REVIEW

Adenosine and cardioprotection: What can we learn from nature's genetic polymorphism?

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Abstract

Adenosine is an endogenous nucleoside that has been shown to be beneficial for the myocardium in different settings by a large number of experimental studies. In this article, we 1) outline adenosine's metabolic pathways, 2) address cardioprotective properties of adenosine, and 3) discuss possible implications of the two recently published clinical studies disclosing a positive effect of adenosine monophosphate deaminase 1 (AMPD1) gene mutation on cardiovascular survival in heart failure and ischemic heart disease. (Fig. 2, Ref. 84.)
Key words: adenosine, cardioprotection, AMPD1 gene mutation.

Adenosine is an endogenously occurring nucleoside that participates in modulation of numerous physiological functions. In relation to cardiovascular system, it was in 1929 when Drury and Szent-Györgyi first described its bradycardic, vasodilatatory and blood pressure lowering effects (1). A large number of studies published over the last two decades, offering experimental evidence adenosine may be beneficial for the myocardium in different settings, has lead to the tenet that this nucleoside is a cardioprotective metabolite (2–8). However, the extremely short half-life of adenosine and tachyphylaxis after its prolonged administration dissuaded investigators from exploring potentially favorable effects of up-modulation of this substance on a long-term basis in patients with heart diseases. In this article, we will 1) outline adenosine's metabolic pathways, 2) briefly address cardioprotective properties of adenosine, and 3) discuss the possible revolutionary implications that may arise from the two recently published clinical studies disclosing a positive effect of adenosine monophosphate deaminase 1 (AMPD1) gene mutation on cardiovascular survival in heart failure (9) and ischemic heart disease (10).

Metabolism of adenosine

Adenosine is a purine nucleoside comprised of adenine and ribose joined by a glycosidic bound (Fig. 1). It is formed in tissues via dephosphorylation of adenosine 5'-monophosphate (AMP) by 5'-nucleotidase or via hydrolysis of S-adenosylhomocysteine (SAH) by SAH-hydrolase, the former being the major source of cardiac adenosine production.

Adenosine's precursor AMP is produced mainly by adenosine 5'-triphosphate (ATP) breakdown, although production from cyclic AMP (cAMP) by phosphodiesterase has has also been documented in the cardiac fibroblasts (11) and vascular smooth muscle cells (12). AMP can be deaminated by AMP deaminase to form inosine monophosphate (IMP), or dephosphorylated by 5'-nucleotidase to form adenosine (5) (Fig. 2). Two different forms of 5'-nucleotidase play an important role in the adenosine formation (13): the AMP-selective cytosolic 5'-nucleotidase (cN-I) (14–16) and ecto-5'-nucleotidase (17). The ecto-5'-nucleotidase is expressed on the outer membrane of many cell types in the heart, including pericytes, fibroblasts (18), endothelial cells, smooth muscle cells (19) and cardiomyocytes (20, 21). In the heart, adenosine is thus formed both intracellular in cardiomyocytes (22), coronary smooth muscle cells (23) and endothelial cells (24), and extracellular from adenosine nucleotides released from cardiomyocytes, endothelial cells (25) and blood elements.

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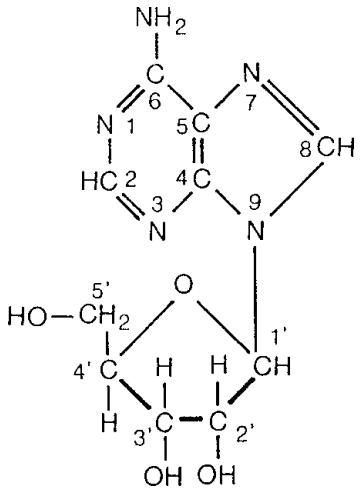

Fig. 1. Structure of adenosine.

Adenosine crosses the cell membranes by facilitated diffusion. It can be rapidly inactivated by phosphorylation to AMP by adenosine kinase, or deaminated to inosine by adenosine deaminase (26). The details about compartmentalization and regulation of adenosine formation in the respective compartments, as well as the transport of this nucleoside out of and into cells is a subject of ongoing experimental research (27, 28) and mathematical modeling (29, 30).

