0.73, p<0.02). In contrast, increased 20-HETE by HI did not correlate with electrolyte excretion in SS. We conclude that previously reported diminished renal synthesis of 20-HETE in SS leads to decreased urine 20-HETE excretion that correlates with their hypertension and salt-sensitivity. Lack of relationship between 20-HETE and Na-Cl excretion in SS, present otherwise in SR and SD, is analogous to our observations in humans. Hence, a dual defect in the production and natriuretic action of 20-HETE is present in salt-sensitive hypertension.

Key Words: Eicosanoids, Salt-Sensitivity, Natriuresis

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**DEXAMETHASONE TREATMENT ALTERS THE 24- HOUR BLOOD PRESSURE PROFILE, ANGIOTENSIN II LEVELS AND THE EXPRESSION OF RAT- AND MOUSE-RENIN IN ADULT TGR(mREN2)27-RATS**

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Transgenic TGR express an additional murine renin gene which results in a severe hypertension and an inverse 24 hour blood pressure profile. Blood pressure levels are high during the resting period, whereas heart rate peaks at night. The activated hypothalamic-adrenal axis is thought to be involved in this process. It has been shown that chronic dexamethasone (DEXA) treatment in young TGR (5 weeks) reduces the increase in blood pressure. DEXA (100 μg/kg s.c. at 7:00 and 19:00) was administered over 3 weeks in order to investigate the effects on blood pressure profile and expression of renin (rRen)-, mouse (mRen2)-renin mRNA and angiotensin II in adults (rats 15). Controls recieved NaCl 0.9%. BP was measured telemetrically under 12:12 LD (light:dark) conditions. Animals were killed 2 hours after light onset (ZT 2). DEXA treatment significantly reduced mRen2 mRNA in the adrenal glands by a factor of four, and in kidneys by a factor of two. rRen expression was only reduced in kidneys. Angiotensin II in plasma was slightly but significantly reduced by DEXA (control vs TGR: 15.6 ±/− 1.9 vs 10.2 ±/− 1.0 pg/ml, p<0.05). Instead of lowering BP treatment with DEXA increased BP during the activity period, leading to an abolished day-night rhythm, mesor and day-mean levels were not significantly changed.

In conclusion, treatment by DEXA of adult TGR with established hypertension decreased mouse- and rat-renin levels, and reduced angiotensin II levels. The inverse 24 hour rhythm in BP was abolished by raising the nighttime BP. Long term expression of the transgene obviously resulted in an irrevocably changed phenotype. On the other hand DEXA acts on other blood pressure regulating mechanisms, e.g. reducing eNOS mRNA or increasing sympathetic activity.

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Key Words: Transgenic-Hypertensive Rats, TGR(mRen2)27, 24h-Blood Pressure Profile, Dexamethasone

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**CHRONIC CYCLOSPORINE-INDUCED HYPERTENSION IS COUPLED TO CALCINEURIN-MEDIATED INHIBITION OF T CELL ACTIVATION IN MICE**

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Immunosuppressive therapy with the calcineurin inhibitor Cyclosporine A (CsA) constitutes the major cause of hypertension in organ transplant recipients. However, the underlying mechanism causing this hypertension has been enigmatic in part due to lack of a chronic animal model. When measured indirectly by tail cuff sphygmomanometry in rats and rabbits, the blood pressure responses to chronic CsA have been rather small and inconsistent. To determine if we could develop a more clinically-relevant and robust mouse model, we first established the immunosuppressive dose range for oral CsA in mice and then tested whether the same dosage produces sustained elevations in intra-aortic pressure measured continuously with radiotelemetry. To simulate the clinical condition of allograft rejection, C57BL6 wild type mice (n=15) were injected with an anti-CD3 monoclonal antibody to cause calcineurin-mediated T cell activation in vivo. These mice were treated for one week with varying doses of oral CsA and the degree of immunosuppression was measured in splenocytes by [H]-thymidine incorporation. The major new findings are two-fold. First, the in vivo immunosuppressive dose of oral CsA in wild type mice is between 10-50 mg/kg/day: T cell activation was inhibited by 40% at 10 mg/kg/d of CsA and by 80% at the 50/mg/kg/d dose. Second and more importantly, these immunosuppressive doses of CsA produce sustained dose-dependent hypertension. As the oral CsA dose was increased progressively from 10 to 50 mg/kg/d over 3 weeks (n=5), the 24h-mean arterial pressure increased from 108±5 mmHg at baseline to 138±10 mmHg (ΔMAP= 29 mmHg, p<0.05) throughout the last two weeks of the protocol, whereas vehicle had no effect (n=5). Thus, these new data establish for the first time a robust mouse model for the genetic dissection of the underlying mechanism of chronic CsA-induced hypertension. The close coupling between the immunosuppressive and hypertensive effects of CsA provide additional support for a common mechanism of action involving calcineurin inhibition.

