Adenosine receptors, heart rate, and cardioprotection

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See article by Fabritz et al. [1] (pages 500-508) in this issue.

In this issue of Cardiovascular Research, a paper by Fabritz et al. [1] investigates the effects of controlled overexpression of the A3 adenosine receptor (A3AR) in the mouse heart. Their findings will feed further the current debate on the use of adenosine receptors (AR) as targets for gene therapy aimed at protecting the myocardium against ischemic damage. Furthermore, Fabritz et al. report interesting observations on the functional role of adenosine receptors in the regulation of heart rate.

1. Adenosine and cardioprotection

In the heart, adenosine regulates pacemaker activity as well as different cellular functions through the A1, A2, and A3AR. ARs are expressed on different cell types, including myocytes, vascular and endothelial cells, fibroblasts, and neutrophils (for review, see Ref. [2]). Furthermore, adenosine activates the cellular mechanisms of protection from ischemic damage. Endogenous release of adenosine during myocardial ischemia induces a potent protective effect in both a paracrine and autocrine way [3]. Particularly, adenosine reduces the infarct size and delays the onset of ischemic contracture by reducing the rate of ATP catabolism. It also improves the postsischemic contractile function and attenuates myocardial stunning. At the cellular level, adenosine induces cardioprotection by directly acting on cardiomyocytes, by inhibiting platelet aggregation and adhesion of inflammatory cells to the endothelium, and by reducing the production of superoxide by neutrophils [3,4]. Administration of adenosine is effective in both ischemic and pharmacological preconditioning [5] and throughout the early [6] and delayed [7] windows of preconditioning.

2. Gene therapy and AR

The observation that exogenous administration of adenosine has antischismic properties during coronary angioplasty has suggested the possibility of developing clinical therapies that mimic adenosine-dependent cardioprotection [8]. However, the use of AR agonists in clinical settings is complicated by the side effects of the drugs on extracardiac tissue and by progressive desensitization of receptors for high doses of adenosine [9]. Second, even if the stimulation of endogenous AR does induce cardioprotection, the high extracellular level of adenosine reached during ischemia can reduce the efficacy of systemic administration of AR agonists [10,11]. To overcome these limitations, research on gene therapy has focused on the overexpression of AR for enhancing the receptor density coupled to intracellular signalling pathways responsible for cardioprotection [11]. Choice of the A1AR or the A3AR for developing candidate transgenes is of importance. Indeed, differences exist in the properties of cardioprotection observed when A1AR and A3AR receptors are stimulated. For example, pharmacological stimulation of the A3AR by specific agonist induces sustained protection as compared to stimulation of the A1AR receptor, which is less long lasting [12]. The development of a transgenic mouse model in which the expression of the A3AR has been enhanced is thus an important step toward the development of cardioprotective gene therapy. However, given the functional importance of ARs in the regulation of the heartbeat, possible complications of the use of the A1AR or A3AR receptor for gene therapy may arise. Indeed, we can expect consequences for heart rhythm and conduction due to overexpression of ARs also in the sinoatrial node (SAN) and the conduction centres of the heart: the atrioventricular (AV) node and the Purkinje fibres. This point is particularly relevant, because changes in heart rhythm and rate can lead to serious alterations in myocardial contractility and performance.

These expectations have been confirmed to some extent by a previous study dealing with a transgenic mouse line...
overexpressing the A1AR in the heart [11,13]. These mice have shown that both the heart rate and susceptibility to ischemic damage are affected in A1AR transgenic mice. Here, overexpression by about 1000-fold of the A1AR induced SAN bradycardia in transgenic animals. In contrast, no change in heart contractility and coronary function was observed, indicating that cardiac A1AR overexpression may not have deleterious effects on heart performance. Furthermore, transgenic hearts showed increased time to ischemic contracture as well as improved functional recovery after reperfusion. However, mice overexpressing the A1AR also showed partial AV block and increased susceptibility to episodes of atrial arrhythmias when challenged with exogenous adenosine [13]. These studies have thus supported the hypothesis of the usefulness of the manipulation of AR expression for cardiac gene therapy, but they have also highlighted the necessity to moderate receptor expression.

