Editorial

Adenosine
A Homeostatic Metabolite in Cardiac Energy Metabolism

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Oxygen supply via the coronary circulation normally exactly matches the oxygen requirements of the heart so that cardiac energy usage relative to the delivery of oxygen is in equilibrium. Whenever the work of the heart increases, an adaptive increase in coronary blood flow occurs, which brings the system back to a new equilibrium. Thus, metabolic regulation of coronary blood flow, in essence, is maintaining cardiac energy metabolism balance. Understanding this concept is important because the vasodilator adenosine is metabolically directly linked to the catabolism of high-energy phosphate compounds. When blood supply to the heart is compromised, more adenosine is formed by the hypoxic heart in an attempt to restore coronary blood flow.

Aside from affecting coronary flow, adenosine exhibits several other important effects on cardiac function, some of which have only recently been discovered. At present, the known cardiac actions of adenosine include the following observations. 1) Adenosine is a potent dilator of coronary resistance vessels, which has been known since the first description by Durty and Szent-Gyorgyi 60 years ago. This observation formed the basis for the adenosine hypothesis of coronary flow regulation, the role of which has not been fully clarified up to now, despite intensive efforts during the past 20 years. 2) Adenosine inhibits the hemodynamic and metabolic effects of β-adrenergic stimulation by presynaptic and postsynaptic mechanisms. This antiadrenergic action of adenosine may serve to reduce the energy expenditure of the heart when oxygen supply becomes limiting. 3) Adenosine reduces heart rate by inhibition of impulse generation and conduction in the sinus and AV-nodes, respectively. Bradycardia in the hypoxic heart appears to be mediated by endogenously formed adenosine, and adenosine has been shown clinically to effectively terminate supraventricular tachycardia. 4) Adenosine inhibits superoxide anion generation by human neutrophils; this effect may attenuate the neutrophil-mediated injury to endothelial cells. During cardiac ischemia, this anti-inflammatory action of adenosine may limit infarct size. 5) Adenosine inhibits platelet aggregation and, thereby, can prevent the embolization of coronary vessels. About 14% of the adenosine released into the coronary circulation is derived from coronary endothelial cells, and adenosine formed at the endothelium-blood interface may, therefore, be antithrombogenic.

In a recent issue of Circulation, Babbit et al. and Gruber et al. reported that adenosine can limit vascular injury after prolonged ischemia and, thus, has the potential to salvage myocardium after reperfusion. In the study of Babbit et al., adenosine was applied by intracoronary infusion after 1 hour of ischemia and caused a striking protection of coronary endothelial cells. This was associated with reduced neutrophil infiltration, attenuated endothelial swelling, improved myocardial blood flow in endocardial regions, and greatly improved ventricular dysfunction (stunning) 3 hours after reperfusion. The study of Gruber et al. on the other hand, used AICA-riboside pretreatment to potentiate endogenous adenosine production during ischemia. The results are surprisingly similar: enhancing endogenous adenosine formation by AICA reduced the granulocyte content in ischemic tissue and increased regional blood flow to the hypoxic myocardium. AICA also reduced the ischemia-induced number of premature ventricular depolarizations and ventricular tachycardia. The action of AICA appears to be specific because it neither affected systemic blood pressure nor basal coronary flow nor increased flow to nonischemic areas. The most likely mode of action of AICA is through adenosine because plasma levels in the coronary venous blood were found to be above 1 μM, a concentration that is certainly within the biologically active range of this nucleoside.

Both studies raise important questions that concern the mechanism by which adenosine brings about its beneficial effect on coronary microvasculature of the ischemic heart, the mechanism by which AICA potentiates adenosine formation only in the ischemic but not in the well-perfused myocardium, and the potential clinical consequences of the new observations reported. These different issues are briefly discussed. In view of the many well-known cardiac
actions of adenosine listed above, adenosine’s beneficial effects on the coronary microcirculation leading to an improved recovery of the stunned myocardium cannot be easily traced down to a single effect. All actions of adenosine can be viewed as serving the same goal: to maintain the balance between oxygen delivery and oxygen demand. During ischemia, adenosine (whether endogenously formed or exogenously applied) can increase coronary flow directly (vasodilation) and indirectly (inhibition of endothelial swelling and prevention of mechanical obstruction of the vessels by neutrophils and platelets) and at the same time may lower oxygen consumption by its antiadrenergic and chronotropic actions. It is difficult to assess at present the relative importance of the individual actions of adenosine on the improved mechanical recovery of the ischemic heart, although it appears that inhibition of leukocyte infiltration may have been a crucial initial step.

