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P4.18: ANTIHYPERTENSIVE ACTIVITY OF LONG CHAIN FATTY ACID DERIVATIVES OF FLAVONOIDS VIA INHIBITION OF RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM (RAAS)

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pg/ml, $p=0.01$ and reduced serum phosphate 3.25 ± 1.18 to 2.60 ± 0.96 mg/dl, $p=0.04$ compared to amlodipine (430.1 ± 145.8 to 411.9 ± 157.6 pg/ml and 2.94 ± 0.56 to 2.69 ± 1.52 mg/dl]. There was a significant between treatment group difference, mean (95% confidence interval), in soluble Klotho, 91.9 (19.9 to 162) pg/ml and serum phosphate levels -0.68 (-0.15 to -1.33) mg/dl with valsartan/hydrochlorothiazide treatment, $p=0.04$ for both. Attained blood pressure was similar in the two groups and levels of soluble Klotho were not associated with Ao-PWV and albuminuria, variables which fell significantly only with valsartan/hydrochlorothiazide.

Conclusions: Treatment with a RAS blocker valsartan is associated with an increase in soluble Klotho which may contribute to the blood pressure independent cardio-renal benefits of these drugs in DKD.

P4.16

EFFECT OF DENERVATION ON VISCOELASTIC PROPERTIES OF LARGE ARTERIES IN POLYCYSTIC KIDNEY DISEASE RATS

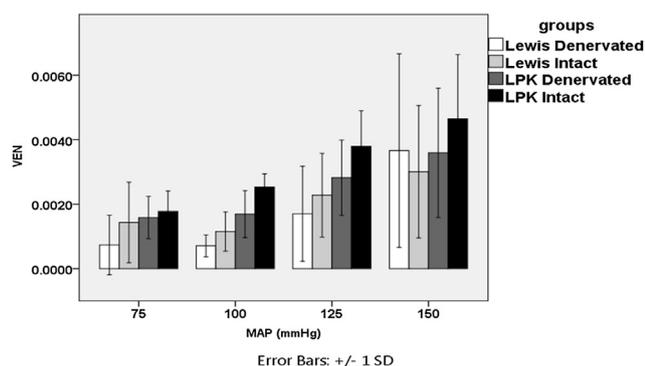
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Objectives: Arterial elasticity is determined by passive mechanical properties of wall components modulated by neurogenic effects on smooth muscle. We assessed denervation effects on viscoelastic properties of the aorta of Lewis Polycystic Kidney (LPK) disease rats, compared to controls (Lewis).

Methods: Abdominal aortic pressure (intravascular, Scisense) and diameter (ultrasound, Artlab) was measured in anaesthetised (urethane, 1.3 g/kg) Lewis ($n=11$) and LPK ($n=5$) rats before and following denervation by ganglionic blockade (intravenous hexamethonium, 20 mg/kg). Bolus intravenous doses of vasoactive agents ($6\ \mu\text{g}$ phenylephrine or sodium nitroprusside) were used to study the rats at mean pressures of 75, 100, 125 and 150 mmHg. Complex elastic modulus (E_c) was calculated from the Fourier decomposition of pressure and diameter. Viscoelasticity ($V_E = \text{Im}(E_c)$) was compared between LPK and Lewis rats in the intact and denervated state across the first three harmonics. Pressure dependency of viscoelasticity was studied using a frequency (thus heart rate) normalised viscoelastic term ($V_{EN} = V_E/\text{frequency}$).

Results: V_E increased with frequency in all but Lewis rats at 150 mmHg. LPK rats had higher V_E than Lewis ($p<0.05$), other than denervated rats at 150 mmHg and intact rats at 75 mmHg. Denervation reduced V_E in both LPK and Lewis groups ($p<0.05$). V_{EN} increased with pressure ($p<0.001$, Figure).

Conclusions: Aortic viscoelasticity was generally greater in LPK rats and was reduced with denervation. This study shows possible relationships between aortic compliance in polycystic kidney disease and sympathetic dysregulation.



P4.17

ACUTE DIETARY SODIUM CHANGES IS A PHYSIOLOGICAL DETERMINANT OF AORTIC STIFFNESS

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Objective: Aortic stiffness evaluation is recommended in standard care as hypertension target organ damage. The main determinants of aortic

stiffness are age and blood pressure. We aimed to evaluate the impact of short-term extracellular volume changes induced by dietetic and pharmacological interventions on aortic stiffness.

