Adenosine receptor subtypes in the heart: therapeutic opportunities and challenges

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FOUR SUBTYPES OF ADENOSINE RECEPTORS (A1, A2A, A2B, and A3 receptors) are known to exist (26). Traditionally, the A1-adenosine receptor has been thought to be the only subtype expressed in ventricular cardiomyocytes. By inhibiting adenylyl cyclase, the A1 receptor attenuates the positive inotropic effect of β-adrenergic receptor stimulation (or other interventions that stimulate adenylyl cyclase). Another function of the A1 receptor is to protect against the injury caused by myocardial ischemia and reperfusion. This latter function of the A1 receptor may be related to its antiadrenergic properties as well as to activation of the ATP-dependent potassium channel. There is increasing evidence, however, that other adenosine receptor subtypes also exist in ventricular myocytes and that they may have important physiological functions. In the February 1999 issue of this journal (AJP: Heart Circ. Physiol.), Norton and co-workers (24) proposed that A2A receptors are expressed in rat ventricular cardiomyocytes and that they serve to counteract the antiadrenergic effects of A1-adenosine receptors. This conclusion is based on the observation that in isolated rat hearts and isolated adult rat ventricular cardiomyocytes, the antiadrenergic effects of adenosine are potentiated in the presence of selective A2A-receptor antagonists; that is, blockade of A2A receptors enhances the ability of adenosine to antagonize the positive inotropic effects of β-adrenergic stimulation. The report by Norton and colleagues (24) is the first indication that A2A receptors exert proadrenergic effects in the intact rat heart.

Although the physiological and pathophysiological roles of cardiomyocyte A2A receptors remain to be determined, the modulating influence of A2A receptors on adrenergic function is a potentially important observation that may have implications for a variety of clinical settings such as coronary artery disease and heart failure. The effects of A2A-receptor agonists and antagonists in these settings are likely to be complex and will require further investigation. On the one hand, it can be envisioned that antagonists of A2A receptors may provide a therapeutic benefit in situations in which an enhanced antiadrenergic response is desirable, such as during acute myocardial ischemia. On the other hand, there is evidence that stimulation of A2A receptors after reperfusion is beneficial by inhibiting neutrophil function (11) and, possibly, augmenting coronary flow. With the increasing interest in the clinical use of adenosine or A1 agonists to protect the ischemic myocardium (14, 15, 18–20, 22), it will be important to determine whether selective manipulation (activation/antagonism) of A2A receptors can be used to potentiate the anti-ischemic effectiveness of A1-receptor activation.

Another area that warrants investigation pertains to the pathophysiological roles of A1 and A2A receptors in modulating the response to adrenergic stimuli in patients with congestive heart failure, a condition in which plasma adenosine levels are increased (8). The significance of the pro- and antiadrenergic actions of A1 and A2A receptors, respectively, in this setting needs to be elucidated. From a therapeutic standpoint, adenosine agonists or antagonists that selectively target A1 or A2A receptors may be useful either to protect the failing heart from chronic, excessive adrenergic stimulation or to potentiate the inotropic response to such stimulation when clinically indicated. The clinical implications of the proadrenergic action of adenosine A2A receptors, however, are not limited to myocardial ischemia and heart failure. For example, it is conceivable that selective antagonists of A2A receptors may enhance the effectiveness of adenosine in terminating supraventricular arrhythmias.

