909 Potassium Channels and Coronary Vascular Tone

Wednesday, April 1, 1998, 4:00 p.m.–5:00 p.m.
Georgia World Congress Center, Room 256W

4:00

909-1 Altered ATP-dependent Potassium Channel Activity in the Coronary Microvasculature in Experimental Hypercholesterolemia

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Background: ATP-dependent potassium (K ATP) channels contribute to the regulation of coronary vascular tone. Experimental hypercholesterolemia (HC) is characterized by altered coronary vascular reactivity. This study was designed to test the hypothesis that experimental HC is characterized by altered activity of coronary K ATP channels.

Methods: Pinacidil, a selective K ATP channel opener at 2 μg/kg/min (group 1, n = 5) or glibenclamide, a K ATP channel inhibitor at 50 μg/kg/min (group 2, n = 5) was selectively infused into the left anterior descending artery of pigs prior to and following 10 weeks of high cholesterol diet.

Results: Coronary artery diameter (CAD) was measured utilizing quantitative coronary angiography, and coronary blood flow (CBF) was calculated utilizing intracoronary Doppler; values were expressed as percent change from the baseline.

	Pinacidil		Glibenclamide	
	normal	high chol	normal	high chol
%ΔCBF	59 ± 12	111 ± 10*	5 ± 6	−17 ± 5*

*p < 0.05 vs normal

There was no significant effect on CAD. This study demonstrates an enhanced coronary effect of pinacidil and glibenclamide in HC primarily at the level of the microcirculation.

Conclusions: These findings suggest an alteration of K ATP channel activity in experimental HC and underscores the importance of K ATP in regulation of coronary vascular tone in pathophysiologic states.

4:15

909-2 Endothelial Dysfunction Associated With Insulin Resistance Is due to Impaired Hyperpolarization via Potassium Conductance

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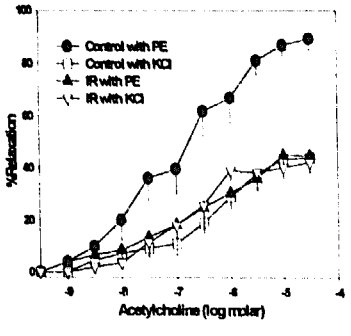
Background: We have shown that insulin resistance (IR) is associated with endothelial dysfunction, but it is not due to a defect in nitric oxide or prostacyclin. Hence, we propose that IR induced endothelial dysfunction is due to a defect in endothelial dependent hyperpolarizing factor (EDHF).

Methods: Sprague Dawley rats were randomized into two groups: (1) control (C) (n = 15) or (2) IR (n = 16). IR was induced by fructose rich diet. Intraluminal diameter was measured (in vitro) in mesenteric arteries (≈225 μM). Vessels were constricted to ≈40% of resting diameter with either KCl (inhibits EDHF) or phenylephrine (PE), and endothelial mediated relaxation to acetylcholine (Ach) was determined.

Results: Dose response curves (figure) show that KCl constriction decreased relaxation to Ach in C compared to PE constriction (maximal relaxation (Emax): 43 ± 5% vs. 89 ± 5%, p < 0.01). Conversely, KCl constriction in IR did not affect Ach relaxation compared to PE (Emax: 41 ± 4% vs. 44 ± 4%).



Conclusions: These data show that endothelial mediated relaxation in C is dependent on hyperpolarization through K+ channels while IR vessels have lost this mechanism. Thus, impaired endothelial function in IR vessels is likely due to a defect in EDHF.

4:30

909-3 Dietary Potassium Depletion Enhances Vasoconstriction and Attenuates Endothelium-dependent Vasorelaxation in Rabbits

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High potassium (K^+) intake reduces blood pressure in populations at high risk for hypertension and protects myocardium from injury. We examined the basis of vaso-protective effect of dietary on cardiovascular function. New Zealand white rabbits were fed diet containing normal amount of K^+ or low K^+ diet for 7 days (n = 7, each group). Carotid arteries and hearts were excised. The contractile and relaxant responses of carotid artery to norepinephrine (NE) and endothelium-dependent relaxants (acetylcholine and calcium ionophore A23187) were examined. Isolated hearts were subjected to global ischemia (40 min) and reperfusion (30 min) in a Langendorff set-up. Dietary K^+ depletion reduced plasma K^+ levels to 3.3 ± 0.7 vs. 5.1 ± 1.mEq/L in control animals and urinary K^+ to 24.9 ± 10.2 vs. 142 ± 67 mEq/L (both $P < 0.05$). This was associated with an enhanced contraction of carotid arterial rings in response to NE and attenuated relaxation in response to both acetylcholine and calcium ionophore A23,187 (both $P < 0.01$ compared to responses in rabbits fed control diet). Ischemia-reperfusion in isolated hearts resulted in similar increase in coronary perfusion pressure and left ventricular end-diastolic pressure, and similar decrease in developed left ventricular pressure in hearts from both control and low K^+ diet-fed rabbits (P = NS). However, hearts from low K^+ diet-fed rabbits revealed high frequency of ventricular arrhythmias (38% vs 14% in control group, $P < 0.05$). These observations indicate that low K+ diet enhances the sensitivity of arteries to NE (leftward shift in dose-response curve) and decreases response to endothelium-dependent relaxants (rightward shift in dose-reponse curve). These observations may explain blood pressure lowering and cardioprotective effects of dietary K^+ supplementation.

4:45

909-4 Potassium Currents in Pericytes From Bovine Heart

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Background: The role of pericytes in the coronary microcirculation is still ill-defined. Recent histological and ultrastructural studies revealed the presence of pericytes at the transition from coronary arterioles to myocardial capillaries. These cells could influence coronary blood flow by generating electrical signals - e.g. as a response to vasoactive substances - that could propagate along the wall of microvessels.

Methods: We studied transmembrane currents of coronary pericytes with the patch-clamp technique in the whole-cell configuration at room temperature.

Results: The membrane potential was −44.3 ± 5.7 mV (mean ± S.D., n = 36) in solution containing 5 mM K^+ and −18.3 ± 2.1 mV (mean ± S.D., n = 23) in solution containing 60 mM K^+. The membrane capacitance was 155 ± 136 pF (mean ± S.D., n = 27). All cells showed potassium outward currents that were activated at around −50 mV. These currents could be nearly completely blocked with either 4-Aminopyridine (n = 10) or TEA (n = 8). As a response to depolarizing voltage steps currents rose in a sigmoid manner. Blockade of the outward currents led to a pronounced depolarization of the cells. Most likely outward currents are mediated by the opening of delayed rectifier type potassium channels. In addition 21 of 37 cells showed inward currents with the properties known for currents mediated by the opening of inward rectifier K^+ channels.

Summary: Regulation of the two types of potassium currents described determines the membrane potential of coronary pericytes and may therefore influence coronary blood flow.