Methods: 74 healthy male subjects, age (median [IQR]) 23,9 [5,7] years, non-smokers, were assigned to a low sodium/high potassium diet during seven days, followed by a high sodium/low potassium diet for 14 days, the last seven with concomitant administration of amiloride. Carotid-femoral pulse wave velocity (PWV) (SphygmoCor[®]) was measured at baseline, 7th, 15th and 21st days.

Results: PWV was stable during the low sodium/high potassium diet, significantly decreased during the high sodium/low potassium diet (-0.4 m/s, CI 95% -0.7 to -0.2 , $p<0.001$) (day 7 to 15), and came back to baseline after the concomitant administration of amiloride (day 15 to day 21). In a mixed model analysis, mean daytime blood pressure (MBP), age and visit day 15 were independent determinants of changes in PWV. For each increase of 10 mmHg on MBP, PWV increased by 0,3 m/s (CI 95% 0,1 to 0,5, $p=0,006$), for each increase of 10 years of age, PWV increased by 0,4 m/s (CI 95% 0,1 to 0,7, $p=0,01$), and at visit 15 (high salt diet), PWV decreased by 0.3 m/s (CI 95 %, $-0,52$ to $-0,12$, $p=0,002$).

Conclusions: Short-time increase in extracellular volume is associated with a significant decrease in aortic stiffness in a blood pressure independent manner.

P4.18

ANTIHYPERTENSIVE ACTIVITY OF LONG CHAIN FATTY ACID DERIVATIVES OF FLAVONOIDS VIA INHIBITION OF RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM (RAAS)

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Hypertension is a contributing factor to pathophysiology of vascular damage and accelerated arterial stiffening. Renin-angiotensin-aldosterone system (RAAS) inhibitors are widely used for treatment of persistent hypertension. Along with conventional antihypertensive therapy, nutritional intervention has also gained attention as arterial and vascular complications are closely associated with dietary and lifestyle risk factors. Flavonoids and omega-3 polyunsaturated fatty acids (PUFA) are the key antihypertensive biomolecules emerging to prevent and manage hypertension. In the current study, twelve long chain fatty acid derivatives of isoquercitrin (Q3G) and phloridzin (PZ) were investigated for inhibition of angiotensin-converting enzyme (ACE), renin and aldosterone synthase in comparison to their parent compounds in vitro. The linoleic and α -linolenic esters of PZ were the strongest (IC₅₀ 69.9-70.8 μM) while Q3G and PZ (IC₅₀ >200 μM) were the weakest renin inhibitors in vitro ($p<0.05$). Similar to renin inhibition, PZ derivatives exhibited stronger ACE inhibition compared to Q3G. The eicosapentaenoic acid (EPA) ester of PZ (IC₅₀ 16.03 μM) was the strongest, while PZ (IC₅₀ 123.96 μM) was the weakest ACE inhibitor ($p<0.05$) among all tested compounds. However, all investigated compounds had no effect on aldosterone synthase inhibition ($p<0.05$). Overall, the results showed that phloridzin derivatives were stronger antihypertensive agents than isoquercitrin. It is indicated from our study that these novel compounds as dual RAAS inhibitors may be used as potent bioactive ingredients to develop functional foods and nutraceuticals for prevention and treatment of high blood pressure.

P4.19

THE EFFECT OF AN 8-WEEK, MODERATE-INTENSITY, AEROBIC EXERCISE INTERVENTION ON MMP-9 AND VASCULAR HAEMODYNAMICS

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Objective: The Matrix Metalloproteinase-9 (MMP-9) enzyme is involved in degrading extracellular matrix (ECM) proteins, including collagen and elastin. Increased MMP-9 levels are associated with increased vascular remodelling and arterial stiffness. Exercise improves age-related vascular stiffening. It is therefore hypothesised that participation in an aerobic, moderate-intensity exercise programme will down-regulate mRNA expression of MMP-9.

Methods: Thirty-six healthy, sedentary individuals (43 ± 14 yrs) joining an aerobic, moderate-intensity exercise programme, were recruited. Exercise (measured using IPAQ MET-minutes), supine blood pressure, augmentation