CELLULAR AND MOLECULAR MECHANISM(S) OF CORONARY FLOW REGULATION BY ADENOSINE

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Summary

There is strong evidence in favor of a major role for adenosine in the metabolic regulation of blood flow to the heart. The exact nature of the molecular and cellular events leading to the vasodilatation by adenosine are poorly understood. In the present report we have provided experimental evidence that: (i) hypoxia of cardiac cells resulted in the production of adenosine (and its degradative products) which can be responsible for the hypoxic dilation observed by several workers; (ii) the release of metabolites such as potassium and inorganic phosphate was unchanged due to a 30-minute hypoxia of cardiac cells; (iii) the release of prostaglandin E but not F was enhanced due to hypoxia of cardiac cells which may be due to the storage pools in the cells; (iv) prostaglandin E_2, E_3 and F_2α inhibited the uptake of adenosine at pharmacological concentrations but not at physiological concentrations; (v) prostaglandin synthetase inhibitors (aspirin and indomethacin) nonspecifically inhibited the uptake of adenosine in the cardiac cells; (vi) lowering of pH resulted in inhibition in the uptake of adenosine and its incorporation into adenine nucleotides in cardiac cells; (vii) lowering the pH of the perfusion medium resulted in the increased release of perfusate adenosine (and its degradative products) with a simultaneous increase in coronary blood flow; (ix) specific adenosine receptor sites were found in cardiac muscle, coronary arteries, and carotid arteries of the dog and rabbit aorta, which satisfy the basic characteristic of receptor binding; and (x) these receptor binding sites were different from the adenosine uptake protein and were competitively blocked by theophylline or aminophylline. It is concluded that adenosine plays a major role in blood flow regulation to the heart and acts through specific receptors to produce vasodilatation.

Introduction

The vasoactivity of adenosine has been known for a long time, but it was not until in 1963 that Berne described its physiological effects in the regulation of coronary blood flow. Several extensive reviews (including a symposium) on the role of adenosine in the heart and other mammalian tissues have recently appeared. Thus, the present report will mainly focus on the recent experimental observations made by the author.

According to the adenosine hypothesis for the regulation of coronary blood flow, a reduction in myocardial oxygen tension produced by low coronary flow, hypoxemia or increased metabolic activity of the heart leads to the breakdown of adenine nucleotides to adenosine by membrane bound 5'-nucleotidase. The adenosine, thus formed, diffuses out of cardiac cells and induces dilation of coronary resistance vessels. This dilation results in an increase in coronary blood flow, which in turn enhances the
washout of adenosine, and reduces its formation by raising myocardial oxygen tension towards normal levels until a new steady state is reached.

If adenosine plays a role as one of the mediators of metabolically induced coronary vasodilation, it should be present in the well-oxygenated heart and be released in a graded manner by myocardial cells at a rate proportional to the magnitude of the negative oxygen balance. Measurements of the adenosine concentration of pericardial fluid of the normal well-oxygenated dog heart revealed its presence. These concentrations were increased several fold following coronary occlusion or hypoxemia. Adenosine has also been detected in the coronary sinus blood of patients with coronary artery disease during cardiac pacing. All of these studies suggest that adenosine is involved in the regulation of coronary blood flow.

Most of the studies in support of the adenosine hypothesis have been derived from the experiments of myocardial ischemia, hypoxia or anoxia or under conditions in which oxygen delivery was decreased. Recently, several workers demonstrated an increase in the formation of adenosine by the myocardium in situ during conditions of increased oxygen demand (acute elevation of aortic resistance, stellate ganglion stimulation or isoproterenol infusion). Also, fluid introduced into the pericardial sac of the open chest dog, on analysis, showed a significant increase in adenosine levels during stellate ganglion stimulation and simulated exercise produced by repetitive electrical stimulation of the motor nerves to limb muscles. Wiedmeier and Spell did parallel experiments using catecholamines and histamine in isolated perfused guinea pig hearts and measured the release of adenosine (and degradative products) into the perfusates together with coronary flow and coronary sinus pO₂. Increases in oxygen demand (or consumption) due to catecholamine and histamine administration resulted in an increased production of adenosine and its degradative products with a simultaneous increase in coronary blood flow. Thus, adenosine production by the heart in vivo appears to be responsive to the level of cardiac activity and to increases in oxygen demand. These findings suggest that adenosine is a regulator of metabolic vasodilation not only during hypoxia or ischemia, but also under more physiological conditions such as increased oxygen demand.

Metabolites other than adenosine (such as potassium ion, osmolality, inorganic phosphate) may account for the initial changes (transient) in coronary vascular resistance, however, the sustained increase in flow accompanying a prolonged increase in metabolic activity of the heart is better explained by adenosine, whose concentration remains elevated and to which the vessels fail to show any tachyphylaxis.

In regard to the mechanism(s) of action of adenosine after it is formed and released from the cardiac cells into the interstitial fluid and its interaction action with vascular smooth muscle, several possibilities exist (either alone or in combination). One is that adenosine increases the concentration of cyclic AMP in vascular smooth muscle as has been shown to be the case in brain tissue. It has also been shown that the relaxation of vascular smooth muscle is associated with an increase in cyclic AMP levels. However, recently, Herlihy et al. using hog carotid artery strips showed that only at high concentrations of adenosine (10⁻³ M) was the level of cyclic AMP increased significantly. Similar negative results were found by Verhaeghe in dog saphenous vein with 10⁻⁴ M adenosine and by McKenzie et al. in rabbit colon muscle (longitudinal) at 1 μM adenosine. These findings tend to rule out the involvement of cyclic AMP at physiological concentrations. However, Kukovez et al. have reported increases in cAMP due to adenosine at concentrations greater than 10⁻⁵ M in relaxing cattle coronary strip preparations. Thus, the involvement of cyclic AMP in the vasodilatory action of adenosine is doubtful and requires further investigation.

A second mechanism that may be involved in the relaxing effects of adenosine on vascular smooth muscle is by blockade of calcium uptake and/or alterations of the membrane potential. Schrader et al. using a superfused guinea-pig atrium in which the fast sodium channels were blocked by tetrodotoxin or partial depolarization with K⁺ ion found that adenosine (1 × 10⁻⁶ M) blocked the calcium current (produced by electrical stimulation in the presence of norepinephrine). This current was restored on