting adrenergic activation of metabolism and contractility in compromised myocardium.

Pathobiology: There is some evidence of shifts in AR control of inotropy and adrenergic function in disease models. For example, Dobson and colleagues found that A_1AR-mediated anti-adrenergic responses in rats are impaired with pressure overload hypertrophy (44). Similarly, Tang *et al.* found that effects of A_1 and A_{2A}ARs on cardiomyocyte adrenergic responsiveness are inhibited or abolished in hypertensive animals, independently of hypertrophy (45). Repression of A_1AR-mediated inhibitory effects in settings of hypertrophy or hypertension could enhance the vulnerability of hearts to chronic shifts in sympathetic activity. As outlined in a later section, alterations in AR expression and function may play a role in the contractile dysfunction (and remodeling) that occurs in hypertrophic and failing hearts.

The inhibitory effects of ARs may also underlie repression of adrenergic signaling and responsiveness in ischemic or hypoxic myocardium. A study by Burgdorf *et al.* supports the idea that post-ischemic repression of cardiac sympathetic neurotransmission (neuronal stunning) involves intrinsic A_1AR activity (43). In other work, Gergs *et al.* identified an unexpected positive inotropic response to adenosine in atrial tissue from 25% of coronary heart disease patients (46). The response was sensitive to A_1AR antagonism, reflecting an overlooked A_1AR-dependent inotropy in some subjects. Its relevance is not clear at this stage. Though not a disease state, the process of aging predisposes to cardiovascular diseases and is also associated with shifts in AR-mediated anti-adrenergic and inotropic actions. Specifically, age impairs adrenergic sensitivity of rodent hearts in part via enhanced A_1AR activity (47,48). Age also modifies the

release of adenosine from hearts, myocytes and fibroblasts (49-52). This highlights the importance of addressing AR responses in older and diseased tissues rather than young healthy subjects, as both age and disease impact on AR functionality (which may be relevant to age-related cardiovascular diseases). Analysis of AR-mediated anti-adrenergic effects in human myocardium is required to clarify the potential physiological and clinical importance of this control mechanism.

2.2. Cardiac impulse generation and conduction

One of the earliest observed actions of adenosine was slowing of heart rate and impulse conduction (53). Adenosine inhibits impulse generation in supraventricular tissue (SA node, AV node) and the His-Purkinje system. Negative chronotropy is A_1AR-mediated, and involves inactivation of the inwardly rectifying K^+ current ($I_{K,Ado}$ or $I_{K,Ach}$), together with inhibition of the inward Ca^{2+} current (I_{Ca}) and the 'funny' hyperpolarization-activated current (I_f) (54). Indirect anti-adrenergic effects of the A_1AR contribute through modifying I_f and inhibiting activation of I_{Ca}. The relative roles of these currents differ in specific tissues. For example, *in vivo* data supports a greater role for I_f in His-Purkinje fibers *vs.* SA nodal tissue (55). Tissue differences may reflect differential K^+ channel expression: the $I_{K,Ado}$ is prevalent in atrial *vs.* ventricular myocytes, and adenosine thus has minor if any direct effects on ventricular action potentials. In atria adenosine also exerts modest inhibition of the basal L-type Ca^{2+} current ($I_{Ca,L}$), but not the T-type current ($I_{Ca,T}$). Adenosine can also activate ventricular I_{KATP}, though the functional relevance of this effect is not clear at present. These alternate mechanisms may account for the ~50% component of adenosine-induced bradycardia that appears resistant to $I_{K,Ado}$ deletion (56).

Adenosine delays impulse conduction in addition to generation, prolonging P-R and A-H intervals and generating AV block. The dromotropic effects appear primarily restricted to the AV node with no effects on the H-V interval. This negative dromotropic action has been attributed to A_1AR activation of $I_{K,Ado}$ and inhibition of ß-adrenergic activation of $I_{Ca,L}$. However, since

adenosine has a negligible impact on the basal L-type Ca^{2+} current in AV nodal cells (in the absence of adrenergic stimulation), the indirect mechanism will only contribute to AV conduction delay under conditions of sympathetic activation. Moreover, since A_1AR agonism prolongs AV conduction in mice lacking $I_{K,Ado}$ (56), the importance of this current to the response is unclear. The A_1AR has also been shown to slow conduction in ischemic myocardium in a pertussis sensitive G-protein dependent manner (57), and there is evidence low levels of adenosine mediate negative dromotropy via a K^+ current with delayed rectifying properties (58).

Interestingly, Rubio and colleagues provide evidence that the dromotropic action of intravascular adenosine is initiated via endothelial ARs and transduced by NO and prostaglandins (59). These data raise the possibility of differing electrophysiological responses to locally produced *vs*. exogenously applied or circulating adenosine. This is consistent with the observation of Rajasekaran *et al.* that adenosine and superoxide delay AV conduction synergistically via an NO-dependent mechanism independent of $I_{K,Ado}$ (60). This adenosine/radical synergism is speculated to contribute to arrhythmogenesis in post-ischemic tissue, where both triggers are elevated.

Pathobiology: As with anti-arrhythmic drugs, adenosine has the potential to be either anti- or pro-arrhythmic, for example inducing atrial flutter or fibrillation in humans and animal models. This results from a shortened action potential and refractory period due to $I_{K,Ado}$ activation. Studies support an important role for locally produced adenosine in mediating arrhythmias or slowing rate and conduction under pathological conditions in animal models (57, 61-63). Both animal and human studies support a role for adenosine in AV block with infarction (64-66), and data also supports A_1AR involvement in atrial fibrillation in infarct and coronary artery bypass graft patients (67,68). A recent report from Alvarado-Tapias *et al.* identifies markedly augmented arrhythmogenesis with adenosine in an animal model of chronic Chagas cardiomyopathy (69). The actions of adenosine are also consistent with a role in sick sinus syndrome (70), though mechanistic involvement is yet to be fully established. The poorly

selective AR antagonists aminophylline and theophylline do suppress symptoms in aged patients with this disorder (71, 72). Decay of ventricular fibrillation is accelerated by A_1AR antagonism in a swine model (73), though this effect of endogenous adenosine does not impact on short-term outcomes (74). On the other hand, beneficial anti-arrhythmic effects of preconditioning (PreC) in animal models may involve the actions of endogenous adenosine (75).

Given potent electrophysiological actions of A_1ARs, and evidence of involvement in arrhythmogenesis, it is not surprising that varied A_1AR agonists have been trialed as anti-arrhythmics. Adenosine itself is employed as an effective treatment for termination of paroxysmal supraventricular tachycardia (Adenocard), and has also been used 'off-label' as an electrophysiological diagnostic aid. More select A_1AR agonists such as tecadenoson ((2*R*,3*S*,4*R*)-2-(hydroxymethyl)-5-(6-((*R*)-tetrahydrofuran-3-ylamino)-9*H*-purin-9-yl)-tetrashydrofuran-3,4-diol)) and selodenoson ((2*S*,3*S*,4*R*)-5-(6-(cyclopentylamino)-9*H*-purin-9-yl)-*N*-ethyl-3,4-dihydroxytetrahydrofuran-2-carboxamide) have been trialed as type-IV anti-arrhythmics, being shown to be safe and well tolerated in Phase I trials, and effectively targeting supraventricular tachycardia and atrial fibrillation respectively (76). With ongoing research efforts in this area, new AR-based approaches to the treatment and diagnosis of arrhythmias are likely to emerge over coming years.