In addition to the A2A-adenosine receptor, there is also evidence that A3-adenosine receptors may be expressed in ventricular cardiomyocytes. The A3-adenosine receptor is the most recently identified subtype; like the A1-adenosine receptor, it is negatively coupled to adenylyl cyclase. Using embryonic chick cardiomyocytes, Strickler and co-workers (30) observed that A3-adenosine-receptor agonists inhibit isoproterenol-induced increases in cAMP and that activation of A3-adenosine receptors provides tolerance against hypoxic injury. Thus it has been hypothesized that both A1 and A3 receptors are expressed in cardiomyocytes and that they serve similar functions. It appears that the protection afforded by A3 receptors occurs via a protein kinase C-dependent pathway (2, 16). Whether A3 receptors are expressed in adult cardiomyocytes, however, is still unclear. The present observations by Norton et al. (24) that AB-MECA [N6-(4-aminobenzyl)-5’-N-methylcarboxamido-adenosine], a moderately selective A3-receptor agonist, did not exert an antiadrenergic effect in isolated rat hearts seem to support the concept that A3 receptors may not be present in the ventricular...
myocardium in rats. On the other hand, there is strong evidence that A3-receptor agonists can protect against ischemia-reperfusion injury in rabbits. Tracey et al. (31) and Lasley et al. (13) have shown that activation of A3 receptors reduces infarct size and alleviates myocardial stunning in isolated buffer-perfused rabbit hearts. Furthermore, Auchampach and co-workers (2) have recently demonstrated that the A3-selective agonist IB-MECA [N-8-(3-iodobenzyl)-5’-N-methylcarboxamido-adenosine] protects against stunning and infarction in conscious rabbits without causing any hemodynamic alterations (a major impediment to the use of A1-receptor agonists in patients). These studies suggest that, compared with the use of A1-receptor agonists, therapeutic strategies targeting the A3 receptor may have greater applicability in the clinical setting. It is not clear, however, whether the cardioprotection provided by A3-receptor agonists in these studies (2, 13, 31) was the result of actions on A3 receptors expressed in cardiomyocytes or on A3 receptors expressed in other cell types within the heart. Furthermore, A3-receptor agonists produce hypotension in rats and mice (but not in rabbits) by stimulating mast cells to degranulate (10). Whether this mast cell response occurs in humans remains to be determined.

A2B-adenosine receptors have also been suggested to be expressed in ventricular cardiomyocytes based on studies in isolated embryonic cells (17). Like A2A receptors, A2B receptors are positively coupled to adenylyl cyclase and appear to antagonize the antiadrenergic effects of A1-adenosine receptors (17). Thus, similar to A2A receptors, agonists and antagonists of A2B receptors may have clinical utility in disease states in which it is desirable to modulate adrenergic function. One unique feature of A2B receptors, however, is that they can also couple to mitogen-activated protein kinase pathways via Gq/11 proteins (Refs. 1, 6, 7; J. Linden, personal communication). It is therefore possible that A2B receptors may modulate cellular hypertrophy. Although a regulatory function of A2B receptors in the growth of cardiomyocytes has not been shown, A2B receptors have been found to inhibit growth of cardiac fibroblasts and vascular smooth muscle cells (4, 5).

Much remains to be learned regarding the expression and function of the various adenosine receptor subtypes in the heart. Because most of the evidence for the existence of multiple adenosine receptor subtypes in cardiac myocytes is based on studies in immature cells in culture, additional studies [such as the investigation by Norton et al. (24)] are needed to verify whether these receptors are also functionally expressed in adult cells and whether they are involved in physiological and pathophysiological processes. Such studies will become more feasible as newer, more subtype-selective agonists and antagonists are developed. It must be recognized, however, that because adenosine receptors are widely distributed throughout the body, pharmacological therapies targeting adenosine receptors in cardiomyocytes are complicated by potentially undesirable systemic side effects. For instance, A2A-receptor antagonists may provide useful positive inotropic effects in patients with heart failure, but they may also inhibit coronary vasodilation by blocking vascular A2A receptors. Although the clinical use of A1-receptor agonists to protect the ischemic myocardium is conceptually attractive and supported by solid experimental evidence, it is severely limited by the negative chronotropic and dromotropic effects of these agents as well as by the renal vasodilatation they can cause. Local (intracoronary) delivery of adenosine (or A1-receptor agonists) may circumvent the problem of systemic side effects and has been shown to be effective in protecting the human myocardium against ischemic injury (14, 15), but it is not practical in the vast majority of situations. With the notable exceptions of coronary artery bypass surgery (22) and coronary angioplasty (14, 15), harnessing the therapeutic potential of adenosine or adenosine-receptor agonists in the clinical arena requires systemic administration.

