Adenosine, the Heart, and Coronary Circulation

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Adenosine is known to regulate myocardial and coronary circulatory functions. Adenosine not only dilates coronary vessels, but attenuates β-adrenergic receptor-mediated increases in myocardial contractility and depresses both sinoatrial and atrioventricular node activities. The effects of adenosine are mediated by two distinct receptors (i.e., A1 and A2 receptors). A1 adenosine receptors, located in atrial and ventricular myocardium and sinoatrial/atrioventricular nodes, are responsible for inhibition of adenylyl cyclase activity. A2 adenosine receptors, located in coronary endothelial and smooth muscle cells, are responsible for stimulation of this enzyme activity. During increased myocardial oxygen demand due to rapid pacing and exercise, although both coronary blood flow and adenosine concentrations in the myocardium and coronary efflux increased, there is no clear consensus explaining its cause and effect relation at present. However, ischemia/reperfusion-induced coronary hyperemia is believed to be mostly attributed to released adenosine, and it has been proven that adenosine attenuates the severity of ischemia due to its coronary vasodilatory action. The beneficial effects of adenosine during ischemia/reperfusion processes do not seem simple. This is because myocardial ischemia and reperfusion injury is caused by 1) activated leukocytes and platelets, 2) ATP depletion and calcium overload of myocardium, and 3) catecholamine release from the presynaptic nerves as well as 4) the impaired coronary circulation. Intriguingly adenosine attenuates all of these deleterious actions and thereby attenuates ischemia/reperfusion injury. Indeed, adenosine attenuates the severity of contractile dysfunction (myocardial stunning) and limits the infarct size. Thus, administration of adenosine or potentiators of adenosine production in the ischemic myocardium may be beneficial for the attenuation of ischemic and reperfusion injuries, although further clinical investigations are necessary. (Hypertension 1991;18:565-574)

Adenosine receptors mediate a great variety of biological responses in the central nervous system, heart, kidney, endocrine glands, smooth muscles, blood cells, and adipose tissue. Thus, adenosine, a metabolite of adenine nucleotides, exerts a variety of functions in various organs, among which vasodilation may be a major action in almost all organs mainly through A2 adenosine receptor-mediated action.

Adenosine in the Heart

From the pharmacological actions of adenosine and its derivatives, adenosine receptors are classified into two subtypes, A1 receptors that are responsible for inhibition of adenylyl cyclase activity and A2 receptors that are responsible for stimulation of this enzyme activity. Both A1 and A2 receptors are blocked by methylxanthines. Adenosine receptors have been classified on the basis of structure–activity relations for various compounds. N6-substituted adenosine analogues, for example, N6-cyclohexyladenosine (CHA) and N6-cyclopentyladenosine (CPA) bind to A1 receptors with high affinities, whereas 5'-substituted adenosine analogues, for example, 5'-N-ethylcarboxamidoadenosine (NECA) and 5'-(N-cyclopropyl)-carboxamidoadenosine (CPCA) preferably bind to A2 receptors. Since A1 receptors are distributed mainly on myocardial cells and A2 receptors are on coronary vascular smooth muscle in the heart, vasodilator action of adenosine could be attributed to A2 receptor-mediated action.

It has been thought that stimulation of A2 receptors activates adenylyl cyclase in the coronary arteries to produce cyclic adenosine monophosphate (cAMP) and relaxes coronary vascular smooth muscle. However, it is not yet established whether cAMP mediates adenosine-induced vasodilation. In helical strips of dog coronary arteries, a significant increase in cAMP is only observed when the vessels are exposed...
to high concentrations of adenosine (1 x 10^{-3} M). 16 In this study, coronary arteries were dissected from the dog hearts and incubated in physiological salt solution for 2 hours. After treatment of the coronary arteries for 14-18 minutes with 1 x 10^{-7} to 1 x 10^{-4} M adenosine the coronary arteries were frozen rapidly between aluminum clamps precooled in liquid nitrogen, and cAMP content was determined. These doses of adenosine did not produce any changes in the cAMP content of the vascular strips. These results do not support a role for cAMP in the adenosine-induced relaxation of coronary smooth muscle cells. Several studies suggest that low concentrations of adenosine relax vascular smooth muscles primarily by decreasing intracellular Ca^{2+} levels either by reducing sarcolemmal permeability to Ca^{2+} 17 or by enhancing Ca^{2+} sequestration. 18