In this respect, the work by Fabritz et al. [1] constitutes a promising step in this direction. Indeed, this group has specifically investigated the cardiac phenotype of two mouse lines expressing low (A3<sub>low</sub>) and high (A3<sub>high</sub>) amounts of the A3AR. When compared to the A1<sub>low</sub> mice, the A3<sub>high</sub> mouse line shows about fivefold higher A3AR density. By extending previous observations on the same mice [14], Fabritz et al. show that low expression of the A3AR has almost no detrimental effect on the transgenic hearts except for a slight slowing of the AV conduction. In addition, A3<sub>low</sub> transgenic hearts show a significant increase in cardioprotection as assessed by an ischemia–reperfusion protocol [14]. In contrast, high expression of the A3AR in A3<sub>high</sub> mice leads to a complex phenotype that includes SAN bradycardia, brady-cardia–tachycardia syndrome, and complete AV block. In addition, A3<sub>high</sub> mice develop severe cardiomyopathy, possibly as a consequence of the chronic atrioventricular block and incessant supraventricular arrhythmia. The phenotype of the A3<sub>high</sub> mice is of particular interest, because establishment of atrial arrhythmias during the first postnatal weeks precedes the onset of cardiomyopathy, which then progressively worsens during adulthood. End-stage A3<sub>high</sub> hearts display atrial dilatation, structural and biochemical remodelling, fibrosis, and ventricular contractile dysfunction. It is thus tempting to suggest that the A3<sub>high</sub> mouse constitute a promising mouse model for studying in vivo the mechanisms of progression from chronic supraventricular arrhythmias to heart failure and, more generally, the mechanisms of cardiac structural remodelling linked to chronic rhythm dysfunctions.

3. Perspectives for the study of heart rate regulation

Interestingly, A3<sub>high</sub> mice described by Fabritz et al. [1] also display constitutive antiadrenergic effects mediated by ARs. Indeed, in A3<sub>high</sub> mice both bradycardia and AV block cannot be relieved by β-adrenergic receptor stimulation. This rather surprising observation is strongly suggestive of a high tonic activation of inwardly rectifying K<sup>+</sup> currents, such as I<sub>KACB</sub>. Furthermore, it is also possible that A3AR can control the heart rate in vivo by interacting with different G-proteins, each interaction inducing a particular effect on heart rate. A3AR could thus act with G<sub>q</sub> to prevent elevation of intracellular cAMP or with G<sub>i</sub> to activate I<sub>KACB</sub>. The phenotype of A3<sub>high</sub> mice seems to support these hypotheses, since both constitutive antiadrenergic effect and tonic AV block are observed. In addition, comparison of findings from A3<sub>high</sub> mice with previous results from mice overexpressing the A1AR [13], mice in which β-adrenergic stimulation did reverse bradycardia and AV-block, indicates that the A1AR and A3AR exert different types of control of heart rate. Thus, the study of the functional role of these receptors in heart rate regulation is of much interest.

4. Conclusions

In summary, recent studies such as that by Fabritz et al. [1] show that it is possible to significantly improve the resistance of the heart to ischemic damage by increasing the expression of A3AR without detrimental side effects on heart rate and systolic function. This work also indicates unequivocally that the possibility of a successful gene therapy will be critically dependent on a tight control of the level of expression of A3AR. However, it would also be interesting to study cardioprotection in mice expressing the A3AR specifically in the ventricle. The A3AR is expressed in the human heart [15]. Gene therapy approaches might thus consider targeting A3AR expression to the ventricle. Such specificity should also help in limiting the possible side effects of overexpressing the A3AR in the atrium as well as in the SAN and AV node. In addition, the progressive cardiomyopathy developed by A3<sub>high</sub> mice further stress the tight physiological link existing between heart rhythm, cardiac pathology, and cardioprotection.

References