In tissues that are dependent on oxidative phosphorylation such as the heart, a decreased oxygen supply relative to the workload leads to an energy-deficient state. This situation shifts the metabolism of adenine nucleotides towards the degradation of ATP with augmented generation of adenosine 5'-diphosphate (ADP) and thence, AMP, the direct substrate for adenosine production. Moreover, cN-I and ecto-5'-nucleotidase have been noted to be activated by ischemia (31), the later also by α-1-adrenergic receptor stimulation (32), which would further contribute to the increased adenosine formation in the energy-deficient state. The total production of adenosine in the heart has been documented to be markedly elevated in hypoxia and ischemia (5), both in experiments (33–36), and in the clinical setting of ischemic heart disease (37) and heart failure (38).

In summary, the most important source of adenosine in cells and in the interstitial tissue is the "ATP→ADP→AMP→adenosine" pathway. Hypoxia and ischemia strongly enhances adenosine production. Thus, adenosine can be considere a signal of inadequate oxygen supply for the tissue (39, 40).

Cardioprotection by adenosine

The majority of adenosine's effects can be viewed as directed towards restoring the energy balance in the setting of relative shortage of oxygen supply. It acts to decrease the workload of the heart: negative dromo-, chrono- and inotropic effects, as well as to increase the oxygen supply for the tissues: dilatation of coronary arteries, vasodilatation in other vascular beds, stimulation of breathing (2, 40). These properties of adenosine lead to the concept this nucleoside acts in the cardiovascular system as a retaliatory metabolic counteracting the mismatch between energy supply and demand and this way protecting the heart (41). Furthermore, it has been noted in the past decade the beneficial effects of adenosine surpasses its retaliatory function (3, 5, 7, 8). Adenosine has been shown to be one of the major triggers involved in the mechanism of ischemic preconditioning, the most potent mechanism protecting the heart against ischemia known to date.

Ischemic preconditioning is a striking phenomenon that has been first described in 1986 by Murry et al: a significant reduction in infarct size has been observed when the heart was previously subjected to shorter episodes of ischemia (42). Early and delayed phases of preconditioning have been described, where the initial ischemic episode conveys cardioprotection against a following ischemic event that can occur either immediately – phase of preconditioning!, or 24–72 hours later – "the delayed phase", or "second window of preconditioning." Although much work is still needed in order to elucidate the entire sequence of events responsible for the cardioprotective effect of short-term ischemia, the mechanism of ischemic preconditioning has been explained in part. Namely distinct extracellular triggers have been detected and intracellular mediators and downstream signaling pathways of preconditioning described (43).

Adenosine is quickly released into extracellular fluid during ischemia and has been shown to be one of the most important triggers implicated in ischemic preconditioning. Infusion of adenosine (44, 45), as well as adenosine A1 (46–49) and A3 (50––54) receptor agonists, mimics the preconditioning effect of short-term ischemia, and protects the heart both against early and delayed ischemic insult (55–59). Moreover, these effects can be blocked by adenosine receptor antagonists (60). The downstream signaling pathway activated by A1 and/or A3 adenosine receptors, both of them G-protein coupled acting through inhibition of adenylyl cyclase (A3 possibly also through increase in activity of phospholipase C), involve opening of mitochondrial K_{ATP} channels (61), generation of free radicals (62), translocation of the epsilon isoform of protein kinase C (63, 64) and activation of the family of mitogen activated protein kinases (65). The latter induce the transcription of certain enzymes, such as superoxide dismutase, inducible NO synthase (66) and heat-shock proteins (67, 68), which can account for the second window of protection in the delayed phase of preconditioning.

Clinical studies on AMPD1 gene mutation

On the experimental level, extensive evidence has been gathered that adenosine can exert cardioprotective effects. However, clinical studies analyzing its potential cardioprotective effects in humans have been limited to trials using short-term administration of adenosine in acute ischemia (69), preconditioning before percutaneous transluminal interventions (45, 70) and coronary artery bypass grafting (71), and its use in cardioplegic solutions

