Angiotensin II (ANG II) activates cGMP phosphodiesterase resulting in increased (12.4 ± 3.3 vs 2.7 ± 1.3 uEq/min, p<0.05) in association with a marked increase in urinary cGMP excretion (1558 ± 200 vs 139 ± 45 pmol/mg, p<0.05) as compared to the non-treated group. The natriuretic response to chronic AT1 receptor antagonism was localized to the inner medullary collecting duct by the thin limb clearance technique, a nephron site rich in NPs receptors and sensitive to NO, as distal tubular fractional sodium reabsorption decreased in the AT1 blocker group vs non-treated group (97.6 ± 0.3 vs 98.0 ± 0.5, p<0.05). These renal responses where selective as they occurred in the absence of any changes in plasma renin, aldosterone, and serum potassium concentrations.

CONCLUSION: We conclude that chronic AT1 receptor antagonism in experimental overt CHF enhances renal cGMP production, the common secondary messenger for the NPs and NO system resulting in improved renal tubular function and sodium excretion. This study provides insight into renal and humoral pathophysiological actions of ANG II and the AT1 receptor in CHF and mechanisms by which AT1 receptor antagonism may mediate beneficial therapeutic properties by targeting the kidney in this disease state.

ANTAGONISTS II Receptor Antagonist and Ace inhibition Ameliorate Hyperinsulinemia and Obesity in a Murine Model of Polygenic Obesity

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Background: ACE inhibitors are well established in the prevention of hypertension-associated complications of the metabolic syndrome. This study was performed in order to assess the effects of the ACE inhibitor captopril and of the angiotensin II receptor antagonist losartan on other conditions of the metabolic syndrome in an animal model.

Methods: Male NZO/BL6 F1 mice were treated with captopril, losartan, or placebo for 11 weeks. Weight gain, body weight, plasma levels of insulin, cholesterol, triglycerides and creatinine, cardiac weight, liver and kidney weight were determined. Results: Control animals treated with placebo developed a metabolic syndrome with gain of body weight (BW), increased glucose intolerance (2.2 ± 0.9 and 1.8 ± 0.8 Hm2). In addition captopril and losartan prevented the development of obesity (42.2 ± 3.5 and 38.3 ± 2.8 g) and hyperinsulinemia (3.6 ± 1.5 and 1.8 ± 0.8 mU/L). Treatment with ACE inhibitor or angiotensin II receptor antagonist significantly (p<0.01) reduced hypertension (73 ± 5 vs 97 ± 5 mmHg). Cardiac hypertrophy (203 ± 26 and 202 ± 18 mg) and atherosclerotic plaques in the ascending aorta (3.6 ± 1.5 mm2) were significantly reduced by captopril and losartan. Treatment with losartan prevented the development of hyperinsulinemia (p<0.05).

Conclusion: In a mouse model of the obesity associated metabolic syndrome, long term treatment with an ACE inhibitor or an angiotensin II receptor antagonist can ameliorate obesity and hyperinsulinemia.

Chronic Angiotensin II (AT1) Receptor Antagonism Selectively Enhances Renal cGMP Production With Improved Renal Function in Experimental Overt Congestive Heart Failure

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BACKGROUND: Recent studies have reported that preservation of renal function is an important predictor of survival in congestive heart failure (CHF). A hallmark of overt CHF is the development of renal dysfunction (MDM) which results from decreased renal cGMP production, decreased cGMPmediated renal vasodilation and the loss of beneficial actions of endothelial NOS-derived NO.

METHODS: We studied the effects of chronic angiotensin II blockade (valsartan, Novartis) in a canine model of rapid ventricular pacing induced over CHF (246 bpm for 10 days) as compared to a non-treated group (n=5). RESULTS: After 10 days of chronic AT1 receptor antagonism, urinary sodium excretion increased (12.4 ± 3.3 vs 2.7 ± 1.3 uEq/min, p<0.05) in association with a marked increase in urinary cGMP excretion (1558 ± 200 vs 139 ± 45 pmol/mg, p<0.05) as compared to the non-treated group. The natriuretic response to chronic AT1 receptor antagonism was localized to the inner medullary collecting duct by the thin limb clearance technique, a nephron site rich in NPs receptors and sensitive to NO, as distal tubular fractional sodium reabsorption decreased in the AT1 blocker group vs non-treated group (97.6 ± 0.3 vs 98.0 ± 0.5, p<0.05). These renal responses were selective as they occurred in the absence of any changes in plasma renin, aldosterone, and serum potassium concentrations.

CONCLUSION: We conclude that chronic AT1 receptor antagonism in experimental overt CHF enhances renal cGMP production, the common secondary messenger for the NPs and NO system resulting in improved renal tubular function and sodium excretion. This study provides insight into renal and humoral pathophysiological actions of ANG II and the AT1 receptor in CHF and mechanisms by which AT1 receptor antagonism may mediate beneficial therapeutic properties by targeting the kidney in this disease state.

DNA Chip Analysis of Angiostatin Mediated Cardiac Gene Expression in Living Rats

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Background: Direct injection of angiostatin into the heart is useful for studying reporter gene constructs. However, most studies rely on postmortem analysis. We have validated a novel method of studying rat cardiac gene expression of CMV driven freely luciferase (Ad-CMV-flu) utilizing a cooled Charged Coupled Device (CCD) camera.

Methods: Rats underwent standard thoracotomy, in one group, 1x10^9 pfu was injected into left ventricular wall (n=3). Another group received serially diluted titers (1x10^7 to 1x10^6 pfu). Control rats were injected with 1x10^6 pfu of Ad-CMV-HSV1-sr96 expressing mutant thyrotropic hormone (n=3). Images were acquired on days 2 and 5 after injection of luciferin (125 mg/kg) and data expressed as relative light unit per minute (RLU/min). Results: Rats injected serially showed cardiac FL activity at day 2: 1,462 RLU/min (1x10^7 pfu) and 248 RLU/min (1x10^6 pfu). All values are statistically significant (p<0.05) compared to control rats showing background signals (10x5 RLU/min).

Conclusion: In summary, this study demonstrates the feasibility of imaging the location, magnitude, and persistence of cardiac reporter gene expression in rats over time. The cooled CCD camera produces consistent results and the detection sensitivity is very high, down to 1x10^6 pfu. This is the first demonstration of imaging cardiac gene expression in a living subject.