HYPERGLYCEMIA SELECTIVELY INCREASES THE EXPRESSION OF CYCLOXYGENASE-2 IN HUMAN AORTIC ENDOTHELIAL CELLS

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The conversion of arachidonic acid to vasoactive prostanoids including prostacyclin, prostaglandins and thromboxanes is mediated by cycloxygenase (COX). Two isoforms of enzyme have been shown: a constitutive (COX-1) and an inducible form (COX-2). Products of the arachidonic acid metabolism may be involved in the impairment of endothelium-dependent vasodilatation observed both in experimental models and in patients with diabetes mellitus. To determine the effect of hyperglycemia on COX-1 and COX-2 expression, human aortic endothelial cells (HAEC) were exposed to normal (5.5mM) and high (22.2mM) concentrations of glucose for 5 days. Cells were also treated with mannitol (22.2 mM) to rule out an effect due to osmolality changes. COX-1 and COX-2 mRNA and protein expressions were analyzed by Southern and Western blotting, respectively. Treatment with high glucose was associated with a two-fold increase of both COX-2 mRNA ($P<0.05$) and protein levels ($P<0.05$), whereas no changes were observed for COX-1. Moreover high concentration of mannitol did not exert any significant effect. The present study demonstrates that both isoforms of COX are normally expressed in HAEC, but only COX-2 was stimulated after exposure to high glucose. The results of the present study may provide molecular basis to understand hyperglycemia-induced endothelial dysfunction.

Key Words: Hyperglycemia; human endothelial cells; COX-1 and COX-2

ENDOTHELIUM DEPENDENT AND INDEPENDENT VASODILATION IN SALT-SENSITIVE AND SALT-RESISTANT ESSENTIAL HYPERTENSION

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The aim of the study was to evaluate endothelial function in essential hypertensives (EH) classified according to the presence of salt-sensitivity (SS) or salt-resistance (SR). Thirty-seven never treated EH patients without evidence of target organ damage were studied. Salt-sensitive hypertension was defined as a significant rise ($p<0.05$) in 24-hour mean BP, measured by means of ABPM, from a 7-day period of low-salt intake (50 mmol/day) to a 7-day period of high-salt intake (250 mmol/day). At the end of the high-salt period, endothelial function was determined by means of the forearm vascular response (by strain-gauge plethysmography) to intrabrachial infusion of increasing doses of acetylcholine, an endothelium-dependent vasodilator, or sodium nitroprusside, an endothelium-independent vasodilator, with and without the presence of the NO synthase inhibitor L-NMMA. When compared to SR hypertensives ($n=16$), SS patients ($n=21$) exhibited a significant decreased endothelium-dependent vasodilation. The maximal acetylcholine induced vasodilation was (mean±sem) 358±36% in SS hypertensives and 518±39% in SR patients ($p=0.005$). The addition of L-NMMA significantly reduced acetylcholine induced vasodilation in SR patients (from 518% to 318%), but not in SS patients (from 358% to 292%). The endothelium-independent vasodilation did not differ between groups (maximal response to sodium nitroprusside infusion: 411±32% in SS vs. 378±30 in SR; $p=0.464$), and it was unmodified with the addition of L-NMMA. In conclusion, salt sensitivity of essential hypertension is associated with a decrease in acetylcholine-induced vasodilation, indicating an impairment in endothelial L-arginine NO pathway.

Key Words: Endothelium; nitric oxide; dietary salt; salt sensitivity

IN PRIMARY ALDOSTERONISM HYPERTENSIVE PATIENTS ENDOTHELIAL DYSFUNCTION IS CAUSED BY AN IMPAIRMENT IN NO AVAILABILITY

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Hypertensive patients with primary aldosteronism (PA) are characterized by an impaired endothelium(END)-dependent vasodilation (VD). Aim of the study was to evaluate whether this alteration is secondary to high blood pressure levels and caused by a defect in the L-arginine-NO pathway. In $n=10$ normotensive subjects (N, 49.5±16.8 years; 121.4±3.6/80.4±3.1 mmHg) and $n=7$ PA (51.4±6.5 years; 166.8±13/108.4±8.6 mmHg; plasma potassium (K pl) 2.9±0.3) we studied the forearm blood flow changes (FBF: strain-gauge venous plethysmography) induced by intra-arterial acetylcholine (ACH: 0.15, 0.45, 1.5, 4.5, 15 μg/100 ml/min), an END-dependent agonist, or sodium nitroprusside (SNP, 1, 2, 4 μg/100 ml/min), an END-independent vasodilator. ACH was repeated during L-NMMA (100 μg/100 ml/min), an NO-synthase inhibitor. VD to ACH was significantly (*$p<0.05$) reduced in PA (FBF % increase above baseline: 13±15, 34±20, 98±34, 198±44*, 319±47*) as compared to N (FBF %: 25±1, 58±5, 155.6±32, 369±48, 547±53), while response to SNP was similar in the two groups (FBF %: PA: 88±20, 199±32, 323±58; N: 109±14, 219±38, 361±77, N.S.). L-NMMA blunted (*$p<0.05$) VD to ACH in N (FBF%: 9±10, 38±18, 96±27*, 154±34*, 237±45*), while was ineffective in PA (FBF %: 5±15, 35±19, 114±33, 201±45, 310±47). In PA the study was repeated within 3 months after surgical removal of adrenal adenoma, when blood pressure (119.8±4.4/83.1±3.4 mmHg) and K pl (3.9±0.4) were normalized. VD to ACH significantly (*$p<0.01$) increased (FBF % 19±17, 55±25, 148±39, 327±41*, 491±35*) and was no longer different from N. L-NMMA significantly (*$p<0.05$) blunted VD to ACH (FBF %: 16±12, 24±9, 72±18*, 131±38*, 244±58*). VD to SNP was unchanged (FBF%: 87±17, 190±39, 349±56). In conclusions these data shown that endothelial dysfunction in PA is caused by an impairment of NO availability, an alteration which can be reversed by removal of adrenal adenoma and BP normalization.

Key Words: Endothelium; nitric oxide; primary aldosteronism