2.3. Vascular control

Adenosine and its receptors modify vascular tone, and may play a role in vasculogenesis/angiogenesis and vascular remodeling (the latter discussed under **4** below). In their early study Drury and Szent-Györgyi also reported on vasoregulatory effects of adenosine (53). An 'adenosine hypothesis' of coronary vasoregulation was later forwarded in 1963, proposing regulation of coronary tone via purine signals coupled to cellular energy state (77,78). The coronary vasoregulatory functions of adenosine and ARs have been studied intensely since that time, and are still debated. Despite evidence ARs and adenosine play little role in control of

basal coronary tone or functional hyperemia (79,80), and are only relevant during significant O_2 supply:demand mismatch, this remains contentious. Studies in human hearts reveal decreased basal flow with increased coronary resistance and O_2 extraction following AR antagonism (81, 82). In sedated pigs enhanced deamination of adenosine increases baseline coronary tone (83), and limits early hyperemia during ß-adrenergic stimulation (84). Duncker *et al*. also found that AR antagonism shifts the relationship between MVO_2 and coronary resistance in conscious pigs, implicating a role for endogenous adenosine in control of basal tone and influencing (but not being essential for) exercise-dependent hyperemia (85). Mouse gene knockout studies also implicate ARs in control of coronary tone, albeit *in vitro* (15,26). While a role in reactive or hypoxic hyperemia is well established, the importance of adenosine and ARs in regulating coronary tone under physiological conditions *in vivo* remains unclear.

The A_{2A} and A_{2B}ARs are expressed in both smooth muscle and endothelium, and contribute to what appears to be primarily endothelial-dependent, but also direct smooth muscle, relaxation. The A_{2A} and A_{2B}ARs affect coronary vasodilatation in a species-specific manner - A_{2A}ARs play a role in human (86), pig (87), guinea pig (88,89) and mouse (90), whereas A_{2B}ARs are also active in humans (91) and may contribute in the rat (92). There is evidence of A_{2B}AR-mediated coronary dilatation in mice, though this predominates only when A_{2A}ARs are deleted (93). As an aside, the observation that deletion of the A_{2A}AR leads to compensatory up-regulation of coronary A_{2B}ARs itself supports an important regulatory function of A_{2A}ARs.

Second messenger and effector involvement in coronary A_2AR responses remains to be fully detailed, particularly in human vessels. The A_{2A} and A_{2B}AR couple to G_s to activate adenylate cyclase, cAMP accumulation and PKA activity, and these cAMP signals appear important in coronary responses. Other pathways have nonetheless been implicated in AR-mediated coronary dilatation, including p38-MAPK in murine vessels (94) and inositol 1,4,5,trisphosphate signaling in pig vessels (95). Coronary vasodilatation via adenosine has been linked to NO and K_{ATP} channel activation in animal models (91,96,97). In human coronaries

A_{2B}AR responses also involve K_{ATP} channels, but may not rely on NO (91).

While the vasoactive properties of the A_2 sub-types have been most extensively studied, there is also evidence for coronary responsiveness to A_1 and A_3ARs. The A_1AR may trigger direct coronary constriction and inhibit A_2AR-dependent dilatation (26,86). This is consistent with co-expression of A_1, A_{2A} and A_{2B}ARs in coronary vessels (98). The A_3AR has also been attributed with vasoregulatory properties, although it is not clear how such responses are mediated since expression in vascular cells is very low or not detected. Wang and colleagues observe mRNA expression for all 4 ARs in porcine coronary vessels, and protein expression of all except the A_3AR (98). This reflects the somewhat elusive nature of cardiovascular A_3ARs, which also appear to be minimally expressed in myocytes despite mediating powerful cardioprotection. Coronary vascular effects of A_3ARs may involve indirect signaling through non-vascular cells such as mast cells. Duling and colleagues describe a role for mast cell activation in A_3AR-dependent constriction of peripheral vessels (via release of histamine and thromboxane) (99). Degranulation of mast cells by A_3ARs appears highly species-dependent, however, and there is also some evidence of A_3AR expression in aortic smooth muscle (100), while pharmacological approaches hint at functional coronary A_3ARs (101-103). Talukder *et al.* acquire evidence from knockout mice that the A_3AR inhibits A_{2A}AR-dependent dilatation (104). On the other hand, there is evidence coronary responses to A_3AR agonists may actually involve activation of A_{2A}ARs (105). Other studies report coronary insensitivity to A_3AR agonists in guinea pig (89) and mouse (106). Available data is thus mixed regarding vascular effects of A_3ARs in different beds and species, with further interrogation required.

As noted above, studies of AR gene deletion identify alterations in coronary vasoregulation and support regulatory roles of endogenous adenosine. Phenotypic outcomes with CD73 deletion include a decline in baseline coronary flow, supporting vasodilatation by extracellular adenosine (15). However, there was no shift in reactive hyperemia, arguing against an essential contribution of this adenosine pool to that response (or compensation via other

mediators). Baseline coronary tone was unaltered or slightly reduced with A_1AR knockout (26, 107), supporting some A_1AR-dependence of basal tone, though it is unclear whether A_1AR deletion modifies tone directly or by altering $A_{2A}/_{2B}$AR responsiveness. Deletion of the A_{2A}AR impairs adenosine-mediated dilatation, but does not consistently modify basal tone (93,108), though induction of A_{2B}ARs may compensate (94). Again, a mix of data exists regarding AR control of coronary tone in murine models.

Peripheral vascular control: The peripheral vasculature impacts on the heart through shifts in pre- and afterload. Exogenous adenosine modifies vascular tone in peripheral vessels, and studies of gene deletion support AR control of peripheral tone and blood pressure. Ledent *et al.* reported that A_{2A}AR deletion significantly elevates systemic pressure (109), though whether this phenotype arises from local vascular or central/renal changes is uncertain, as the A_{2A}AR may modify nervous control of pressure (110). Other gene deletion studies suggest some impact of ARs on blood pressure control, though again these may reflect shifts in central and renal blood pressure regulation rather than direct vascular effects. Deletion of A_1ARs also elevates blood pressure, which has been linked to altered renin release (111). Knockout of the A_3AR increases cardiac and vascular cAMP levels without altering baseline blood pressure, although animals are sensitized to systemic hypotension in response to adenosine, supporting an inhibitory effect of the A_3AR (112).

Pathobiology: There is evidence of alterations in AR-dependent vascular control in disorders relevant to coronary or peripheral circulations. Several studies support impaired AR-mediated vasoregulation in hypertension (113,114), though this may reflect broad-spectrum inhibition of endothelium-dependent vasomotor control. The anti-hypertensive activity of adenosine and AR agonists (115), and induction of hypertension with AR antagonism or knockout (109,116), does support roles for adenosine in regulating peripheral tone and pressure. However, whether altered AR responses are important in progression of hypertensive disease is not clear. In a gene association study no linkage was detected between arterial blood pressure and

variants of A_1ARs, A_{2A}ARs, or adenosine deaminase (117). Effects of ARs on central and renal control mechanisms are more likely contributors to hypertension than shifts in direct vascular responses (113). Nonetheless, AR control of remodeling and vessel growth may well play a role in the vascular tissue changes associated with hypertension, as supported by vascular remodeling in response to inhibition of endogenous adenosine (116).

