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EFFICACY OF LOSARTAN VS. AMLODIPINE IN PATIENTS WITH CHRONIC NONDIABETIC PROTEINURIC NEPHROPATHY: GLOMERULAAR STUDY

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Aims: To evaluate the effect of losartan vs. amlodipine on the control of blood pressure (BP), renal function, 24 hour proteinuria, and plasmatic and urinary TGF-beta in patients with chronic nondiabetic proteinuric nephropathy.

Design and Methods: 97 patients (72M, 25F), with a mean age of 48.41 (22-76) years and a mild to moderate arterial hypertension (SiSBP: 140-170mmHg and SiDBP 90-105mmHg) affected of a chronic nondiabetic proteinuric nephropathy (24 hour proteinuria $>$ 1.5 g.) were included in this study. After 2 to 8 weeks of placebo, patients were randomized and followed during 20 weeks on active, double-blind treatment: losartan 50 mg or amlodipine 5 mg, with titration to losartan 100/HCTZ 25 or amlodipine 10/HCTZ 25 if it was necessary in order to reach a BP below 140/90. The samples for proteinuria and TGF-beta were analyzed in a central laboratory.

Results: Table 1 shows the antihypertensive and laboratory efficacy from baseline to week 20.

Conclusions: Losartan significantly reduced proteinuria in patients with chronic nondiabetic proteinuric nephropathy, through a marked reduction in renal TGF-beta excretion. Amlodipine did not produce any significant change. It could be speculated that these differences may have a long term impact on the prevention of chronic renal failure.

	SiSBP (mmHg) Baseline*	SiSBP (mmHg) Reduction wk20**	SiDBP (mmHg) Baseline*	SiDBP (mmHg) Reduction wk20**
Losartan (n = 50)	149.02	−17.38	93.75	−10.19
Amlodipine (n = 47)	149.43	−12.43	92.64	−7.26
p-value		0.063		0.0573
	Treatment	Baseline	Week 20**	p-value
24 hours Proteinuria (mg/24h)	Losartan	3155	1421	0.0001
	Amlodipine	2598	2578	
Urinary TGF-beta (ng/24 h.)	Losartan	16,5	12,5	0.03
	Amlodipine	16,1	17,7	
sCreatinine (mg/dL)	Losartan	1,40	1,43	n.s.
	Amlodipine	1,26	1,36	

Data are expressed as mean (95% CI) Absolute reduction of mean (95% CI)*

Key Words: Chronic Nondiabetic proteinuric Nephropathy, TGF-β, Losartan

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AN AT1 SIGNALLING MEDIATES INTERACTIONS BETWEEN ENDOGENOUS SODIUM PUMP LIGANDS (SPL) IN NACL LOADED DAHL SALT-SENSITIVE RATS (DS)

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In DS on a high NaCl intake, a centrally acting endogenous ouabain (OU) contributes to the onset of hypertension via an ATII sensitive pathway (Huang and Leenen, Hypertension, 1998, 32, 1028-33). Recently, we demonstrated that in NaCl loaded DS, transient increases in pituitary OU preseded sustained increases of marinobufagenin (MBG), a vasoconstrictor bufadienolide SPL with high affinity to alpha-1 Na pump (main kidney isoform)(Fedorova et al, Circulation, 2000, 102, 3009-14). We hypothesized that in NaCl loaded DS, OU stimulates brain ATII, which, in turn, stimulates MBG. In 10 week old DS treated with nonimmune serum (Vehicle), antibodies to MBG (MBG ab) or OU (OU ab), or losartan (LOS), we studied effects of 3 hr NaCl loading (12.5 mmol/kg, IP) on renal excretion of SPL, systolic BP (SBP), Na pump in proximal convoluted tubules and pituitary ATII. NaCl loading was associated with a natriuretic response, inhibition of renal Na pump, and with increases in SPL excretion, SBP and brain ATII. The MBG ab blocked MBG excretion, restored renal Na pump and lowered SBP. The OU ab reduced brain ATII, increased renal Na pump activity and blocked both OU and MBG excretion. LOS blocked MBG, but not OU excretion. Table: (*)-$P<0.05$, (**)-$P<0.01$ vs baseline, ($^{\#}$)-$P<0.05$, ($^{\#\#}$)-$P<0.01$ vs vehicle (one way ANOVA and Neuman-Keuls test); $n=8$ for each group. We conclude that in NaCl loaded DS, OU stimulates ATII which activates MBG. MBG inhibits the renal Na pump and contributes to BP elevation. An ATII mediated interaction between OU and MBG may be relevant to pathogenesis of chronic NaCl sensitive hypertension.

	Baseline	NaCl + Vehicle	NaCl + MBGab	NaCl + OUab	NaCl + LOS
Na pump (mmol Rb/mg prot/min)	45 ± 2	28 ± 1**	40 ± 4$^{\#\#}$	36 ± 2$^{\#}$	37 ± 2$^{\#}$
Systolic BP (mm Hg)	121 ± 1	187 ± 4**	117 ± 5$^{\#\#}$	125 ± 2	138 ± 3$^{\#\#}$
MBG excretion (pmol/kg/hr)	1.5 ± 0.3	6.1 ± 1.1*	2.0 ± 0.4$^{\#\#}$	1.8 ± 0.4$^{\#\#}$	2.0 ± 0.5$^{\#\#}$
OLC excretion (pmol/kg/hr)	2.0 ± 0.1	5.3 ± 1.3*	4.3 ± 1.0$^{\#\#}$	0.8 ± 0.4$^{\#\#}$	4.1 ± 0.9$^{\#}$
Na excretion (mmol/kg/hr)	0.5 ± 0.4	2.8 ± 0.3**	1.5 ± 0.4$^{\#\#}$	2.0 ± 0.2*	1.2 ± 0.2$^{\#}$
Brain ATII (ng/g tissue)	1.6 ± 0.3	3.9 ± 0.3**	n.d.	2.0 ± 0.2$^{\#}$	n.d.

Key Words: Salt Sensitivity, Renin-Angiotensin System, Endogenous Sodium Pump Inhibitors

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EFFECTS OF A COMPREHENSIVE INTERVENTION INCLUDING LOSARTAN ON RENAL OUTCOMES IN YOUNG URBAN BLACK MEN WITH HYPERTENSION

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The purpose of this investigation was to assess the effect of an educational-behavioral-pharmacological intervention using a Losartan based regimen on the progression of renal dysfunction in young, urban, black men with hypertension. Data were analyzed from the time of randomization through 36-month follow-up on 277 men who were enrolled in an on-going hypertension control clinical trial. The primary end point was the time to the first event of a 50% increase in serum creatinine concentration. A secondary outcome was change in proteinuria (the urinary albumin-to-creatinine ratio, ACR). At baseline, the mean age was 41.4 (± 5.6) years, mean BP was 146 (± 19.4)/99 (± 14.5) mm Hg, mean serum creatinine was 1.3 (± 1.2) mg/dL, and there were 24.5 % with microalbuminuria (ACR 17-250 mg/g), and 11.2% with gross proteinuria (ACR $>$ 250 mg/g) based on a spot urine/creatinine ratio. The primary end point was reached in 21 (14.3%) of 147 men in the special intervention group, as compared to 28 (21.5%) of 130 men in the usual care group; throughout the 36 months of follow-up, the special intervention group had a trend towards a lower incidence rate than the usual care group (annual incidence rates of 5.2% and 8.0%, respectively, $p=0.08$).