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NA/K-ATPase (NKA) ISOFORMS AND SODIUM PUMP LIGANDS (SPL) DURING DEVELOPMENT OF LEFT VENTRICULAR HYPERTROPHY (LVH) AND TRANSITION TO CHRONIC HEART FAILURE (CHF) IN DAHL HYPERTENSION

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NaCl loading of Dahl salt sensitive rats (DS) stimulates two SPLs, an endogenous ouabain (OU) and a bufadienolide marinobufagenin (MBG) which exhibits high affinity to the ouabain-resistant rat alpha-1 NKA isoform, the major isoform in the myocardiocytes (Fedorova et al., Hypertension, 2001; 37: 462-466). The present goal was to study whether changes in SPL production during development of LVH and transition to CHF in DS occur and are associated with the changes in myocardial NKA isoforms and their sensitivity to MBG and OU. DS developed hypertension and LVH, following 4 wks on an 8 % NaCl intake, which progressed to CHF at 8-12 wks of an 8% NaCl intake. During development of LVH the increases in blood pressure (174± 9 vs. 110± 2, P<.01) were by accompanied an increase in plasma MBG, an increased sensitivity of LV sarcolemmal NKA to MBG at the level of high affinity binding sites, and an increase in alpha-1 NKA protein. In contrast, plasma levels of the alpha-3 NKA ligand, OU, did not change during LVH, and the sensitivity of LV NKA to OU was decreased. The transition to CHF was accompanied by a decrease in alpha-1 NKA protein, a reduction in plasma MBG to control levels, and a decrease in LV NKA sensitivity to MBG. Conversely, during CHF the neonatal alpha-3 NKA was produced within LV sarcolemma, plasma OU increased 3-fold to control, and the sensitivity of LV NKA to OU enhanced 7-fold to control. Thus, during LVH and CHF a shift in endogenous NKA ligands production is linked to a shift in myocardial NKA isoforms.

	Control	LVH	CHF
LV end diastolic diameter (mm)	5.14 ± 0.16	6.46 ± 0.33**	7.43 ± 0.15**‡
Plasma MBG (nmol/L)	0.31 ± 0.03	1.22 ± 0.22**	0.36 ± 0.04‡
IC50 for MBG NKA inhibition (nmol/L)	4.6 ± 0.1	0.8 ± 0.02*	29 ± 2*†
Plasma OU (nmol/L)	0.27 ± 0.06	0.37 ± 0.08	1.01 ± 0.13**‡
IC50 for OU NKA inhibition (nmol/L)	15 ± 0.9	318 ± 0.8*	1.4 ± 0.05*†

** P < 0.05, ** P < 0.01 vs. control; † P < 0.05, ‡ P < 0.01 vs. LVH. One-way ANOVA and Newman-Keuls test. n = 10–12 for each group*

Key Words: Na,K ATPase, digitalis-like factors, left ventricular remodeling

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EFFECT OF AMLODIPINE VS CANDESARTAN ON LEFT VENTRICULAR HYPERTROPHY IN HYPERTENSIVE TYPE 2 DIABETIC PATIENTS

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Aim of the study is to evaluate the efficacy of amlodipine in comparison with candesartan in hypertensive diabetic patients with left ventricular hypertrophy (LVH). A total of 119 mild to moderate hypertensive non albuminuric type 2 diabetic patients with LVH (LVMI> 131 g/m^2 in men and >100 g/m^2 in women) after a 4 week placebo period were enrolled in a 24 month randomized, double blind parallel group study to compare the effects of candesartan (8 mg o.d.) with amlodipine (5 mg o.d.): after 2 months of treatment the patients non responders (DBP > 85 mmHg) were given a double dose of each drug; the patients yet non responders at the 3rd month were given additional treatment with hydrochlorothiazide 12.5 mg. The patients non responders at the 4th month of treatment were discontinued.

A total of 49 candesartan and 51 amlodipine treated patients completed the study. Echocardiographic evaluation was performed at the end of the placebo period and after 6, 12 and 24 months of active treatment.

Patients of both groups were similar with regard the duration of diabetes, hypertension, SBP and DBP at rest, degree of LVH and metabolic control. Both drugs were equally effective in reducing BP (amlodipine: from 161±12/100±6 to 140±10/82±5 mmHg; candesartan from 160±11/99±6 to 141±9/83±5 mmHg) but not in reversing LVH because it decreased significantly more in the amlodipine group as compared with the candesartan group (20.4±3 vs 10.1±5 g/m^2 respectively, 10.3(1.14-22.3) g/m^2 mean difference (95% CI); p= 0.036).

Our results show that in hypertensive type 2 diabetic patients amlodipine induces a regression of LVH greater than candesartan independent of reduction in systemic blood pressure. It suggests that in this type of patients calcium channel blockade is more important than Angiotensin II antagonism for reversing LVH.

Key Words: Amlodipine, type 2 diabetes, left ventricular hypertrophy

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OLDER AGE DOES NOT ATTENUATE HYPERTROPHY REGRESSION DURING ANTIHYPERTENSIVE TREATMENT IN HYPERTENSIVE PATIENTS WITH LEFT VENTRICULAR HYPERTROPHY (THE LIFE STUDY)

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Aging is associated with cardiac remodeling and hypertrophy in hypertensive patients, but less is known about the influence of age on changes in left ventricular (LV) mass and geometry during antihypertensive treatment. We related age to clinical and echocardiographic findings before and after four years of antihypertensive treatment in a subset of 592 hypertensive patients without concurrent disease in the Losartan Intervention For Endpoint reduction in hypertension study in which patients were randomized to blinded losartan or atenolol based treatment. Patients ≥ 65 years (older group, n=311) included more women and patients with isolated systolic hypertension or albuminuria (all p< 0.05). Compared to patients < 65 years, older patients had higher pulse pressure (PP), LV mass/body surface area and prevalence of concentric hypertrophy at baseline (78 versus 69 mmHg, 127 versus 116 g/m^2, and 30 versus 15 %, respectively, all p<0.01), while mean blood pressure (BP) did not differ. Over 4 years, the reductions in LV mass index and mean BP were similar while PP reduction was larger in the older group (13 versus 11 mmHg, p<0.05). However, more patients in the older group had residual LV hypertrophy (32 versus 16%, p<0.001) with a preponderance of eccentric geometry. In multivariate analysis of 4-year change in LV mass, controlling for baseline LV mass, larger LV mass reduction was associated with female gender and losartan treatment, while age and reduction in body mass index and PP did not enter (Multiple R^2=0.39, p<0.001). Thus, in hypertensive patients below 80 years of age with electrocardiographic LV hypertrophy, age does not significantly influence echocardiographic LV mass reduction over 4 years antihypertensive treatment, although residual LV hypertrophy is more prevalent in the older patients as a consequence of higher initial LV mass.

Key Words: Hypertension, age, hypertrophy regression