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RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

ANTISENSE OLIGONUCLEOTIDES TARGETING HEPATIC ANGIOTENSINOGEN DOSE-DEPENDENTLY REDUCE ATHEROSCLEROSIS AND LIVER STEATOSIS IN HYPERCHOLESTEROLEMIC MICE

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Objective: Liver-derived angiotensinogen (AGT) is the substrate from which renin and ACE generate angiotensin (Ang) II. Ang II not only increases blood pressure, but also is a major determinant of atherosclerosis in hypercholesteremic mice. Here we investigated the effect of hepatocyte-specific (N-acetylgalactosamine-conjugated) antisense oligonucleotides targeting AGT (GalNAc AGT ASOs) on blood pressure and atherosclerosis in hypercholesterolemic mice.

Design and method: Eight-week-old male LDL receptor deficient mice were fed a Western diet for 12 weeks, after receiving vehicle, GalNAc control ASO, or 1, 2.5 or 5 mg/kg of GalNAc AGT ASO on day 1, 3, 5 and 7 in the week prior the start of the diet (n = 6–10/group). Treatment was continued thereafter on a weekly basis. Systolic blood pressure (SBP) was monitored by tail cuff. After 12 weeks, mice were euthanized and plasma was collected. Plasma AGT concentration was measured by ELISA kit, and aortic atherosclerotic lesion area was measured by an en face method.

Results: The 3 GalNAc AGT ASO doses decreased plasma AGT from 10.3 ± 0.8 to 1.4 ± 0.1, 0.9 ± 0.1 and 0.7 ± 0.1 g/mL, respectively. These decreases were paralleled by dose-dependent SBP reductions from 114 ± 3 to 96 ± 2, 92 ± 2, and 84 ± 2 mmHg, respectively, and atherosclerotic lesion area reductions from 27.4 ± 0.9 to 15.1 ± 1.4, 10.8 ± 1.2, and 7.7 ± 1.0%, respectively. Yet, the attenuation of liver steatosis (liver triglyceride/weight from 139.7 ± 35.7 to 26.8 ± 4.5, 19.9 ± 1.2 and 36.0 ± 3.6 g/mg, liver total cholesterol/weight from 19.8 ± 1.6 to 8.6 ± 0.9, 6.1 ± 0.6 and 8.2 ± 0.7 g/mg) was identical for each GalNAc AGT ASO dose. GalNAc control ASO did not have effects on plasma AGT, SBP, atherosclerosis lesion area, or liver steatosis vs. vehicle.

Conclusions: In hypercholesterolemic mice, inhibition of hepatic AGT reduces systolic blood pressure and atherosclerosis dose-dependently, while liver steatosis was prevented in dose-independent manner.

THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM IN THE PREGNANT RAT

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Objective: Preeclampsia is the leading cause of maternal and fetal morbidity and mortality in the United States, affecting ~2–5% of all pregnancies. Women with a history of preeclampsia have a 4-fold increased risk for developing hypertension, 2-fold increased risk for developing stroke, and 2-fold increased risk for developing ischemic heart disease later in life. Although it is known that intact renin-angiotensin-aldosterone system (RAAS) signaling is critical to a healthy pregnancy and that the RAAS is altered in preeclampsia the pathogenic mechanisms are largely unknown and a comprehensive examination of RAAS metabolism and receptor expression is lacking in the literature. The purpose of this study is to understand how the vasculature becomes refractory to the reported high circulating angiotensin II (ANGII) during pregnancy. This work provides basic information needed to understand blood pressure regulation and volume expansion in normal pregnancy, and why it fails to occur in women with preeclampsia, resulting in hypertension and fetal growth restriction.

Design and method: We performed AT1 receptor autoradiography in kidneys of virgin (V) and late pregnant (LP) rats. We also performed equilibrium RAAS Fingerprinting in the plasma and kidneys of LP rats and V rats using a new LC/MS technique.

Results: Using this new method, ANGII levels were decreased in the plasma and unchanged in the kidney of LP animals. This was surprising as it is inconsistent with historical data, however, other methods of measuring ANGII are problematic and often unreliable. There was a very high Aldosterone/ANGII-ratio (AA2) in both plasma and kidney of LP animals. The AA2-ratio provides information about the adrenal aldosterone-releasing response to ANGII. We also found that AT1R expression is decreased in the kidneys of LP compared to V rats.

Conclusions: These results suggest a systemic down regulation of renal ANGII signaling with increased adrenal signaling. Continuing studies are assessing the RAAS signaling cascade to further validate these data, which may revolutionize the way we think about the RAAS in pregnancy, leading to improved treatment of women with preeclampsia.

ASSOCIATION OF BASELINE ALDOSTERONE/RENIN WITH MAGNITUDE OF BLOOD PRESSURE REDUCTION FROM FIRST-LINE TREATMENT IN TREATMENT-NAÏVE HYPERTENSIVE PATIENTS

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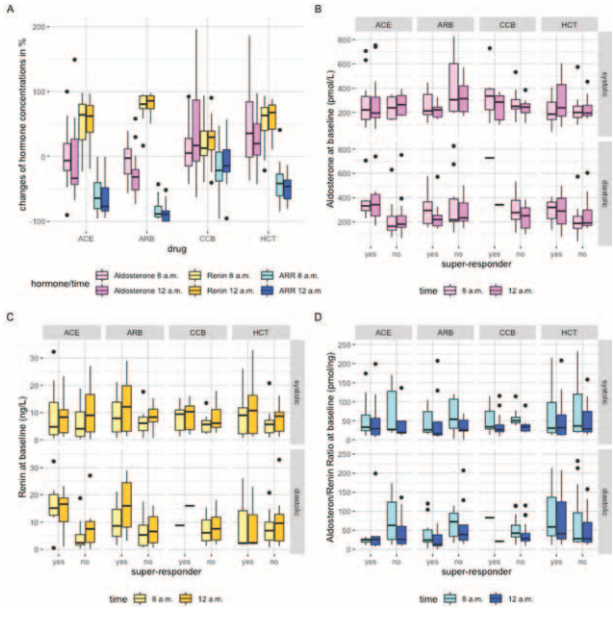
Objective: Aldosterone and renin play an important role in the regulation of blood pressure. While it is well known that treatment causes distinct alterations in the concentrations of aldosterone/renin, less is understood regarding baseline hormone concentrations and its association with response to treatment.

Design and method: Patients with newly diagnosed arterial hypertension according to 24h-BP measurements (ABPM) were randomized into four arms in a 1:1:1:1 fashion to either 5 mg perindopril (ACE), 20 mg olmesartan (ARB), 5 mg amlodipine (CCB), or 25 mg hydrochlorothiazide (HCT). Aldosterone, renin and its ratio (ARR) were measured before treatment initiation and after 4 weeks of treatment at 8 a.m. and 12 a.m. at both visits. All values were analyzed separately. ABPM was repeated after 4 weeks of treatment. Super-response was defined as a BP-reduction > = 10 mmHg of the 24 h mean ABPM values.



Results: 80 patients were randomized: 20 (25.0%) to ACE, 20 (25.0%) to ARB, 21 (26.3%) to CCB, and 19 (23.8%) to HCT. Mean age was 48 (±14) years, mean BMI