Endothelium is also involved in the vasodilator action of adenosine. 19 The vasodilator effect of adenosine is attenuated by removal of the endothelium in the isolated dog coronary artery, and this effect is greater when adenosine is applied to the luminal side than when applied to the adventitial side. 20 Therefore, the action of adenosine might be different on the endothelium and on the vascular smooth muscle. It has been recently reported that adenosine activates guanylate cyclase and increases the intracellular cyclic guanosine monophosphate (cGMP). 21 This action of adenosine may be mediated by adenosine receptors since it is attenuated by theophylline. 22 The rank order of potency of adenosine agonists for increasing cGMP (CHA > NECA > adenosine) indicates that the involved adenosine receptor is of the A_1 type. These observations are compatible with the concept that endogenous adenosine released from the cardiomyocytes may act on the coronary vascular smooth muscle (A_1 receptor-mediated) in a different way from the exogenous adenosine acting on the endothelial cell receptors (A_2 receptor-mediated). Adenine nucleotides may enhance endothelium-derived relaxing factor (EDRF) release from vascular endothelial cells. EDRF is also released by a flow-dependent mechanism, 22 and thus, adenosine may accelerate the release of EDRF by its vasodilatory action.

Role of Adenosine in Regulation of Coronary Blood Flow

Adenosine is released from the heart during any event in which oxygen supply is inadequate for oxygen needs (i.e., ischemia, hypoxia, and enhanced oxygen consumption). 23-26 Conversely, adenosine release is decreased when excess oxygen is supplied by overperfusion. 27 A similar relation between blood flow and adenosine release has been observed in the brain. 28-29 These observations suggest that adenosine plays a crucial role in the local regulation of blood flow. However, this hypothesis should be tested from the following aspects. Criteria for a role for adenosine as a local regulator of coronary blood flow are: 1) Administration of physiological concentrations of adenosine should increase coronary blood flow. 2) Adenosine must be produced by the heart (cardiomyocytes, vascular smooth muscle, or endothelial cells) when coronary blood flow increases. 3) There should be a direct correlation between the amount of adenosine in the interstitial fluid or the coronary venous blood and the changes in coronary blood flow. 4) Adenosine receptor antagonists and enhanced adenosine degradation should attenuate increases in the coronary blood flow produced by a decrease in the oxygen supply/demand ratio.

In the isolated heart preparation, adenosine elicits vasodilation at very low concentration (5.0 x 10^{-9} M). 27 The ED50 is 5.7 x 10^{-7} M in conscious dogs. 30 Therefore, adenosine may fulfill the first criterion.

Roles of Adenosine in Coronary Hyperemic Flow Due to Ischemia and Increased Myocardial Oxygen Demand

When myocardial oxygen demand is increased during exercise or cardiac pacing, adenosine release is increased as much as in conditions that restrict oxygen supply (ischemia and hypoxia) 31 (criterion 2). Correlations between amounts of released endogenous adenosine and the extent of the increase in blood flow have been observed in brain, 28 skeletal muscle, 29 and cardiac muscle 27 (criterion 3). Recently it was reported that adenosine in epicardial fluid is linked to changes in cytosolic metabolism (log [ATP]/[ADP][Pi]) when cardiac energy metabolism is enhanced by norepinephrine infusion in isolated perfused guinea pig hearts. 32 Aminophylline reduces vasodilation in the canine gracilis muscle during exercise. 33 The effects of adenosine deaminase on vasodilation are very similar to those of adenosine receptor antagonists (e.g., methylxanthines). Adenosine deaminase also reduced exercise-induced vasodilation in the cremaster muscle by 25-30%. 34 However, in the heart, 8-phenyltheophylline does not affect exercise-induced coronary vasodilation. 35 Furthermore, adenosine deaminase had no effects on coronary resistance in the unstressed heart, 36 and the extent of reactive hyperemic flow during exercise was not altered by adenosine deaminase in conscious dogs. 37 Thus, the results with adenosine and adenosine deaminase do not support the adenosine hypothesis as a mechanism of coronary flow regulation during exercise (criterion 4). The differences in the flow responses to methylxanthines and adenosine deaminase in the cardiac muscle and skeletal muscle may be due to differences in tissues, in species, or both.

