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Is the sarcolemmal or mitochondrial K_{ATP} channel activation important in the antiarrhythmic and cardioprotective effects during acute ischemia/reperfusion in the intact anesthetized rabbit model?

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Abstract

The relative contributions of cardiomyocyte sarcolemmal ATP-sensitive K^+ (K_{ATP}) and mitochondrial K_{ATP} channels in the cardioprotection and antiarrhythmic activity induced by K_{ATP} channel openers remain obscure, though the mitochondrial K_{ATP} channels have been proposed to be involved as a subcellular mediator in cardioprotection afforded by ischemic preconditioning. In the present study, we sought to investigate the effects of administration of ATP-sensitive K^+ channel (K_{ATP}) openers (nicorandil and minoxidil), a specific mitochondrial K_{ATP} channel blocker (5-hydroxydecanoate (5-HD)) and a specific sarcolemmal K_{ATP} channel blocker (HMR 1883; (1-[5-[2-(5-chloro-*o*-anisamido)ethyl]-2-methoxyphenyl]sulfonyl-3-methylthiourea) prior to coronary occlusion as well as prior to post-ischemic reperfusion on survival rate, ischemia-induced and reperfusion-induced arrhythmias and myocardial infarct size in anesthetized albino rabbits. The thorax was opened in the left 4th intercostal space and after pericardiotomy the heart was exposed. In Group I ($n=88$), occlusion of the left main coronary artery and hence, myocardial ischemia-induced arrhythmias was achieved by tightening a previously placed loose silk ligature for 30 min. In Group II ($n=206$), arrhythmias were induced by reperfusion following a 20-min ligation of the left main coronary artery. Both in Group I and Group II, intravenous (i.v.) administration of nicorandil (0.47 mg/kg), minoxidil (0.5 mg/kg), HMR 1883 (3 mg/kg)/nicorandil and HMR 1883 (3 mg/kg)/minoxidil before coronary artery occlusion increased survival rate (86%, 75%, 75% and 86% vs. 55% in the control subgroup in Group I; 75%, 67%, 67% and 75% vs. 46% in the

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control subgroup in Group II), significantly decreased the incidence and severity of life-threatening arrhythmias. In Group II, i.v. administration of nicorandil and minoxidil before coronary artery occlusion significantly decreased myocardial infarct size. However, i.v. administration of nicorandil or minoxidil before reperfusion did neither increase survival rate nor confer any antiarrhythmic or cardioprotective effects. The antiarrhythmic and cardioprotective effects of both nicorandil and minoxidil were abolished by pretreating the rabbits with 5-HD (5 mg/kg, i.v. bolus), a selective mitochondrial K_{ATP} channel blocker but not by HMR 1883 (3 mg/kg). In the present study, higher levels of malondialdehyde (MDA) and lower levels of reduced glutathione (GSH) and superoxide dismutase (SOD) in necrotic zone of myocardium in all the 16 subgroups in Group II suggest little anti-free radical property of nicorandil and minoxidil. We conclude that intervention by intravenous administration of nicorandil and minoxidil (through the selective activation of mitochondrial K_{ATP} channels) increased survival rate and exhibited antiarrhythmic and cardioprotective effects during coronary occlusion and reperfusion in anesthetized rabbits when administered prior to coronary occlusion. The cardiomyocyte mitochondrial K_{ATP} channel may be a pharmacologically modulable target of cardioprotection and antiarrhythmic activity.
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Introduction

The major objectives of therapeutic intervention during myocardial infarction are prevention of lethal ventricular arrhythmias and preservation of myocardial tissue from irreversible damage. The former is a major problem during the acute phase of myocardial infarction, the latter is of vital importance when the patient has survived the first hours after infarction (Lepran et al., 1996). Reperfusion of the myocardium can lead to ventricular arrhythmias including ventricular fibrillation (VF), ventricular tachycardia (VT) and ventricular premature beats (VPB) in both experimental animals and humans (Picard et al., 1998; Maxwell and Lip, 1997).

ATP-sensitive potassium (K_{ATP}) channels exist in high density in the sarcolemmal membrane as well as the mitochondrial membrane of cardiomyocytes. The K_{ATP} channel is a weakly inward-rectifying K^+ channel that is inhibited by intracellular ATP and activated by intracellular nucleoside diphosphates. Both sarcolemmal and the more nebulous mitochondrial K_{ATP} channels in the cardiovascular system might have a physiological role in modulating cardiac function, particularly under conditions of metabolic stress, such as hypoxia, ischemia, and metabolic inhibition when intracellular ATP stores are reduced. Under normoxic conditions, the K_{ATP} channel exists mainly in a closed, inactive form. However during myocardial ischemia, as the intracellular ATP concentration falls and ischemic metabolites (ADP, lactate, H^+) accumulate, the probability of the channel being open increases. This results in an enhanced outward repolarizing flow of K^+ and cell membrane hyperpolarization. Consequently, the myocardial action potential duration (APD) is shortened, the voltage-dependent calcium current and myocardial contractility are decreased thereby leading to ATP preservation during ischemia. Thus, it is thought that K_{ATP} channels exert a protective property in myocardial ischemic diseases (Fujita and Kurachi, 2000). Recent studies hint that mitochondrial K_{ATP} channel opening rather than sarcolemmal (surface) K_{ATP} channel opening may play a dominant role in affording cardioprotection in ischemic hearts due to its energy-modulating property (Liu et al., 1998; Garlid et

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