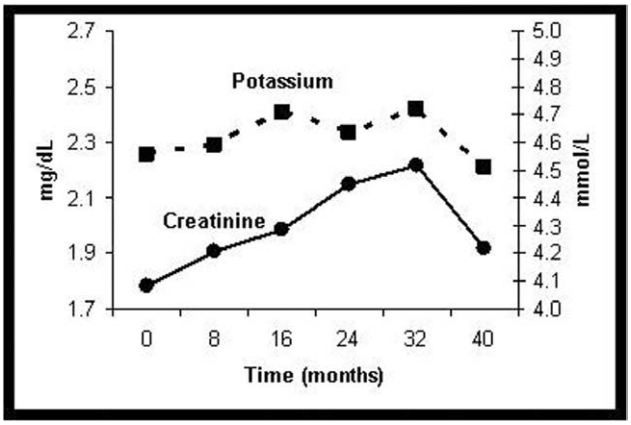

serum creatinine or potassium and is thus a safe therapeutic approach to further reduce proteinuria.

Key Words: Angiotensin Receptor Blocker Therapy, Chronic Kidney Disease, Hypertension

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ROLE OF HSD11B2 POLYMORPHISMS IN ESSENTIAL HYPERTENSION AND THE DIURETIC RESPONSE TO THIAZIDES

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The renal 11beta-hydroxysteroid dehydrogenase type 2 (11beta HSD2) enzyme inactivates 11-hydroxy steroids in the kidney, thereby protecting the non-selective mineralocorticoid (MR) receptor from occupation by glucocorticoids. Loss-of-function mutations in the gene encoding 11beta HSD2 (HSD11B2), result in overstimulation of the MR and cause salt-sensitive hypertension. We have investigated the role of HSD11B2 in hypertension in 377 genetically homogeneous essential hypertensives from North Sardinia. Thirty of these patients displayed increased urinary cortisol metabolite ratios (greater than or equal to 2) (tetrahydrocortisol [THF]+allotetrahydrocortisol [aTHF]/tetrahydrocortisone [THE]) reflecting a mild reduction in 11beta HSD2 activity. No mutations in HSD11B2 were detected in these patients. All 377 patients were genotyped for a CA repeat microsatellite in intron 1 of HSD11B2 and a G534A polymorphism in exon 3 of HSD11B2. CA repeat length was associated with the (THF+aTHF)/THE ratio which in turn was significantly related to PRA levels. No associations were found between the G354A polymorphism and the other parameters. There were no differences in blood pressure (BP) levels between HSD11B2 genotypes but, in a subgroup of 91 patients that underwent diuretic therapy, CA repeat length was strongly associated with the BP response to hydrochlorothiazide. This study highlights the role of this HSD11B2 polymorphism in sodium handling and is consistent with a role in the BP response to thiazide diuretics.

Key Words: 11Betahydroxysteroid Dehydrogenase Type 2, Genetic Polymorphisms, Pharmacogenomics

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EFFECTS OF BENAZEPRIL ON EXPRESSION OF AQUAPROTEIN-2 IN SHR AND WKY KIDNEY

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To explore the effect of benazepril on the expression of water channel-2 (aquaporin 2, AQP2) in spontaneously hypertensive rat(SHR) kidneys,16 male SHR, aged 12 wks, weighed 200- 300 g, were randomly divided into 2 groups: benazepril(SHR_{ben})and saline control(SHR_{ctrl}). After 8 weeks' medication, the rats were decollated, and plasma concentration of vasopressin(AVP) was measured with radioimmunoassay. The expression levels of AQP2 mRNA and AQP2 protein were determined with RT-PCR and immunohistochemistry. All data were expressed as mean+/-SD. There was no difference of initial blood pressure of SHR before treatment. After 8 weeks' administration of benazepril, the blood pressure of SHR_{ben} was significantly lower than that of SHR_{ctrl}. The expression levels of AQP2 mRNA(0.48 ± 0.11 vs 0.72 ± 0.17,$P<0.05$)and AQP2 protein(0.47 ± 0.09 vs 0.62 ± 0.12, $P<0.05$)and concentrations of AVP(61.79 ± 9.19 vs 87.16 ± 8.2 pg/ml,$P<0.05$) was significantly decreased as compared with SHR_{ctrl}. It is concluded that Benazepril may inhibit the high expression of AQP2 in SHR kidney.

