ABSTRACT

Part I. The aldosterone synthase gene (CYP11B2) polymorphism T-344C in blood pressure and left ventricular hypertrophy.

BACKGROUND: Aldosterone is a key cardovascular hormone, it significantly influences volume, pressure and electrolyte balance. Aldosterone plays an important role in development of left ventricular (LV) hypertrophy and myocardial fibrosis. The aldosterone synthase gene (CYP11B2) is an important candidate gene region in essential hypertension.

DESIGN AND METHODS: We assessed the influence of the T-344C polymorphism of aldosterone synthase - the rate-limiting enzyme in aldosterone biosynthesis - on the structure of the left ventricle in young normotensive men. The population included 113 normotensive mid-European Caucasian men aged 18-40 years (mean 27 +/- 5 years).

We also studied the association of -344T/C polymorphism of the CYP11B2 gene with the presence and severity of hypertension in 369 individuals, of whom 213 were hypertensive patients (139 controlled hypertensive, 74 resistant hypertensive) and 156 were healthy normotensive subjects.

The genotype was assessed using polymerase chain reaction with subsequent cleavage with restriction enzyme HAEIII (restriction fragment length polymorphism method) and visualization with ethidium bromide. Plasma renin activity (PRA) and plasma aldosterone were measured by conventional RIA using Immunotech kits. LV mass was assessed by echocardiography by using M-mode based ASE formula.

RESULTS: In the population of normotensive young men the distribution of the genotypes was TT 23%:TC 55%:CC 22%. There were no differences in blood pressure among the groups. Men with the TT genotype had significantly higher levels of PRA (2.7 +/- 1.7 vs 1.8 +/- 1.0 vs 1.8 +/- 1.1 ng/ml/h, $p < 0.01$) and slightly higher plasma levels of aldosterone (113 +/- 64 vs 93 +/- 43 vs 87 +/- 39 pg/ml, $p = 0,12$). In the whole population, LV mass index (LVMI) did not differ significantly among the genotypes (92 +/- 16 vs 86 +/- 18 vs 84 +/- 16 g/m, $p=0.20$). In the population divided according to PRA, subjects with high renin had significantly higher LVMI in presence of the TT genotype (95 +/- 17 vs 84 +/- 16 vs 81 +/- 15 g/m_2, $p < 0.05$).

The distribution of genotypes in normotensive controls and hypertensive subjects were: TT 25.6 vs. 31.9 %, TC 51.9 vs. 57.3 % and CC 22.4 vs. 10.8 %. The -344T/C variant was associated with hypertension. Subjects carrying the -344T allele had a greater risk of hypertension compared to those having C allele ($chi(2)=5.89$, $p<0.05$). The frequency of CC genotype was significantly lower in hypertensive patients than in normotensive controls ($chi(2)=9.44$, $p<0.01$). A stepwise logistic regression analysis confirmed these findings.

CONCLUSIONS: We found that the TT genotype of T-344C polymorphism of aldosterone synthase gene was associated with significantly higher levels of PRA in normotensive men. In subjects with high PRA, the TT genotype was associated with higher values of the LVMI. We did not find any association of -344T/C variant with the resistance of hypertensive patients to combination therapy, but we observed an association of -344T/C polymorphism of aldosterone synthase gene with increased risk of hypertension. These results support a potential role of -344T/C CYP11B2 gene polymorphism in genetic predisposition to develop hypertension.

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Part II. : Circulating cell adheison molecules and markers of endothelial dysfunction in uncomplicated essential hypertension and the effect of treatment with angiotensin converting enzyme inhibitors

BACKGROUND: The endothelium lines all blood vessels in the human body,its impaired function is a basic factor in the genesis and development of vascular disease. Risk factors of cardiovascular diseases such as hypertension, hyperlipidaemia, hyperglycaemia, smoking damage the function of endothelial cells and cause the development of endothelial dysfunction. In patients with arterial hypertension endothelial dysfunction is characterized by an impaired endothelium dependent relaxation, increased adhesion and permeability of endothelial cells, structural changes of the vascular wall. When the endothelium is damaged

by released cytokines an increased expression of adhesion molecules occurs, adhesion and migration of inflammatory cells across the vascular wall. Cytoadhesion molecules are released from the surface of the endothelium into the circulation where the rise of their plasma levels can serve as a marker of endothelial damage. Endothelial dysfunction in hypertensive subjects contributes way to the development and progression atherosclerosis. Improvement of the damaged endothelial function is therefore at present a desirable therapeutic objective in the treatment of hypertension.
DESIGN AND METHODS: The aim of our study was to examine whether the circulating cell adhesion molecules, von Willebrand factor (vWf) and endothelin-1, are elevated in patients with essential hypertension with no other risk factors for atherosclerosis and thus may serve as a markers of endothelial dysfunction in uncomplicated hypertension. We also studied the effect of treatment with the ACE inhibitor, quinapril, on levels of endothelial dysfunction markers.
The levels of adhesion molecules (intercellular cell adhesion molecule-1 [ICAM-1], Eselectin, P-selectin), von Willebrand factor (vWf) and endothelin-1 were measured in patients with hypertension without any other risk factors of atherosclerosis before (after a 3 weeks washout period from previous antihypertensive treatment) and after treatment with quinapril (n = 22) and in normotensive controls (n = 22).
RESULTS: Compared with normotensive subjects, the hypertensive patients had significantly higher levels of ICAM-1 (238 vs 208 ng/ml, $P = 0.02$), vWf (119 vs 105 IU/dl, $P < 0.05$) and endothelin-1 (5.76 vs 5.14 fmol/ml, $P < 0.05$). Three-month treatment of hypertensive patients with quinapril led to a significant decrease in the levels of endothelin-1 (5.76 vs 5.28 fmol/ml, $P < 0.01$). We did not observe significant changes in the levels of adhesion molecules and vWf after ACE inhibitor treatment, although a trend toward a decrease was apparent with all these parameters.
CONCLUSIONS: Patients with uncomplicated hypertension with no other risk factors of atherosclerosis had significantly elevated levels of ICAM-1, vWf, and endothelin-1. Our data suggest that these factors may serve as markers of endothelial damage even in uncomplicated hypertension. In hypertensive patients, treatment with the ACE inhibitor quinapril resulted in a significant decrease in endothelin-1 levels. These findings indicate a beneficial effect of ACE inhibitors on endothelial dysfunction in hypertensive patients.