Roles of adenosine in reactive hyperemia after myocardial ischemia seem substantial. In other studies on the isolated perfused guinea pig heart, administration of α, β-methylene adenosine 5'-diphosphate (AOPCP), which inhibits 5'-nucleotidase, attenuated the reactive hyperemic response after a brief period of ischemia associated with a corresponding reduction in myocardial epicardial fluid adenosine levels. 31 Postocclusion-induced hyperemia is potentiated by dipyridamole both in conscious dogs and in anes-
Role of Adenosine in Autoregulation of Coronary Blood Flow

When coronary perfusion pressure is altered in the range that does not cause ischemia, coronary blood flow is kept constant: "coronary autoregulation." When coronary perfusion pressure is reduced, adenosine is reported to increase to maintain coronary blood flow, suggesting the role of adenosine in coronary autoregulation. However, adenosine deaminase does not affect vascular resistance during graded reduction in perfusion pressure, indicating that adenosine does not play a role in autoregulation of coronary blood flow. Similar results were obtained by blocking the adenosine receptors with theophylline. In fact, since intra-arterially administered adenosine deaminase was detected in cardiac lymph, it is probable that infused adenosine deaminase is distributed in the interstitial space. Other observations suggest that the interstitial adenosine concentration may be too low to elicit vasodilation and that the concentration does not change during autoregulation. Therefore, it is likely that mechanisms other than those related to adenosine are involved in autoregulation.

Myogenic mechanisms have been proposed to explain autoregulation of blood flow. This mechanism, however, has not yet been proven, and the contribution of metabolic factors may be more important. Among possible metabolic mediators, oxygen and carbon dioxide are the most probable factors, although the combination of PO2 and PCO2 could explain only 40% of the total autoregulatory changes in coronary blood flow in dogs. Thus, at present, we do not know the mechanism for coronary autoregulation.

Adenosine and Coronary Vasodilation During Myocardial Ischemia

Adenosine Formation

The schematic diagram of adenosine metabolism is shown in Figure 1. Major pathways of adenosine formation are the dephosphorylation of 5'-AMP by adenylate kinase or 5'-nucleotidase (EC 3.1.3.5) and the hydrolysis of S-adenosylhomocysteine (SAH) by SAH-hydrolase (EC 3.3.1.1). During normoxia, a major source of adenosine is SAH formed from S-adenosylmethionine (SAM) through the transfer of the methyl group to a variety of methyl acceptors. SAH is hydrolyzed by SAH-hydrolase to adenosine and homocysteine. Adenosine that originates from either SAH or 5'-AMP is phosphorylated by adenosine kinase or deaminated by adenosine deaminase. The overall adenosine production rate is reported to be approximately 800 pmol/min/g in isolated perfused guinea pig heart, which is very close to the hydrolysis rate of SAH (750 pmol/min/g). This result suggests that during normoxia, most of the synthesized adenosine is derived from SAH. During ischemia or hypoxia, however, the major pathway of adenosine production is shifted to the 5'-AMP pathway.

In liver and polymorphonuclear leukocytes, a decrease in the adenylate energy charge (ATP+ADP)/(ATP+ADP+AMP) may trigger the activation of cytosolic 5'-nucleotidase and enhance adenosine production. It has been reported that 5'-nucleotidase is present as ecto-5'-nucleotidase bound to membranes and cytosolic 5'-nucleotidase in the cytoplasm, which has a higher Km for AMP than the cytoenzyme, and may be a primary source of adenosine derived from 5'-AMP. In recent years, however, the contribution of vascular endothelium to adenosine production has attracted much attention. Since extracellular adenine nucleotides derived from...
endothelium, adrenergic nerves, and erythrocytes can be a substrate of ecto-5'-nucleotidase, both cytosolic and membrane-bound 5'-nucleotidase may play an important role for adenosine production.