Key Words: Aquaporin 2, Benazepril, Spontaneously Hypertensive Rats

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EFFECTS OF LOSARTAN AND AMLODIPINE ON MACROALBUMINURIA AND 24-H BLOOD PRESSURE IN HYPERTENSIVE TYPE 2 DIABETIC PATIENTS WITH OVERT NEPHROPATHY

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In hypertensive type 2 diabetic patients with overt nephropathy, a loss of nocturnal blood pressure (BP) reduction due to impaired diurnal autonomic nervous rhythm is associated with albuminuria. However, few studies have assessed whether 24-h BP control achieved by antihypertensive agents improves macroalbuminuria. We evaluated the effects of losartan and amlodipine on 24-h BP and autonomic nervous activity using multi-tasking ambulatory BP monitoring devices and 24-h urinary albumin excretion in these patients. The study was designed as an open-label, parallel-prospective, randomized study for 24 weeks, comparing the effects of losartan (n=44) and amlodipine (n=43). BP and urinary albumin excretion for 24 h were measured before and after treatment. Simultaneously, power spectral analysis of the heart rate was performed to calculate the low frequency (LF) components, high frequency (HF) components and LF/HF ratios as an index of the sympathovagal balance. Losartan significantly ($P<0.01$) decreased BP (systolic/diastolic) from $162\pm15/91\pm10$ to $150\pm15/82\pm10$ mmHg during waking and from $146\pm16/82\pm10$ to $137\pm15/74\pm10$ mmHg during sleeping. In the amlodipine group, BP also decreased ($P< 0.01$) from $159\pm13/90\pm9$ to $147\pm14/82\pm8$ mmHg during waking and ($P<0.01$) from $143\pm15/81\pm12$ to $131\pm15/72\pm11$ mmHg during sleeping. After both treatments, LF and HF components did not change, with no alteration in the sleeping/waking ratio for the LF and HF components. Consequently the sleeping/waking ratio for the LF/HF ratio also did not differ after treatment in both groups, showing no change in the diurnal autonomic nervous rhythm. In the losartan group, the 24-h urinary albumin excretion was 1.0 ± 0.6 g/day before treatment and significantly decreased ($P<0.01$) to 0.7 ± 0.5 g/day after treatment. The amlodipine group showed no difference ($P>0.05$) in 24-h urinary albumin excretion before and after treatment (1.0 ± 0.6 vs. 1.0 ± 0.8). Our results suggest that in type 2 diabetes with overt nephropathy, 24-h BP regulation alone is not

enough to reduce macroalbuminuria and additional effects of losartan are crucial for the antiproteinuric action.

Key Words: Ambulatory Blood Pressure, Diabetic Nephropathy, Renoprotective Effect

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INTERACTION OF D_1 DOPAMINE AND ETB ENDOTHELIN RECEPTORS IN RENAL PROXIMAL TUBULE AND VASCULAR SMOOTH MUSCLE

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Dopamine plays an important role in the regulation of blood pressure by inhibition of sodium transport in renal proximal tubules (RPTs) and by relaxation of vascular smooth muscles. The ETB receptor, like the D_1 and D_3 dopamine receptors, inhibits sodium transport in the RPT; however, activation of ETB, unlike these dopamine receptor subtypes, can directly constrict vascular smooth muscles. There is abundant expression of ETB receptors in RPT, and D_3 receptors increase ETB receptor expression in RPT cells from Wistar-Kyoto (WKY) RPT cells. In addition, the natriuretic effect of D_3 agonist can be blocked by an ETB antagonist. Because the D_1 and D_3 receptors can regulate each other, we tested the hypothesis that there is also an interaction between D_1 and ETB receptors in RPT cells and vascular smooth muscle cells. In immortalized RPT cells, the D_1-like agonist, fenoldopam, decreased ETB receptor protein in a time- and concentration-dependent manner (EC_{50} = 1.6 x 10^{-10} M, $t_{1/2}$ = 15.3 hr, n=5-6), an effect that was blocked by the D_1-like antagonist, SCH 23390 (10^{-7}M/24 hr, n=7). D_1 and ETB receptors colocalize in RPT cells. Fenoldopam also decreased ETB receptors (EC_{50} = 9.6 x 10^{-8}M; $t_{1/2}$ =15.8 hr, n=7-8) in a vascular smooth muscle cell line (A10 cells), similar to its effects in RPT cells. We next studied the effect of the ETB receptor on D_1 receptor expression; activation of ETB receptors with BQ3020 decreased D_1 receptor expression in time- and concentration-dependent manner (EC_{50} = 6.5 x 10^{-10} M, $t_{1/2}$ = 14 hr, n=8-10), an effect that was blocked by the ETB receptor antagonist BQ877. Although both D_1 and ETB receptors inhibit sodium transport, the reciprocal negative inhibition of their expression suggests that the inhibitory effect of D_1-like receptors on renal proximal sodium transport is not mediated by ETB receptors. However, the long-term inhibitory effect of D_1-like receptors on ETB receptors in vascular smooth muscles may aid in the vasodilatory effect of dopamine. This differential regulation in smooth muscle and RPT cells is an example of cell specific signal transduction.

Key Words: Dopamine, Endothelin, Receptor