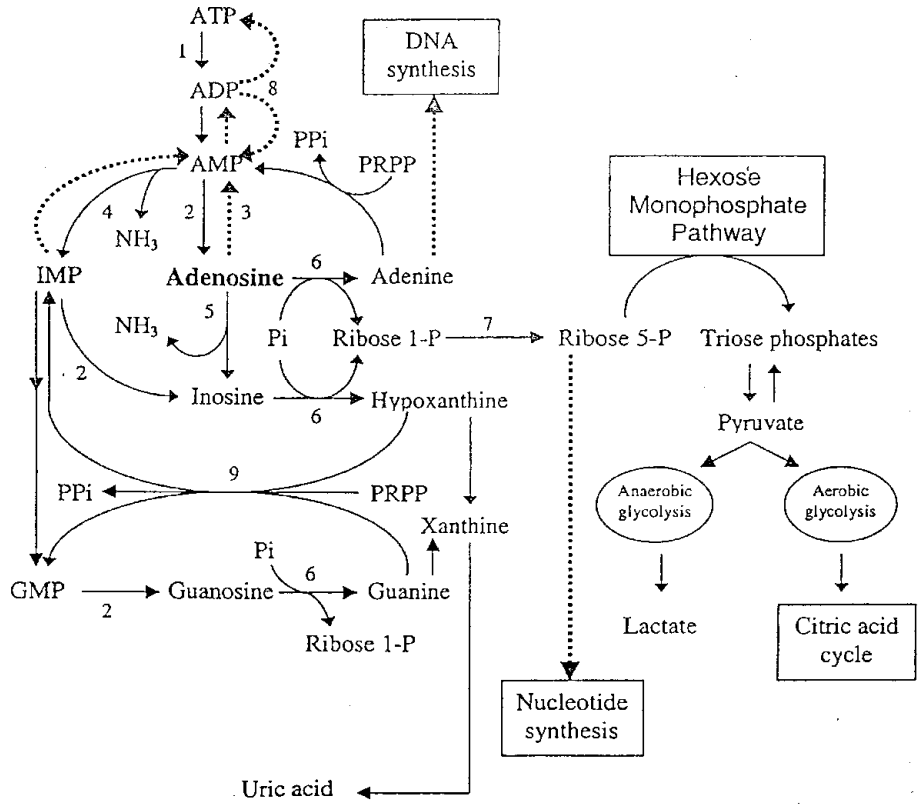

Fig. 2. Metabolism of adenosine. 2–5‘ nucleotidase, 4–AMP-deaminase.

(72, 73). Although these studies are showing promising results in terms of improvements of certain clinical parameters within the short follow-up period, the long-term outcome, which is the most important challenge for clinical medicine, remains unknown. The crucial questions is whether and low properties of adenosine can be harnessed to prolong life of patients with cardiovascular diseases. This has not been answered yet. Nevertheless, two recently published clinical studies on AMPD1 gene mutations are offering indirect indices that improved survival in heart failure and coronary artery disease indeed could be related to adenosine. Briefly, AMPD1 is the isoenzyme of AMP deaminase that is highly expressed in skeletal muscle and, to a lesser extent, together with AMPD2, in the cardiac muscle. About 10—20 % of Caucasians and Afro-Americans, but not Asians, are carriers of a nonsense mutation in the exon 2 of the AMPD1 gene. This mutations is a C to T transition at nucleotide 34 that leads to a premature peptide chain termination and production of a truncated catalytically inactive enzyme (74). Individuals with deficiency of the AMPD1, formerly called myoadenylate deficiency, may develop metabolic myopathy and experience muscle pain and cramps associated with exercise. In their retrospective study (9), Loh and co-workers have investigated the association between AMPD1 genotype and clinical outcome in patients with congestive heart failure (CHF). A total number of 132 patients of non-Asian origin with advanced CHF referred for cardiac transplantation evaluation was included in the study, and their AMPD1 genotype was determined. The results of this study has demonstrated that the probability of survival after the first hospitalization for CHF symptoms is significantly longer in a patients with a mutant AMPD1 allele than in a non-carrier (9). Limitations of this study included its retrospective nature and a narrow sample of study subjects, nevertheless another investigation has supported and extended their inferences. Anderson and co-workers have conducted a prospective study on 367 patients with coronary artery disease (10). Again, survival statistics compared carriers of the mutant AMPD1 allele with non-carriers. Cardiovascular mortality was 4.4 % in mutant AMPD1 allele carriers compared with 11.9 % in non-carriers during the 5 years of follow-up. In multiple variable regression analysis, only age and mutant AMPD1 carriage were independent predictors of cardiovascular mortality. In this study, AMPD1 gene mutation carriage has not been associated with a reduction of non-cardiovascular mortality. Interestingly, AMPD1 variant did not predict development of coronary artery disease, rather the effect appeared to be in prolonging survival when heart disease was already present (10).