There is also evidence of altered vascular AR signaling with elevations in dietary salt and in early stage metabolic syndrome. Nayeem *et al*. report on potential adaptation of AR control, with down-regulation of A_1ARs (reducing arterial constriction) and up-regulation of A_{2A}ARs (producing K_{ATP} channel dependent dilatation) in mice on a high *vs*. normal salt diet (118). Bender *et al.* have also found that AR mechanisms of coronary dilatation are shifted prior to overt decrements in coronary dilator reserve in early metabolic syndrome. The relevance of these changes and their roles in disease pathogenesis are as yet unclear (119).

Diabetes, which promotes cardiovascular disease and worsens outcomes, is associated with impaired vascular AR responses (114). Vascular responsiveness to a variety of stimuli is impaired in diabetes, likely revolving around ROS-dependent endothelial dysfunction (120). Thus, ARs are not selectively modified, and the roles of individual vascular changes in the pathobiology of diabetes have not yet been clearly established. Diabetes modifies other AR responses that may be relevant to cardiac pathology, including protective conditioning responses attributed to adenosine.

Investigations reveal AR-mediated coronary vascular protection that may be relevant to adenosines role in disease. Exogenous AR agonists can limit coronary dysfunction and damage following ischemic insult (121,122). In addition, AR antagonism exaggerates coronary vascular injury in rodents, supporting a role for intrinsic A_1AR activity in protecting the vasculature during periods of stress (122). This vasoprotection, which preserves endothelial function and vascular control, may also be relevant to the impact of ARs on vascular lesion development and re-stenosis.

The vasoregulatory properties of ARs have been capitalized upon clinically in humans, although for purposes of diagnosis rather than treatment of coronary artery disease. Adenosine (Adenoscan) has been employed as a substitute for exercise stress in myocardial perfusion imaging. Its use is limited somewhat by side-effects, including AV conduction delay, chest pain, and bronchospasm. These issues may be mitigated by development of more selective A_2 sub-type agonists, and several A_{2A}AR selective agonists have been trialed (binodenoson, apadenoson) or recently approved for such use (regadenoson).

2.4. Regulation of myocardial substrate metabolism

Adenosine exerts significant effects on glucose metabolism and fatty acid availability. These actions may be important in modulating myocardial responses to hypoxic or ischemic stress, and potentially play roles under physiological conditions (*eg.* sympathetic activation) and in disease (*eg.* diabetes). Observations regarding effects of adenosine on glucose metabolism have been conflicting, and responses in humans are yet to be assessed. A number of studies support adenosine and AR stimulation of myocardial glucose uptake (123-127), a response that may reflect potentiation of insulin's actions (128-130). Indeed, some work indicates that the effects of insulin require functional AR activity (130). However, there is also evidence of distinct mechanisms underlying the effects of adenosine and insulin on glucose uptake (125). Responses to AR antagonists do implicate a role for endogenous adenosine in promoting glucose uptake under normoxic (126,127,131) and hypoxic (124,131) conditions. Beneficial effects of cardiac PreC during ischemia-reperfusion have also been linked to enhanced glucose utilization, which is dependent upon AR activity (132). The effects of adenosine appear to be independent of coronary flow, work rate or adrenergic activity, and while initially thought to involve A_1ARs may additionally involve the A_{2A}AR. In a recent study in fetal sheep, Maeda and Koos (131) found that intrinsic A_1AR (but not A_{2A}AR) activity reduces plasma glucose, lactate and insulin levels, whereas exogenous adenosine increases plasma glucose and lactate via A_{2A}ARs (a response

countered by A_1AR activity). Hyperglycemia with hypoxia was partly mediated by A_1 and A_{2A}AR activation. They conclude that A_1AR activity facilitates at least 12% of normoxic glucose utilization.

In contrast to such studies, Gao *et al.* reported that AR blockade increases glucose uptake under normoxic and low-flow ischemic conditions, supporting inhibition of utilization by endogenous adenosine (133). Fraser *et al.* also present evidence that A_1ARs may partially inhibit glycolysis and thus improve coupling of glycolysis to glucose oxidation, reducing H^+ generation and limiting post-ischemic damage and dysfunction (134). Reasons for differing observations regarding ARs and glucose metabolism are unclear, though a majority of studies support facilitated glucose uptake under most conditions. As indicated in the work of Fraser *et al.*, however, the balance of glycolysis *vs.* glucose oxidation (rather than uptake *per se*) is also an important regulatory factor.

Effects of adenosine in other organs will impact on cardiac substrate handling - hepatic glucose can be liberated via intrinsic A_3AR agonism, for example, which might serve to mobilize glucose during ischemia/hypoxia (135). Cardiac substrate metabolism will also be sensitive to anti-lipolytic actions of adenosine. Activation of adipocyte A_1ARs inhibits cAMP generation and lipolysis (136,137). Reducing the release and availability of fatty acids has the potential to improve cardiac insulin resistance and glucose handling, and dyslipidemias. For example, Shearer *et al.* recently showed that a partial A_1AR agonist lowers circulating fatty acids and improves cardiac glucose clearance in a model of diet-induced insulin resistance (138). Anti-lipolytic A_1AR-based therapies to modulate lipid levels and potentially insulin resistance have entered early-phase clinical trials.

Pathobiology: The role of AR-dependent control of glucose uptake (and lipolysis) in pathological conditions such as diabetes and hyperlipidemia has not been extensively assessed. Adenosine responses themselves may well be regulated by changes in substrate levels. For example, AR expression in cardiac fibroblasts is sensitive to glucose and insulin, with glucose

up-regulating A_1 and A_{2B}ARs and repressing A_3ARs, whereas insulin suppresses A_1 and A_{2B}AR expression (139). There is thus an interplay between AR function and circulating substrate that may be relevant to diabetes and metabolic syndrome. Experimental streptozotocin-dependent diabetes is associated with up-regulation of cardiac A_1 and A_3ARs (140), an effect countered by insulin treatment. As already noted, vascular responses to ARs are also impaired in diabetes (114), and modified in early metabolic syndrome (119). However, the contribution of altered AR responses to these disorders is yet to be established.