**Adenosine for Coronary Vasodilation in Ischemic Hearts**

Increased release of adenosine, inosine, and hypoxanthine has been demonstrated during hypoxia, ischemia, and early reperfusion. In perfused hearts there is a close relation between tissue adenosine, the rate of release of adenosine into the perfusate, and coronary blood flow during hypoxia. This evidence may support the hypothesis that adenosine plays a major role in coronary vasodilation in ischemic and hypoxic hearts. A primary role of adenosine has been supported by several lines of evidence. The adenosine receptor antagonist theophylline decreases coronary flow during hypoperfusion in isolated, perfused, and in situ hearts. Also, a significant attenuation of increase in coronary flow during systemic hypoxia has been observed after intracoronary administration of adenosine deaminase.

However, there is evidence against the adenosine hypothesis in myocardial ischemia. The absence of reduction in myocardial blood flow by adenosine deaminase administered distal to a coronary stenosis also indicates that adenosine contributes only modestly to maintenance of arteriolar vasodilation in hypoperfused hearts. Failure to resolve this controversy may be due to the fact that adenosine deaminase has not been clearly demonstrated to destroy all of the adenosine in the interstitial space. In addition, factors other than adenosine may be involved in flow changes during ischemia and hypoxia. Thus, another pharmacological "tool" that antagonizes or enhances the endogenous adenosine release is necessary for further testing of the adenosine hypothesis.

Recently, it was reported from our laboratory that the \(\alpha\)-adrenergic receptor antagonist, prazosin, markedly attenuated the release of adenosine from ischemic myocardium either during hypoperfusion or after coronary microembolization; administration of a low dose of prazosin, which did not affect basal coronary blood flow, reduced coronary blood flow and further exaggerated the ischemic damage (i.e., an increase in lactate production and a decrease in regional fractional shortening). Because the contribution of \(\alpha\)-adrenergic activity to the release of adenine nucleotides is also reported to occur from endothelial cells, it is likely that activation of protein kinase C by \(\alpha\)-adrenergic stimulation is involved in the production of adenosine in hypoxic myocardial cells. Protein kinase C may affect the enzymes responsible for adenosine production and degradation, or production of AMP. It should be noted that enhanced release of adenosine by \(\alpha\)-adrenergic stimulation is only observed during ischemia (Figure 2). Thus, the underlying mechanism for this phenomenon may be different from that of adenosine release when \(\beta\)-adrenergic receptors are stimulated. What-ever the mechanisms, this may be another tool to test the role of adenosine in the regulation of coronary blood flow during ischemia.

We have recently found that in contrast to \(\alpha\)-adrenergic activity, \(\alpha\)-adrenergic activity modifies the vasodilatory action of adenosine (Figure 2); a low dose of the \(\alpha\)-adrenergic receptor agonist, clonidine, enhances adenosine-induced coronary vasodilation and low doses of yohimbine and rauwolscine attenuate the coronary flow response to either endogenous or exogenous adenosine. This is consistent with the earlier study by Nayler et al. They observed that phenoxybenzamine blocked the vasodilator action of adenosine in isolated rat and guinea pig hearts. Furthermore, attenuation of ischemia-induced myocardial damage by administration of clonidine in coronary hypoperfusion and in coronary microembolization, strongly suggests that adenosine plays an important role by dilation of the coronary arterial bed; clonidine significantly increased coronary blood flow in both ischemic models without augmentation of adenosine release. These and previous results are summarized in Figure 3. During ischemia, coronary blood flow is regulated by metabolic and neural mechanisms (i.e., adenosine-induced coronary vasodilation and \(\alpha\)-adrenergic receptor-mediated vasoconstriction). Our findings introduce the new concept that the \(\alpha\)-adrenergic receptor stimulation increases both adenosine release and coronary vascular sensitivity to adenosine during ischemia. In summary, we conclude that adenosine released from ischemic myocardium exerts coronary vasodilation and reduces the ischemic changes, although we need to consider the possibility that the coronary vasodilation might result from a combination of adenosine and other factors.
ATP and AMP may be other substances that contribute to vasodilation in ischemic hearts since these adenine nucleotides are quickly converted to adenosine. Also, both ATP and AMP are concomitantly released with adenosine from ischemic myocardium. Recently, ATP-sensitive K+ channels were reported to play a crucial role in coronary vasodilation during hypoxia in isolated guinea pig hearts; an ATP-sensitive K+ channel blocker inhibited the vasodilation produced by hypoxia. Their findings suggest that the trigger for vasodilation may be a decrease in the intracellular ATP concentration that could augment the outward current through ATP-sensitive K+ channels and cause hyperpolarization. It is also of interest that ATP is potent enough to release myocardial prostaglandins, of which PGI2 is a very potent coronary vasodilator. Kallikrein, histamine, and K+ are other factors that are certainly worth considering as local regulators of coronary blood flow during ischemia, although there is at present little supporting evidence.