Key Words: Cyclosporine, T Cell Activation, Radiotelemetry

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**ANGIOTENSIN II (ANG II)-INDUCED STIMULATION OF NADPH CAUSES A BIPHASIC EFFECT ON ERK1/2 IN-VIVO AND IN-VITRO**

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We recently found that a 2-week infusion of subpressor doses of Ang II (SP-Ang II) increases pressor responses to simple stimuli without causing sustained hypertension (HTN). Because pressor doses of Ang II (Pres-Ang II) increase NADPH activity, which in turn stimulates ERK1/2, we tested whether SP-Ang II-enhanced pressor responses are associated with increases in NADPH and ERK1/2 (via the AT1 receptor). Sprague-Dawley rats received an i.v. infusion of either SP-Ang II (50 ng/kg/min; n=15), Pres-Ang II (300 ng/kg/min; n=8), or vehicle (saline; n=6) via osmotic minipumps. Eight of the SP-Ang II rats also received losartan (30mg/kg/day po). We measured blood pressure (BP) continuously by telemetry, and tested pressor responses by monitoring BP during tail cuff plethysmography (TCP). On day 13, we harvested the aortas for Western Blot analysis of p47phox (a NADPH subunit) and ERK1/2. As in our previous studies, SP-Ang II enhanced pressor responses (by 24±8 mmHg during TCP) without causing sustained HTN (124±3 vs. 127±5 mmHg). Pres-Ang II increased pressor responses (by 47±20 mmHg) and caused sustained HTN (130±3 vs. 174±15 mmHg). As expected, Ang II caused a dose-dependent increase in p47phox. Interestingly, SP-Ang II decreased ERK1/2, while Pres-Ang II increased it. Losartan prevented the Ang II-induced changes. Because of the dissociation between the effect of Ang II on p47phox and ERK1/2, we hypothesized that Ang II causes a dose dependent increase in NADPH, which in turn has a biphasic effect on ERK1/2: inhibition followed by stimulation. To test this, we incubated aortic rings with increasing doses of Ang II (10-10 to 10-4 M) in the presence and absence of either losartan (10-5 M) or a NADPH inhibitor (DPI: 10-4 M). We then measured p47phox and ERK1/2. Ang II caused a dose-dependent increase in p47phox. In contrast, Ang II decreased ERK1/2 at low doses (10-8 M decreased it by 35%), but increased it at high doses (10-6 M increased it by 40%). Losartan prevented Ang II-induced increases in p47phox and the biphasic changes in ERK1/2. The NADPH inhibitor also reversed both the inhibitory and stimulatory effects on ERK1/2. In conclusion, in vivo or in vitro activation of the AT1 receptor by Ang II, progressively increases NADPH.
activity, which in turn has a biphasic effect on ERK1/2: it inhibits ERK at low levels but stimulates it at higher levels.

Key Words: Sub-Pressor Ang II, Nadph, ERK1/2

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DOPAMINERGIC MODULATION ON THE CARDIOVASCULAR RESPONSES IN HYPERTENSIVE SUBJECTS

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Dopamine (DA), a neurotransmitter, precursor of noradrenaline, is responsible for cardiovascular and renal actions, such as increase in myocardial contractility and cardiac output, without changes in heart rate, producing passive and active vasodilatation, diuresis and natriuresis. These cardiovascular and renal actions take place through the interaction with dopamine receptors, D1, D2, D3, D4, and D5. Dopamine is known to influence the control of arterial pressure by influencing the central and peripheral nervous system and target organs such as kidneys and adrenal glands, in some types of hypertension. Although dopamine and its derivatives have been shown to have antihypertensive effects, these are still being studied; therefore it is important to explain some physiological and pharmacological aspects of dopamine, its receptors and the clinical uses it could have in the therapy of arterial hypertension.

In previous studies we have demonstrated the role of DA in the insulin secretion, renal circulation and respiratory function. We have studied ten (10) hypertensive patients under the following experimental design: 1) placebo with 5% glucose solution during a 30 min period, 2) Metoclopramide (MTC) a DA2 dopamine blocker, at the intravenous dose of 7.5 mg/Kg/min during a 30 min period, and 3) Dopamine at the intravenous dose of 1 μg/kg/min added to the metoclopramide infusion, during a 30 min period.

MTC decreased blood pressure and heart rate significantly beginning 5 min drug infusion. When dopamine was added to MTC infusion, there was an additional decrease of blood pressure without any alteration of heart rate. We conclude that: 1) There is a dopaminergic modulation during cardiovascular responses, 2) Both drugs MTC and DA act as antihypertensive agents of potential usefulness in the therapy of hypertension.

Key Words: Dopamine, Hypertension, Insuline

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DOPAMINERGIC MEDIATED CARDIOVASCULAR RESPONSES DURING COLD PRESSOR TEST IN DIABETIC SUBJECTS

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In previous work we have demonstrated that during Cold Pressor Test (CPT) (immersing right hand at 4°C during one minute period), blood pressure increases significantly with varying heart rate responses. In this study we are investigating the role of dopamine (DA) during CPT in diabetic subjects. We have studied ten (10) diabetic subjects diagnosed by clinical evaluation, fasting plasma sugar and glycosilated hemoglobin.

The following experimental design was used: 1) a placebo period with 0.9% saline solution during a 30 min period, 2) Metoclopramide (MTC) was infused intravenously at 7.5 mg/kg/min during a 30 min period, and 3) DA was added intravenously at 1 μg/Kg/min dose plus MTC drug infusion.

In placebo period, CPT induced an increase of diastolic and systolic blood pressure accompanied by a decrease of heart rate. 2) MTC induced a significant increase of blood pressure but at a less degree. 3) DA blocked MTC induced increase of blood pressure without any alteration of heart rate.