Though not a direct cardiac effect, shifts in adipocyte lipolysis and thus fatty acid availability clearly impact on the heart and vessels, and there is evidence AR control of lipolysis is modified in obesity (a major and growing risk factor for heart disease). Altered control of lipolysis in obese Zucker rats appears to involve enhanced A_1AR-dependent inhibition of adenylate cyclase (141). This is consistent with evidence of enhanced adipocyte A_1AR sensitivity in *ob/ob* mice (142). Such effects could contribute to progression and maintenance of obesity. A more recent study by Barakat *et al.* identifies increased A_1AR expression in visceral adipose tissue from African-American *vs*. Caucasian women, which may lead to enhanced A_1AR sensitivity and reduced fat mobilization in the former (143). The authors speculate this may underpin maintenance of obesity in African-American women, though this has yet to be tested. On the other hand, the work of Kaartinen *et al.* in human adipocytes reveals impaired AR-mediated adenylate cyclase/cAMP inhibition in cells from obese subjects, involving reduced A_1AR expression and linked to enhanced adipose tissue adenosine (144). The authors suggest augmented adenosine may explain inhibition of lipolysis *in situ* in obesity, while AR desensitization may explain diminished adenosine responses in cells *in vitro*. Nonetheless, a subsequent study has reported that weight-loss after gastric bypass or gastroplasty leads to normalization of A_1AR inhibition of lipolysis (145). This indicates that shifts in AR control may actually be secondary to development of obesity, which does not preclude a role for such changes in obesity maintenance. Ageing may also enhance the anti-lipolytic effects of A_1ARs: Hoffman *et*

al. show that reduced adrenergic activation of lipolysis in aged rodents involves enhanced inhibitory effects of endogenous adenosine (146). Such changes might contribute to age-related shifts in substrate metabolism and availability, and facilitate age-dependent obesity. Further work is required to clarify the roles of ARs in regulating lipolysis and glucose handling in different disease states, and their relevance to disease onset and progression.

As noted above, A_1AR-based therapies have been trialed for manipulating free fatty acid (FFA) levels and improving insulin sensitivity in diabetes, though none have received regulatory approval as yet. For example, tecadenoson, although not initially developed as an anti-lipolytic agent, has been shown to reversibly lower FFA levels in a pilot Phase I study by CV Therapeutics. Similarly, the agent ARA ([1S,2R,3R,5R]-3-methoxymethyl-5-[6-(1-[5-trifluoromethyl-pyridin-2-yl]pyrrolidin-3-[S]-ylamino)-purin-9-yl]cyclopentane-1,2-diol) also lowered fatty acid levels in a Phase I clinical study, though tolerance emerged rapidly (147). While this general approach to lowering FFAs and improving insulin resistance and diabetes is validated by experimental and small trial data, challenges to effective A_1AR agonist-based therapy include widespread receptor distribution (rendering site- or organ-specific targeting difficult), and emergence of tolerance due to receptor down-regulation/desensitization (limiting efficacy of long-term anti-lipolytic therapy). Such problems, relevant to AR pharmacotherapy in other organ systems and disorders, may be overcome to some degree through development of partial AR agonists.

3. Retaliation

Under conditions of severe metabolic insult such as ischemia or hypoxia, beneficial effects of adenosine on function (heart rate, contractility) and energy supply (coronary flow, substrate metabolism) are insufficient to restore the balance between cardiac energy supply and demand (**Fig. 1**). Under these conditions the so-called 'retaliatory' functions of adenosine may

come to the fore, mediating acute and delayed cytoprotective responses that limit reversible and irreversible forms of injury. Adenosine and its receptors have been extensively studied in the context of protection against cellular injury during ischemia-reperfusion (148-151). Greatly enhanced levels of extracellular adenosine activate acute cytoprotective signaling via multiple AR sub-types (148,149). Adenosine is also involved in delayed or adaptive PreC responses (150, 151). Studies in different models and species document powerful protection against infarction and myocyte injury via either pre- (152-159) or post-ischemic (160-169) AR activation. While early work identified and focused on protective functions of the A_1AR, cardioprotective properties have been identified for all 4 AR sub-types (149,150).

3.1. AR contributions to protection during and following ischemia

Cardioprotection was initially thought to be primarily mediated during ischemia, and there is evidence ischemic AR activity is important to expression of protection: Toombs *et al.* found that AR antagonism during ischemia eliminated AR protection (170); specific protective effects of A_1ARs are evident during ischemia *vs.* reperfusion (132,171,172); and AR activity modifies substrate use, energy metabolism, ionic overload, and contracture during ischemia (132, 173,174). Commensurate with these findings, protection via the A_1AR has been shown to involve receptor activity prior to and during ischemia, but not during reperfusion (153,154,174-176), and ischemic PreC requires intrinsic A_1AR activity during but not following ischemic insult (154).

Despite minimal cardiac A_3AR expression, pharmacological evidence also supports A_3AR-dependent protection in myocardium from different species (158,168,172,177,178) including humans (156). Protection is triggered with pre-ischemic A_3AR activation (156,158,159, 167,178). While A_3AR effects, as for the A_1AR, are thought to predominate during ischemia, there is nonetheless evidence that post-ischemic A_3AR activity can also be protective (167-169).

Contrasting work on A_1 and A_3AR responses, a number of studies show that pre- or intra-ischemic A_{2A} or A_{2B}AR agonism does not induce protection (153,167), whereas post-ischemic

activity is highly protective (160,162-166). Indeed, recent work highlights an important protective function for A_{2A} (179-181) and A_{2B}ARs (14,182-184) in post-ischemic myocardium that is relevant to conditioning responses. Generally then, A_1/A_3AR activation of protection is predominantly an ischemic event while A_{2A}/A_{2B}AR protection is mediated during reperfusion. There may nonetheless be important interactions between receptor sub-types in the mediation of cardioprotection (149,150).

Based on findings regarding the A_{2B}AR, Downey and colleagues forward an intriguing model entailing PKC-dependent sensitization of protective A_{2B}ARs (182-184). They present evidence that cardiac protection via PKC activation is A_{2B}AR-dependent (locating A_{2B}ARs downstream of PKC), and that PKC activation and PreC both substantially lower the threshold for AR-mediated phosphorylation of protective kinases. It is proposed that activated PKCδ targets a particular A_{2B}AR sub-type - A_{2B} light4 - to enhance its sensitivity, enabling activation by endogenous adenosine in early reperfusion. This is underpinned primarily by data in rabbit hearts, though A_{2B}AR dependence of conditioning responses is supported by knockout studies in mice (14). Modulation of A_{2B}AR sensitivity is also consistent with PKC-dependent sensitization of A_2AR responses in other cell types (185,186). As discussed below, this mechanism may contribute to both PreC and postconditioning (PostC). Sensitization of A_{2B}ARs may itself be AR-dependent - A_1ARs activated during PreC or ischemia (153,154,170,171,174-176) stimulate PKC, and there is also evidence that A_1AR-triggered protection is dependent upon A_{2A}/A_{2B}AR activity (187). Interestingly, a recent preliminary report describes novel expression of A_{2B}ARs on mitochondria rather than the sarcolemma (188), which may be relevant to interactions between A_{2B}ARs, signaling kinases, and other AR sub-types in cardioprotection.

Since interstitial adenosine (and inosine) levels achieved during ischemia or hypoxia are sufficient to substantially activate cardiovascular ARs (174,189), it is predicted that intrinsic AR activity will impact on myocardial tolerance to ischemic insult. This is borne out in some studies assessing effects of AR blockade or deletion on ischemic responses (14,107,161,170,171,175,

190), although many others do not identify shifts in intrinsic tolerance following AR inhibition. The question of adenosines importance to intrinsic ischemic tolerance thus remains unresolved.