Adenosine and Reperfusion Injury

Adenosine may also attenuate myocardial cellular injury after reperfusion in various species of animals, intracoronary infusion of adenosine results in a 75% reduction in myocardial infarct size in dogs and attenuates contractile dysfunction in rats. This beneficial effect may be attributed to one or more of the following mechanisms: 1) preservation of ATP, 2) inhibition of neutrophil activation, 3) inhibition of platelet aggregation, and 4) an increase in coronary blood flow.

Although adenosine is known as a precursor of ATP synthesis, there is no clear evidence that exogenously administered adenosine is incorporated into ATP during early reperfusion. An increase in ATP in the postischemic myocardium is reported only when exogenous adenosine is administered in the crystalloid perfused isolated hearts. Exogenous adenosine did not restore the decreased ATP pools in the blood perfused hearts probably because adenosine is rapidly deaminated by adenosine deaminase. However, when adenosine is administered throughout ischemic and reperfusion periods, a 90-fold increase of ATP synthesis was obtained in the reperfused myocardium. It is known that 1) adenosine stimulates glycolysis in rat hearts, 2) intracoronary infusion of adenosine increases glucose uptake, and 3) dipyridamole enhances glucose uptake accompanied by an increase in myocardial ATP in the newborn lamb. Thus, enhanced glucose metabolism by adenosine may contribute in part to a decrease in the rate of ATP depletion during ischemia. Another possibility is an inhibitory action of adenosine on adrenergic stimulation. Adenosine is reported to attenuate the β-adrenergic receptor-mediated inotropism through A1 receptor-mediated action. Thus, ATP consumption during ischemia and reperfusion may be attenuated. Catecholamine release from the presynaptic vesicles in ischemic and reperfused hearts is also prevented by adenosine through A2 receptor-mediated action. These mechanisms may inhibit adrenergic stimulation during ischemia and thereby preserve ATP. A 90% decrease in ATP coincidentally develops the irreversible deterioration of the myocardium, leading to the idea that depletion of ATP content in reperfused myocardium may be a critical factor for the process of irreversible injury.

It also has been reported that adenosine attenuates contractile dysfunction after a brief period of ischemia (i.e., myocardial stunning). The beneficial effect of adenosine is supported by our recent observation that administration of methoxamine attenuated myocardial stunning associated with enhanced release of adenosine and that treatment with theophylline completely abolished this beneficial effect of methoxamine. The protective effects of adenosine on myocardial stunning, however, may not be attributed to the preservation of ATP. A decrease in ATP seems to be a concomitant phenomenon in myocardial stunning because the replenishment of ATP does not necessarily restore contractile function. However, since it is argued that ATP compartmentation may mask the role of ATP depletion for the cause of myocardial dysfunction, it is still unclear whether the beneficial effect of adenosine in myocardial stunning is due to preservation of ATP. On the other hand, recent evidence strongly suggests that calcium overload is responsible for myocardial stunning and that adenosine may attenuate myocardial stunning by inhibiting calcium influx through stimulation of A1-receptors.

Adenosine also attenuates the activation of neutrophils: Free radical generation is inhibited through A1-receptor stimulation, and adherence to endothelial cells is attenuated through A1-receptor stimulation. Adenosine specifically inhibits superoxide anion generation by N-formylmethionyl-leucyl-phenyl-alanine-stimulated neutrophils without affecting either degradation or aggregation; these effects were mimicked by NECA, an adenosine A1 receptor agonist. It is reported that adenosine inhib-
its the stimulation of reactive oxygen metabolite production by a chemotactic peptide but not by latex beads. Since the response of neutrophils to a chemotactic peptide is mediated by an increase in intracellular free Ca$^{2+}$ concentrations, adenosine appears to antagonize the Ca$^{2+}$-mediated response of the neutrophil. It is of interest that both endothelial cells and neutrophils normally produce and release adenosine, which in turn inhibits neutrophil-mediated endothelial cell injury. This feedback system via adenosine may play an important role for self defense mechanisms from reperfusion injury.