To date, we can only hypothesize about the pathophysiological mechanism responsible for the prolonged cardiovascular sur-

vival in AMPD1 gene mutation carriers documented in the two aforementioned studies. The decreased AMPD1 activity in the skeletal muscle of patients heterozygous or homozygous for AMPD1 gene mutation presumably leads to accumulation of AMP in their skeletal muscle with the shift of AMP metabolism towards adenosine formation by 5'-nucleotidase (Fig. 2). Given the previously mentioned cardioprotective properties of adenosine, the increased production of this nucleoside appears to be the most plausible explanation for the improved survival of cardiac patients with AMPD1 gene mutation (9, 10, 75). Loh with co-authors suggested that in AMPD1 deficiency circulating levels of adenosine are increased due to its augmented release from the skeletal muscle (9). Yet, the known short half-life of adenosine in human blood lead to doubts if it is the increased formation in skeletal muscle that accounts for the cardioprotective results, and rather an enhanced local production in the cardiac muscle has been proposed (75). However, no skeletal, myocardial or circulating adenosine levels were determined in either study. What the kinetics of adenosine in the setting of AMPD1 deficiency is, and how the nucleoside exerts its protective effects on the cardiac tissue, remains an intriguing question.

We propose the hypothesis that the critical characteristic of adenosine kinetics in AMPD1 deficiency that results in significant cardioprotection is the intermittent manner of the adenosine level increase. There are several lines of evidence to support this.

First, skeletal muscle adenosine levels at rest detected by muscle biopsy from patients with myoadenylate deaminase deficiency have been reported to be comparable to those of non-carriers of AMPD1 mutation (76). If the skeletal muscle is the major site of AMPD1 expression, and its deficiency does no lead to locally increased adenosine levels at this site during resting condition, there is no reason to expect adenosine levels in circulation or in the myocardium would be increased in a continuous fashion. On the other hand, exercise has been shown to elevate adenosine levels in skeletal muscle biopsies up to 16-fold in AMPD1 deficiency comparing to the 2-fold increase with exercise in AMPD1 mutation non-carriers (76), which is not surprising. The increased energy demand during physical activity leads to increased degradation of ATP in skeletal muscle and accumulation of large amounts of AMP that, in deficiency of AMPD1, can be metabolized only by 5'-nucleotidase to form adenosine. This purine is one of chemical mediators of pain, and this could partly explain the clinical observation that patients with myoadenylate deaminase deficiency experience exercise-induced myalgias.

Second, chronic administration of adenosine can lead to desensitization of adenosine receptors (77–81). On the contrary, intermittent application of A1 receptor agonist has prevented the effect of desensitization and maintained the myocardium in the preconditioned state (82). Patients with AMPD1 deficiency presumably release from their skeletal muscles considerable amounts of adenosine each time they exercise, which could result in an intermittent manner of adenosine receptors activation in the heart. Moreover, this activation is likely to be timed during physical activity that impose increased demand on the cardiac muscle as well, offering additional protection against ischemia. Indeed, adenosine-enhanced ischemic preconditioning (adenosine administered simultaneously with preconditioning periods of ischemia) has been shown in experiments to convey a greater degree of protection than either preconditioning stimulus alone (83, 84). As shown by the example of second window of preconditioning, the cardioprotective effect of short-term adenosine receptors stimulation can be delayed up to several days after the stimulus.

In summary, we hypothesize that during physical activity of AMPD1 deficient patient adenosine is released in great amounts from skeletal muscle and possibly from the myocardium. This metabolite can activate cardiac adenosine receptors, which proceed to multiple downstream cascade with beneficial effects for the heart. Most likely, the stimulation of the adenosine receptors in AMPD1 deficiency is not chronic and thus should not lead to their desensitization and loss of the salutary effects. The promising results of Loh's and Anderson's studies encourage further investigation in order to describe adenosine kinetics and clarify the pathophysiological mechanisms responsible for the improved cardiovascular survival in patients with AMPD1 gene mutation. If we succeed in mimicking the biochemical situation that happens in the organism of these patients, we could be able to prolong life of patients with chronic heart diseases.

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