3.2. Roles of ARs in conditioning responses

Conditioning responses are of considerable interest, in unmasking intrinsic cytoprotective mechanisms and as potentially useful therapeutic interventions. Considerable evidence has accumulated supporting an essential role for endogenous adenosine in mediating PreC and PostC responses. Liu *et al.* provided initial evidence that endogenous adenosine mediates PreC (152), and other work confirms that antagonism of ARs or reductions in adenosine levels limits PreC in multiple models and species (132,154,155,174,191-193). In terms of AR sub-types, early work supported A_1AR involvement (152,155,191). However, subsequent studies demonstrate that A_3AR antagonism also inhibits PreC (178,194), or identify contributions from both A_1 and A_3ARs (195,196). Studies in mice support abrogation of PreC with A_1AR knockout (197,198). In terms of human myocardium, Walker and colleagues reported mediation of PreC by ARs (199), Cleveland *et al.* (200,201) confirmed AR-mediated PreC in human tissue, and Tomai *et al.* (202) described A_1AR-dependent PreC in patients undergoing coronary angioplasty. Activation of A_1 and A_3ARs induces PreC in human atrium (156), and Ikonomidis *et al.* (203) demonstrated AR dependence of protection in isolated human myocytes. Collectively, a range of studies in animal and human tissue support roles for A_1 and A_3ARs in triggering/mediating protection with PreC. That said, AR activity during reperfusion is also important in PreC (161,193), and recent work supports a crucial role for post-ischemic A_{2B}AR activity in both PreC and PostC (182-184).

The infarct-limiting effects of PostC are reduced with AR antagonism or knockout (169, 204), and data support roles for A_{2A} (169,205), A_3 (169) and A_{2B}ARs (14) in PostC in mice, and A_{2B}ARs in rabbits (182). Protection via either PreC or PostC is blocked by post-ischemic A_{2B}AR antagonism in rabbits, and A_{2B}AR agonism in early reperfusion mimics this protection (182, 184). As already discussed, Downey and colleagues propose that protection via conditioning

responses involves PKC-dependent sensitization of A_{2B}ARs and subsequent A_{2B}-mediated protection in early reperfusion (151). Both PreC and PostC may thus converge on A_{2B}AR modulation and activation of protective signaling in reperfused tissue (182-184).

This model contrasts data supporting inhibition of PostC in A_{2A}AR knockout mice (205), though it is tempting to speculate that A_{2B}AR sensitization might involve prior A_1 or A_{2A}AR activity. In support of this, Xi *et al.* suggest that both A_{2A} and A_{2B}ARs are required for protection with PostC (206). On the other hand, Eckle *et al.* found that only A_{2B}AR knockout inhibited PostC in mice, whereas deletion of the other 3 sub-types was ineffective (14). The importance and relevance of A_{2B}AR sensitization and signaling thus remains contentious and is yet to be extensively interrogated in different models and species. One small study presents evidence that, in contrast to this scheme, functional AR sensitivity is unaltered by ischemia (207). However, this work only tested shifts in A_1AR-dependent bradycardia (mediated by nodal ARs and G_i control of $I_{K,Ado}$) and A_{2A}AR-dependent coronary dilatation (mediated by vascular ARs, G_s signaling, K_{ATP} channels, and NO). The data are not representative of AR-mediated protective signaling in ventricular myocardium. Sensitivities of A_1AR mediated bradycardia and A_1AR-mediated protection can be dissociated, with ageing for example where the former is unchanged while the latter decreases (208).

3.3. Pathobiology

If, as discussed above, ARs and endogenous adenosine are important in dictating intrinsic ischemic tolerance (14,107,161,170,171,175,190), then AR activity will play a role in outcomes from ischemic heart disease. This is supported by recently described associations between variants of A_1 and A_3AR genes and infarct size in patients with ischemic cardiomyopathy (209). Some disease states may also sensitize the myocardium to dysfunction/ damage by impairing AR and other GPCR-dependent protective responses (210). Diabetes, obesity, hypertrophy and hypertension have all been shown to significantly inhibit or entirely abrogate intrinsic protection

via PreC, PostC, ARs and other GPCRs (210,211). Aging may induce similar changes (208), and other relevant abnormalities may impact on or involve altered AR activity. For example, effects of hyperhomocysteinemia (an independent risk factor for cardiovascular disease linked to impaired ischemic tolerance) in an animal model involve impaired A_1AR activation by local adenosine (212). A general pattern emerges of impaired receptor-triggered protective signaling in aged or diseased tissue, predisposing hearts to injury and infarction. Such effects may contribute to poor clinical translation of experimental protective modalities targeting these paths (210,211). One may speculate that the impact of diseases such as diabetes on the heart and cardiovascular mortality (increasing occurrence and worsening survival) involves impairment of cytoprotective responses. It is also tempting to speculate that age-related shifts in protective pathways reflect an integral component of the aging process, since a decline in cellular stress resistance is a defining feature of the aged phenotype.

Despite potent protective effects of adenosine and ARs experimentally, there have been relatively few trials of adenosine-based cardioprotection in humans, and outcomes have been mixed. In the acute myocardial infarct study of adenosine (AMISTAD), a 3 hr infusion was trialed in infarct patients, with adenosine reducing infarction by 33% relative to placebo. In the sub-set of patients with anterior infarcts, this reduction was greater at 67% (213). These promising outcomes led to AMISTAD II, testing effects of adenosine in ST-segment elevation myocardial infarction (STEMI) patients undergoing reperfusion therapy. The larger trial showed a significant 50% relative reduction in infarct size with adenosine, yet no differences in the longer term primary end-points of heart failure development and re-hospitalization (214). A larger study may be required to determine whether infarct reduction with adenosine is associated with improved long-term outcomes. Post-hoc analysis did find that patients receiving adenosine within 3 hrs of symptom onset exhibited reduced mortality at 1 and 6 months and enhanced event-free survival, demonstrating the critical nature of treatment timing (215). The ADMIRE trial tested differing doses of the A_1/A_{2A}AR agonist AMP579 in STEMI patients undergoing

angioplasty (216). The trial showed no significant effects of treatment on the primary end-point of infarct size, nor on different secondary end-points, although the highest dose of AMP579 employed was only equivalent to the lowest effective doses assessed experimentally. The non-nucleoside A_1AR agonist capadenoson (BAY68-4986) has also been assessed in Phase II trails for use in patients with stable angina and coronary heart disease, and Phase III trails are at or near completion.

Trials of PreC- or PostC-based strategies indirectly assess the therapeutic value of AR-dependent cardioprotection, given evidence from animal and human myocardium that ARs are crucial to these responses. Results of small trials of PreC and PostC are mixed, though several demonstrate significant reductions in reperfusion injury (211,217). Nonetheless, outcomes have been somewhat disappointing, and data is insufficient to recommend widespread clinical use in infarct patients (211,217). One important factor that may limit clinical translation of AR and conditioning-based cardioprotection is the negative influence of age and disease on these responses (210,211). Efficacy of experimental protective interventions should be assessed specifically in aged and relevant chronic disease models prior to implementation of clinical trials.

4. Adaptation (and Maladaptation)

Adenosine can mediate longer-term adaptive responses, including the second or delayed window of protection with PreC - a hormesis response to mild stressor that generates prolonged cellular resistance (148-151). Adenosine also impacts on remodeling processes in cardiac and vascular tissues, modulating cardiac fibroblast proliferation, collagen synthesis, extracellular matrix (ECM) remodeling, myocyte apoptosis, and vascular genesis and development. Modulation of inflammatory processes plays an important role in these effects (32). These actions may be important in adaptive/maladaptive structural responses to hemodynamic, ischemic, oxidative or other stressors. Effects of AR manipulation in these scenarios support the potential

value of AR-based therapies in hypertrophy, heart failure and atherosclerosis/re-stenosis.