Platelet aggregation may cause reperfusion injury since aggregated platelets impede the microcirculation of the coronary vessels. It is known that adenosine also inhibits platelet aggregation through $\alpha_2$-receptor stimulation, and that endogenous adenosine released from the ischemic myocardium inhibits platelet aggregation in the blood-perfused canine heart. When platelet aggregation occurs during ischemia and reperfusion periods, ADP, serotonin, and several prostaglandins are released to provoke vasoconstriction, which may further damage the myocardium. Thus, inhibition of platelet aggregation by endogenous adenosine released from ischemic myocardium may attenuate reperfusion injury. Since adenosine is a potent vasodilator, massive release of adenosine during ischemia and reperfusion may attenuate microcirculatory disturbances. Thus, improvement of the coronary microcirculation by adenosine may largely contribute to prevention of reperfusion injury.

**Clinical Implication**

As previously discussed, adenosine may be beneficial for attenuating ischemic and reperfusion injury of the heart. However, the role of adenosine is not yet fully tested in human hearts. There are several lines of evidence that indicate that endogenous adenosine accumulates during myocardial ischemia in a sufficient concentration to account for the slowing of the heart rate and the appearance of atrioventricular block. A local release of adenosine in patients with acute myocardial infarction may also play a key role in ischemia-induced sinus bradycardia. reperfusion-induced bradycardia is attenuated by aminophylline and potentiated by the nucleoside transport blocker dipyridamole in the isolated blood-perfused dog atria, indicating that endogenous adenosine could cause bradycardia during reperfusion. Atrioventricular prolongation during acute inferior myocardial infarction could be attributed to released adenosine since both adenosine dename and theophylline blunt hypoxia-induced atrioventricular prolongation by 61%. ATP is also used as a provocative test for sick sinus syndrome. This action of ATP is attributed to adenosine generated from ATP hydrolysis. In humans, intravenous administration of adenosine is used for the diagnosis of atrioventricular block and for the treatment of paroxysmal supraventricular tachycardia.

Intravenous administration of adenosine in humans dilates resistance vessels at doses of 30–200 $\mu$g/kg/min in a dose-dependent manner. However, the blood pressure is essentially unaffected because cardiac output is also increased, probably due to sympathetic reflex. Coronary blood flow is increased at infusion rate of 30–50 $\mu$g/kg/min, whereas cerebral blood flow and splanchnic flow are increased at higher doses of adenosine. It is known that exogenously administered adenosine also causes chest pain or chest discomfort that is attenuated by theophylline. This effect of adenosine is considered to be due to afferent reflex activation. Adenosine also activates the chemoreceptors in the carotid sinus, which stimulates respiration. Therefore, administration of a relatively high dose of adenosine may provoke anginalike pain and stimulate respiration, although these side effects of adenosine are only transient.

The release of adenosine in patients with ischemic heart disease has not been extensively studied. Several investigators have demonstrated the release of xanthine from the hearts of patients during pacing-induced angina. However, adenosine release was detected in the coronary sinus blood during angina only when the cellular uptake and degradation of adenosine was blocked by dipyridamole. We observed the release of adenosine into the great cardiac vein during rapid pacing in patients with severe narrowing of the left anterior descending coronary artery. These results indicate that adenosine is released during myocardial ischemia in humans. A big question is whether endogenous adenosine released during myocardial ischemia is sufficient to produce maximal coronary vasodilation and prevention of reperfusion injury. If the endogenous adenosine is not sufficient, exogenous administration of adenosine may be beneficial to the ischemic heart.

Recent observations that superoxide dismutase enhances the release of adenosine in the ischemic heart may also provide a new aspect of the role of adenosine. An adenosine potentiator (e.g., AICA riboside [5-amino-4-imidazole carboxamide-riboside]) is now under investigation for clinical use, since this agent can augment the adenosine release at the site of ischemia.

In summary, we can argue that adenosine plays a critically important role in the pathogenesis of ischemic heart disease. However, further studies are needed for a better understanding of the physiology and pathophysiology of the regulation of coronary blood flow and myocardial ischemia in human hearts.

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