There are several potential approaches for overcoming the limitations imposed by the systemic hemodynamic effects of adenosine and adenosine receptor agonists. One approach to increase the tissue specific...
ity of adenosinergic therapy is to take advantage of receptor reserve and of the intrinsic activity of adenosine-receptor agonists. This approach taken by Bellardinelli and co-workers (23, 28, 29) is predicated on the hypothesis that adenosine agonists will elicit more potent responses in tissues in which the receptors are tightly coupled and are in excess. The ability of some A2a-adenosine receptor agonists to increase coronary conductance without influencing systemic hemodynamics provides evidence that this approach is feasible (28). Another strategy to increase the tissue specificity of adenosinergic therapy is to increase the number of receptors expressed in target organs. The effectiveness of this strategy was recently demonstrated by Gauthier et al. (9) and Matherne and co-workers (21), who showed that cardiac-specific overexpression of the A1-adenosine receptor (using the α-myosin heavy chain gene promoter) in transgenic mice resulted in the attenuation of the positive inotropic response to isoproterenol and increased tolerance to ischemia-reperfusion injury. We have recently developed transgenic mice overexpressing A3 receptors selectively in the heart and found the receptors to be coupled to G proteins (Fig. 1). Thus increasing the number of functional A1- and A3-adenosine receptors in ventricular cardiomyocytes in vivo is feasible. If an increase in cardiac adenosine receptors could be achieved in humans by means of gene transfer or other molecular techniques, it may be possible to chronically enhance the tolerance of the myocardium to ischemia without systemic effects and without the need for continuous administration of receptor agonists. This novel strategy could also enable manipulations of the adenosine receptor that render it less susceptible to desensitization. Furthermore, the expression of adenosine receptors could be controlled by the use of appropriate promoters that are activated by ischemia or hypoxia, thereby targeting the increased receptor population to those regions of the heart that are at risk for ischemic injury. Initial experience with reporter genes supports the feasibility of this approach (25).

Taken together, the above considerations suggest that further characterization of the adenosine receptor subtypes expressed in cardiomyocytes, coupled with efforts to increase the receptor selectivity of adenosinergic therapies and to develop molecular strategies to augment adenosine receptors in the heart, may provide new approaches to the treatment of cardiovascular disorders. The potential benefits to be reaped are considerable. This is underscored by the promising results of several recent studies demonstrating that adenosine is effective in protecting the ischemic myocardium in humans in such diverse settings as coronary angioplasty (14, 15), coronary artery bypass surgery (22), and acute myocardial infarction (18–20). In the coronary angioplasty setting, the cardioprotective effects of adenosine persist after the nucleoside disappears from the circulation (14, 15), indicating that adenosine can precondition human myocardium in vivo, in keeping with experimental data (3). These results suggest that pretreatment with adenosine may be a useful prophylactic measure to increase the safety of angioplasty in patients who are at risk for complications. For example, patients with substantially impaired left ventricular function or large regions of myocardium subtended by the target vessel can develop severe hemodynamic compromise or refractory arrhythmias in the event of abrupt vessel closure. In these situations, the protection provided by adenosine preconditioning may retard the development of necrosis and allow more time for revascularization. In the cardiac surgery setting, combined systemic and local (as an additive to cardioplegia) administration of adenosine has been shown to improve the recovery of left ventricular function and to reduce the requirements for inotropic and vasodilator therapy in the postoperative period, indicating attenuation of myocardial stunning (22), in keeping with experimental data (12, 27). In this setting, adenosine has also been found to reduce the incidence of perioperative infarction (R. M. Mentzer, personal communication). In the setting of acute myocardial infarction, the AMISTAD trial has shown that intravenous infusion of adenosine, given in conjunction with thrombolytic therapy, affected a marked reduction in infarct size in patients with anterior infarction, although no benefit was noted in inferior infarction (18). Another study reported that intracoronary infusion of adenosine in patients undergoing primary angioplasty attenuated the no-reflow phenomenon and reduced the incidence of Q wave infarction and congestive heart failure (19, 20). If these provocative results are confirmed, they would establish adenosine as the first clinically available agent for the prevention of reperfusion injury, thereby opening a major new indication for adenosinergic therapy.

Thus, judging from the experience accumulated so far, it appears that the cardioprotective actions of adenosine documented in experimental animals (3, 12, 27) can be reproduced in humans. Whereas these initial clinical results are promising, it must be noted that they were obtained in relatively small studies (14, 15, 18–20, 22). It is now essential that these results be verified in large (phase III) randomized, placebo-controlled, double-blind trials. Several such trials (e.g., AMISTAD II, LISA, ADMIRE) are ongoing and will soon provide a definitive assessment of the usefulness of adenosine. If the cardioprotective actions of this nucleoside in humans are confirmed, there is little doubt that they could be potentiated by targeting therapy to specific adenosine receptor subtypes and to specific tissues. Adenosinergic therapy may be a major development for cardiovascular medicine in the next few years.

REFERENCES


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