4.1. Myocardial remodeling and hypertrophy

Given effects of adenosine on the ECM, and on cardiac fibroblast, endothelial and smooth muscle growth and apoptosis, local adenosine changes during tissue stress are predicted to impact on repair and remodeling *in vivo*. Cardiacfibroblasts are an important mediator of adverse remodeling, generating excess ECM proteins,fibrosis and contractile dysfunction, and ultimately heart failure. Adenosine inhibits fibroblast proliferation and collagen synthesis, thus limiting remodeling and progression to failure. Studies from Dubey and colleagues identify a specific role for the A_{2B}AR in inhibiting fibroblast proliferation and collagen synthesis (218-220), confirmed subsequently by A_{2B}AR knockout and overexpression (221). However, it is important to note that other fibroblasts may respond differently to AR agonism - pulmonary fibrosis in an adenosine deaminase deletion model appears to be A_{2B}AR-dependent (222), and A_{2A}ARs promote collagen synthesis in skin fibroblasts and hepatic stellate cells (223,224). Thus, adenosine can act via different AR sub-types to either repress or promote fibrosis in different tissues. Recent work suggests that within the heart a combination of A_{2B} and A_{2A}AR triggered cAMP-dependent signals contribute to suppression of fibroblast growth and fibrosis, involving a specific G_s-adenylyl cyclase, cAMP and E_{pac} dependent path acting via PI3K (225,226).

Pro-inflammatory factors such as TNFα and IL-6 are implicated in adverse remodeling and hypertrophy, and are sensitive to control by ARs. For example, Feng *et al.* show that pro-inflammatory IL-6 (a cytokine with pleiotropic effects on remodeling) is induced in cardiac fibroblasts by A_{2B}ARs in a PKCδ/p38-MAPK dependent manner (227). Increased TNFα induces cardiomyopathy (228), and Wagner *et al.* show that adenosine substantially limits myocyte TNFα expression during inflammatory challenge via an A_2AR sub-type (in rodent and human myocardium), and induces IL-6 via A_3ARs in rat but not human tissue (229). Adenosine and ARs

also limit the generation of inflammatory cytokines in invading or resident inflammatory cells, in addition to myocytes and fibroblasts (32).

Remodeling involves enzymatic degradation of the myocardial ECM. Matrix metalloproteinase's such as MMP-9 play a key role, and adenosine differentially modulates MMP-9 secretion in different cell types, activating macrophage MMP-9 secretion via A_3ARs (230), and inhibiting monocyte and neutrophil MMP-9 secretion via A_{2B}ARs and A_{2A}ARs, respectively (231,232). The latter A_{2A}AR effect may inhibit detrimental remodeling after cardiac injury/infarction, when neutrophils are activated and adenosine levels rise substantially. The effects of MMPs may be both cell- and concentration-dependent - Velot *et al.* (230) speculate that low levels of MMP-9 released from macrophages may facilitate revascularization, whereas high levels released from neutrophils degrade the ECM. Thus, A_3AR activation of low-level macrophage secretion may be beneficial, just as A_{2A} and A_{2B}AR inhibition of neutrophil MMP secretion may limit ECM degradation. Other determinants of cardiac structure and function are also sensitive to AR activity. For example, Yuan *et al.* show that A_1 and A_3AR agonism increases cardiac ANP secretion (233,234), and ANP is known to modulate myocyte apoptosis, oxidant stress, fibrosis and hypertrophy (235).

Exogenous AR agonists exert anti-remodeling/hypertrophic actions in different disease models, with all receptor sub-types implicated. Gan *et al.* (236) provide evidence for anti-hypertrophic effects of A_1, A_{2A}, and A_3ARs in phenylephrine-induced hypertrophy, involving repression of NHE1 expression and shifts in G-protein signaling and immediate early gene responses. Stimulation of A_1ARs attenuates both hypertrophy and dysfunction in an experimental pressure-overload model (237). Long-term stimulation of A_{2B}ARs following infarction inhibits development of fibrosis in non-infarcted myocardium, and enhances contractile function (238). This approach also inhibits myocyte apoptosis in remote myocardium, even when commenced post-infarction (239). Signaling involvement has yet to be fully elucidated, though $G\alpha q$ and

modulation of pro-apoptotic PKC-δ/p38-MAPK signaling and Bad may be important (239). Anti-hypertrophic effects of ARs may also involve distinct K_{ATP} channel activation - sarcolemmal K_{ATP} channels for A_1ARs *vs.* mitochondrial channels for A_{2A} and A_3ARs (240).

Pathobiology: There is ample experimental evidence of alterations in adenosine levels, handling and receptor signaling in post-ischemic, hypertensive, hypertrophied and failing myocardium in animal models. Whether these changes reflect mechanistic involvement, compensatory or adaptive changes, or non-specific targets of disease, has yet to be established. The AR system may be beneficially modulated in response to hypertrophy (241), with up-regulation of A_1, A_{2A} and A_3ARs that, when activated, counter development of hypertrophy (236). In a model of compensated pressure-overload hypertrophy, increased interstitial adenosine is accompanied by increased protective A_1AR expression. However, overexpression is no longer evident after transition to failure (242), suggesting secondary rather than primary involvement. Shifts in A_1AR expression may nonetheless be relevant to disease progression, as excess A_1AR expression can induce cardiomyopathy, cardiac dilatation, hypertrophy and dysfunction (dependent upon the timing of expression changes) (243). In addition, cardiac dysfunction in response to TNFα and in models of overload or failure may involve increased A_1AR expression and reduced adenosine levels, contributing to A_1AR dysfunction (244).

Elevations in cardiac adenosine levels and reduced adenosine deaminase activity have also been documented in heart failure patients, together with reduced transcription of A_{2A}, A_{2B} and A_3ARs (245). Increased adenosine can be related to shifts in deaminase and nucleotidase activities, and may reflect compensation for impaired AR signaling. Indeed, augmenting endogenous adenosine via transport inhibition can limit severity of heart failure, supporting a role for altered AR signaling in failure pathogenesis (245). Similarly, augmenting endogenous adenosine prevents development of abnormal ventricular filling, adrenergic dysfunction, and remodeling in hearts from rats subjected to pressure-overload (246).

Studies of gene deletion in mice provide more direct evidence of a role for endogenous adenosine and intrinsic AR activity in development of hypertrophy and dysfunction/failure. Deletion of CD73 increases cardiac fibrosis and hypertrophy with pressure-overload, in association with increased mTOR signaling and ANP expression (247,248). This supports an important role for endogenous adenosine (generated in the extracellular space) in preventing maladaptive remodeling. Knockout of the A_3AR did not exacerbate dysfunction, but rather was found (unexpectedly) to reduce oxidative stress and induce protection against hypertrophy and fibrosis (248). Interestingly, A_1AR knockout failed to modify hypertrophy and dysfunction yet significantly increased mortality. Thus, endogenous adenosine does exert beneficial actions, yet these appear to be countered (paradoxically) by A_3AR activity in this model.