It is particularly striking to see in both studies that adenosine by biochemical and morphological criteria inhibited leukocyte infiltration and, thereby, very likely reduced the formation of free oxygen radicals. Oxidant injury of endothelial cells has been reported to cause profound DNA damage and depletion of ATP. Coronary infusion of adenosine may have helped to replenish the endothelial ATP pool. This notion is supported by the finding that the endothelium is equipped with a highly active nucleoside transport system that can trap more than 90% of the adenosine taken up even when applied in the micromolar range. Pretreatment with AICA, however, did not prevent ATP depletion despite increased adenosine formation. Whether during ischemia there is a redistribution of purines from cardiomyocytes to endothelial cells due to rapid endothelial transport and salvage of adenosine appears possible but is not known.

Recent evidence suggests that the coronary circulation is controlled by nitric oxide (NO), which is formed and released in vasodilatory concentrations. Because superoxide anions are involved in the degradation of EDRF/NO, activated leukocytes can shorten the half-life of NO, which may result in vasoconstriction. Thus, there may be an additional regulatory loop by which adenosine during ischemia may induce vasodilation, which involves a primary inhibition of superoxide anion generation from granulocytes followed by an increase in the availability of NO.

It is usually assumed that adenosine is predominantly formed by dephosphorylation of ATP, AMP being the immediate precursor. This view was recently modified by the demonstration that in well-oxygenated hearts, a substantial fraction of the adenosine is derived from the transmethylation pathway by hydrolysis of S-adenosylhomocysteine (SAH): SAH→L-homocysteine+adenosine. Most of this adenosine, which is formed intracellularly, becomes reincorporated into the adenine nucleotide pool by action of adenosine kinase, whereas only a small fraction is washed out by the coronary circulation (Figure 1). Under conditions of hypoxia and ischemia, however, when adenosine is formed at a greatly accelerated rate, the major metabolic route is by breakdown of ATP. Under this condition, the transmethylation pathway, which is essentially oxygen insensitive, contributes only to a minor degree to cardiac adenosine formation.

From a metabolic point of view, the most intriguing finding in the study of Gruber et al14 is that AICA-riboside pretreatment augmented adenosine concentration only during net ATP hydrolysis. AICA did not alter any functional parameter of nonischemic controls; it decreased, however, coronary venous inosine release. This latter finding is most easily explained by inhibition of AMP-deaminase because inhibition of adenosine deaminase could be excluded. During ischemia when ATP is broken down, this could increase the substrate availability of AMP for the cytosolic 5'-nucleotidase, causing more adenosine to be produced (Figure 1). As was pointed out above, the flux of adenosine in the well-perfused heart mainly is from the transmethylation pathway, and more than 90% of the adenosine formed this way is phosphorylated by internal salvage. AICA-riboside is readily converted by adenosine kinase to AICA-riboside monophosphate and thereby competes with endogenously formed adenosine. Because adenosine kinase in the oxygenated heart is normally not substrate saturated, this would not alter the adenosine formation under control conditions. Under hypoxia, however, with more adenosine being formed from AMP in the presence of AICA, adenosine kinase may become saturated, and this results in greatly augmented adenosine formation. Although this appears to be a plausible explanation on the basis of what we presently know about the metabolism of adenosine, this hypothesis needs to be tested and explored in future studies.

The dog model used in the study by Babbitt et al13 and Gruber et al14 was advantageous because in this species the half-life of adenosine in blood is as long as 3 minutes. This permitted biologically active concentrations of adenosine to be reached in the vascular space. In the human, however, the half-life of adenosine in blood is only 0.6 second, and this
may readily dampen any changes of adenosine. Nevertheless, adenosine and adenosine-related compounds have already shown their therapeutic potential in patients.21,22 The clinical use of AICA pretreatment will depend, as Gruber et al also suggested, on the demonstration of a beneficial effect on myocardial infarction with or without reperfusion.

Adenosine can be considered as a locally acting metabolite that signals changes in the state of the energy metabolism of the heart via changes in the ratio of supply and demand for oxygen.23 Adenosine’s functional role, therefore, is to maintain adequate oxygen supply and to keep energy metabolism balanced. Because adenosine can prevent excessive ATP breakdown, it was termed a retaliatory metabolite.24 This emphasizes the fact that cardiac cells can adjust their own energy supply at a local level. The anti-injury effect of adenosine is a special case in the general concept of the homeostatic role of adenosine in cardiac energy metabolism.

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