Despite evidence for benefit from all 4 AR sub-types in models of hypertrophy and failure, there are at present no direct cardiac-targeted AR therapies for heart failure. However, trials have been undertaken (*eg.* for BG9719) or are underway (*eg.* BG9928, KW3902) into the therapeutic value of A_1AR antagonism in acute decompensated heart failure with renal impairment. This pharmacological approach of renal A_1AR antagonism reduces the detrimental impact of fluid retention/edema through promoting renal vasodilatation, filtration and diuresis. While effects of ARs on fibroblast growth and tissue remodeling suggest considerable potential for other AR-based approaches in hypertrophy/heart failure, these responses are yet to be extensively assessed in human tissue and different disease states.

4.2. Vascular genesis, growth and remodeling

Adenosine and ARs not only regulate vascular tone, but also significantly modulate vessel growth (249). Evidence indicates adenosine plays an important role in neovascularization (including angiogenesis and vasculogenesis). A variety of *in vivo* studies in humans and animals demonstrate myocardial capillary proliferation in response to either exogenous adenosine (250, 251) or augmented endogenous adenosine (252-254). It appears all 4 AR sub-types play a role in

angiogenesis and vasculogenesis (255), involving both direct and indirect effects on endothelial, smooth muscle, fibroblast, and immune cells (256).

Adenosine promotes vessel growth via multiple mechanisms: adenosine is mitogenic and stimulates vascular endothelial cell proliferation, together with migration and tube formation *in vitro* (249); adenosine increases levels of pro-angiogenic molecules (*eg*. VEGF, angiopoetin-1, IL-8) in endothelial cells, monocytes and macrophages; and adenosine promotes endothelial progenitor cell adhesion and homing. While elevated adenosine levels in hypoxia or ischemia may mediate such effects, these pathological angiogenic stimuli also promote expression of relevant ARs. Ahmad *et al.* (257) document pro-angiogenic effects of A_{2A}AR activity in pulmonary vessels, and identified a hypoxia-responsive element proximal to the transcription-start site of the A_{2A}AR gene that is specifically targeted by HIF-2α. Thus, hypoxic stimulation of vessel growth may involve HIF-2α sensitive A_{2A}AR expression with subsequent A_{2A}AR-triggered growth. Additionally, Gessi *et al.* (258) show that adenosine can stimulate HIF-1α expression via all AR sub-types. The hypoxic stimulus for angiogenesis may thus revolve around AR induction of hypoxia-sensitive regulators such as HIF-1α, and subsequent induction of pro-angiogenic ARs in a positive-feedback manner. Similarly, macrophage A_{2B}AR expression is enhanced in response to arterial injury, and regulates inflammatory cytokine release that impacts on vascular growth/remodeling (259).

In vitro, adenosine stimulates endothelial cell migration, proliferation, and tube formation, which is critical to capillary network formation (249,257). These effects are observed with adenosine levels achieved during hypoxia or ischemia, and it is estimated that local adenosine may in fact mediate 50-70% of angiogenic responses to these stimuli (249). Adenosine stimulates endothelial cell growth through A_{2A} and A_{2B}ARs (257,260), while the A_{2B}AR appears to be anti-mitogenic in vascular smooth muscle (261). Other recent work indicates that A_1AR activation is mitogenic in coronary smooth muscle (262,263). Thus, the AR expression profile within different

vascular beds and cells, coupled with differential AR sensitivities, may dictate the precise mitogenic responses of smooth muscle and endothelial cells to adenosinergic stimuli.

The primary angiogenic action of adenosine involves modulation of expression of both pro- and anti-angiogenic substances in vascular and immune cells. Adenosine stimulates endothelial release of IL-8, bFGF, and VEGF in an A_{2B}AR-dependent manner, and inhibits release of anti-angiogenic thrombospondin-1 via A_{2A}AR activity (264,265). Ernenes *et al.* show that A_{2A}ARs trigger VEGF production in human macrophages (266), highlighting adenosine as a unique pro-angiogenic molecule potentially useful in stimulating cardiac repair. In addition, adenosine triggers A_{2B}/A_3AR dependent IL-8, VEGF and angiopoetin-1 expression in mast cells (267), and A_1ARs trigger VEGF release from monocytes to activate vessel growth (256). Inflammatory cell control of angiogenesis may be uniquely regulated by ARs, as Leibovich and colleagues show that A_{2A}AR activation switches macrophage phenotype from pro-inflammatory to pro-angiogenic/VEGF secreting (268). The pro-angiogenic influence of the A_{2A}AR is strongly supported by impaired vessel formation in healing wounds in A_{2A}AR knockout mice (266).

Recently Rhyzov *et al.* (270) demonstrated a role for adenosine in promoting endothelial progenitor cell homing to coronary endothelium, involving A_1 and A_{2B}AR activity and induction of endothelial P-selectin. Adenosine may therefore also stimulate vessel formation and growth through facilitated progenitor homing. Nonetheless, there remains controversy regarding roles for ARs in these processes. For example, A_{2B}AR deletion enhances mesenteric artery adhesion (with augmented endothelial adhesion molecules), suggesting A_{2B}ARs normally suppress endothelial adhesion (271). Ongoing research using A_{2B}AR-deficient mice should aid in delineating these processes, though relevance to the human has yet to be established.

Vascular growth and remodeling requires orchestrated shifts in apoptosis, and adenosine may not only promote growth but also selectively modulate vascular death: endothelial apoptosis is inhibited by A_{2A}ARs (272) and by A_1AR signaling (273). On the other hand, Peyot *et al.* (274) present evidence that A_{2B}ARs facilitate smooth muscle apoptosis, in line with enhanced death in

response to adenosine in cultured endothelial cells (275). Differing AR expression patterns may facilitate modulation of apoptosis in endothelial *vs*. smooth muscle cells. However, the latter studies also assess highly artificial scenarios of exposure to supra-physiological adenosine levels (up to 1 mM) for 24 hrs, with enhanced apoptosis evident after 8 hrs (274). We are unaware of *in vivo* scenarios in which vascular ARs would be exposed to such high adenosine levels (>10 µM) for several hours or more. These studies, as with other work on A_3AR-triggered apoptosis, reflect cell death responses to prolonged and profound AR agonism that may have little relevance *in vivo*.

Pathobiology: Animal studies show that endogenous adenosine promotes vascular growth *in vivo* (252-254), and plays a major role in angiogenesis in response to reductions in oxygenation (249). Adenosine is also implicated in atherosclerotic processes in human cells (258, 276), and may play a role in vascular growth/remodeling under other conditions, including re-stenosis. Edwards *et al.* found in a pig model that A_1AR expression is increased within stents, and that A_1AR activation increases smooth muscle cell proliferation (277). Thus, inhibition of A_1AR signaling holds some promise in the management of in-stent stenosis, supported in principle by the work of Kang *et al.* with A_1AR antagonist eluting stents (278).

In the context of atherosclerosis, the work of Gessi *et al.* indicates that A_{2B}, A_3 or mixed A_{2B}/A_3AR antagonists may be useful in blocking key steps in plaque development (258). Reiss *et al.* show that A_{2A}ARs stimulate expression of proteins involved in reverse cholesterol transport, and inhibit foam cell formation (276). Smooth muscle cells contribute to inflammatory signaling and ECM remodeling associated with atherosclerosis, and Xu *et al.* (279) have shown that A_{2B}AR knockout augments the effects of IFN-γ-on collagen repression. Thus, A_{2B}ARs may normally suppress these detrimental changes.

Effects of adenosine on vascular cells and remodeling involve AR modulation of inflammatory cell signaling (32). As already noted, activation of A_{2A}ARs and toll-like receptors switches macrophages from inflammatory to angiogenic phenotypes, involving induction of the

A_{2A}AR together with VEGF and IL-10, and repression of TNFα and IL-12 (268,280). The A_3AR has also been shown to inhibit IFN-γ induced STAT1 phosphorylation and macrophage activation (281). Since STAT1 is key to IFN-γ inflammation and foam cell transformation, this response might also be targeted in vascular disease. However, despite evidence intrinsic A_3AR activity can impede foam cell formation *in vitro* (258), analysis of the effects of AR deletion suggests no impact of the A_3AR on atherogenesis in animal models of diet-induced atherosclerosis and femoral artery injury (282).

A number of studies identify roles for CD73 (and thus extracellular adenosine) in vascular pathology, stemming largely from modulation of inflammatory processes. Initial analysis of CD73 deletion documented exaggerated platelet activation and leukocyte adhesion to vascular endothelium (15), while later work revealed exaggerated neointima formation following vascular injury (17). More recently, CD73 deletion has been shown to modify progression of cardiac allograft vasculopathy via associated changes in A_{2B}AR expression, leading to increased transendothelial lymphocyte migration and inflammation (18). Deletion of CD73 also enhances pro-inflammatory responses in human endothelium (16). Endothelial targeting and control appears critical to AR effects: inhibition of atherosclerosis by endogenous adenosine involves maintenance of endothelial cells in a non-activated quiescent state (283). These studies collectively support an important role of endogenous adenosine and ecto-nucleotidase activity in regulating vascular responses to injury and inflammation, which may ultimately be important in progression of re-stenosis and atherosclerosis. Further research in human tissue and relevant disease models is needed to clarify the importance of these responses in human atherosclerosis.

5. Conclusions

The roles and functions of adenosine and its receptors have expanded considerably as

research progresses and the tools of gene deletion or expression have been applied to interrogate these receptor systems. Adenosine released in response to perturbations in energy state, myocardial stress, or other stimuli mediates effects that generally improve the balance between energy utilization and energy supply (**Fig. 1**). Under conditions of extreme stress this receptor system limits damage to constituent cells of the heart, and modifies subsequent cell and tissue growth and remodeling. Shifts in AR signaling may play roles in the pathogenesis of a variety of cardiovascular disorders, and it is therefore an attractive system for therapeutic manipulation. However, the ubiquitous distribution of ARs in the body represents a significant challenge in this respect. Profound cardiovascular effects may ultimately be achievable, yet what is required are highly sub-type selective agents, and methods to achieve desired actions at target organs/cells in the face of broad AR distribution and problematic off-target effects. These challenges are surmountable, underpinned by a more complete understanding of the complex biomolecular interactions and functions of the AR family and associated proteins in animal models and specifically in humans.

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Figures

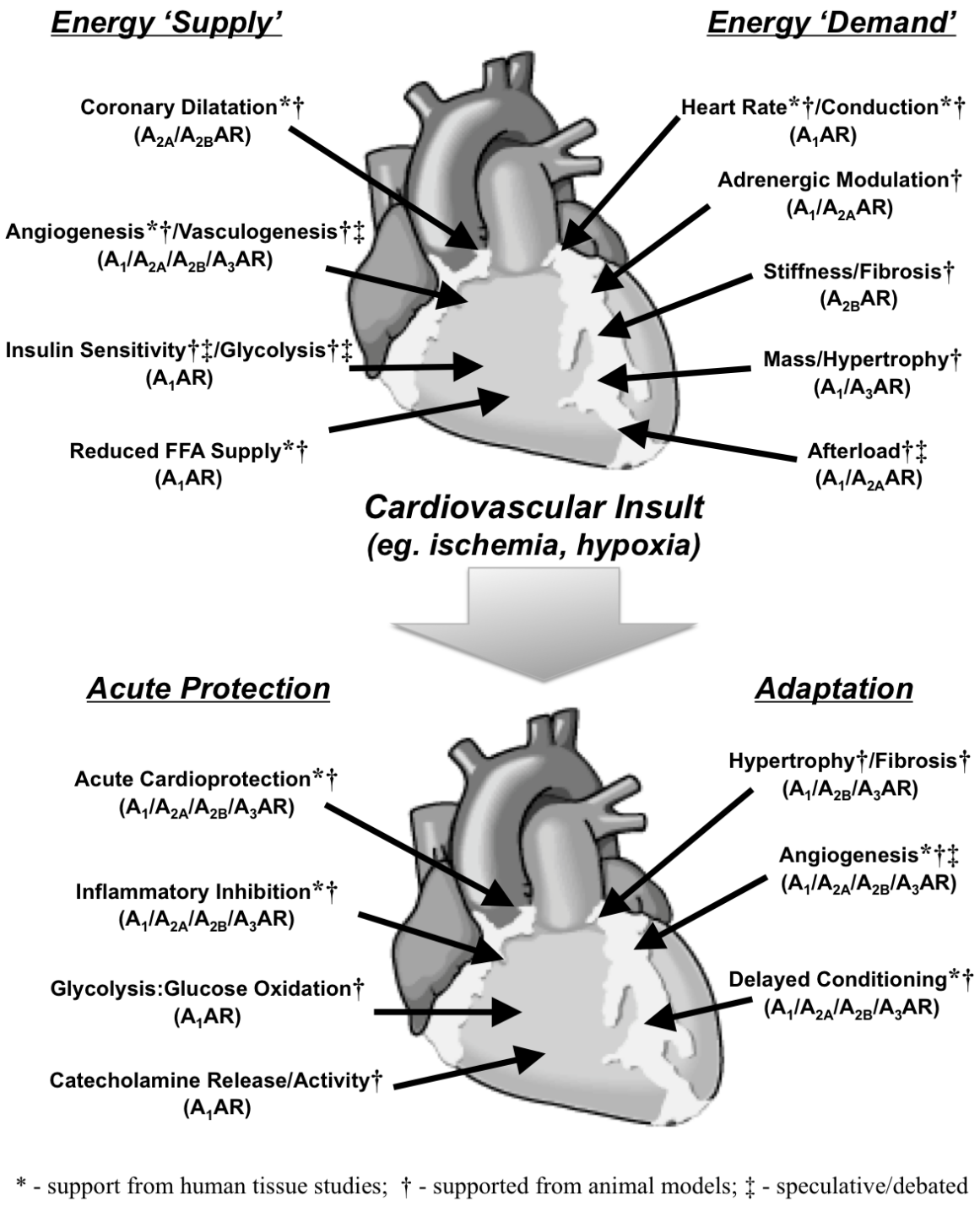

Fig. 1. Simplified depiction of proposed regulatory roles of adenosine and ARs in modulating/optimizing the balance between myocardial energy 'supply' and 'demand' (upper panel), and the impact of ARs in ameliorating injury and promoting adaptation (lower panel) during and following myocardial insult. Responses may be modified in disease states. Receptor involvement (identified in either animal or human studies) is shown. *, supported in human tissue studies; †, supported in animal model studies; ‡, speculative/debated.

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