metabolites were determined, of which 155 were eligible for statistical analyses according to established selection criteria. To identify relevant discriminating metabolites, a series of univariate and multivariate analyses were applied. Since the distribution of the patients between the clinical entities was different according to sex ($p<0.001$) and age ($p=0.001$), analyses were also performed separately for each sex and age group (cut-off 50 years). Thereby, we identified 4 common metabolites (C18:1, C18:2, spermidine, ornithine) from the comparison of PHT with each endocrine hypertension subgroup (CS, PA, PPGL) separately. The ROC curve for discrimination between PHT and EHT built upon these 4 metabolites had an area under the curve (AUC) of 0.79 (95%CI 0.73-0.85). In the comparison of PHT and EHT as a common group 38 metabolites were identified. Using the top 15 metabolites from the latter comparison (C3-DC, C9, C16, C16:1, C18:1, C18:2, arginine, aspartate, glutamate, ornithine, spermidine, lysoPCaC20:4, PCaaC38:6, PCaaC40:6, PCaaC42:1) the AUC was 0.86 (95%CI 0.81-0.91). We conclude that TM is associated with distinct metabolic pattern in PHT and EHT and is a promising pre-screening tool for identifying EHT patients.

Diabetes Mellitus and Glucose Metabolism

LIPIDS, OBESITY AND METABOLIC DISEASE

Metformin Attenuates Sodium Retention and Blood Pressure in Hypertensive Diabetic Mice by Reducing the Phosphorylation of Renal NCC and Its Association With the Actin Cytoskeleton

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Metformin is the first-line drug in the treatment of type 2 diabetes mellitus. The aim of this work was to evaluate the efficacy of metformin treatment in reducing blood pressure and investigate the molecular mechanism using a preclinical animal model. Adult male and female diabetic db/db mice with a blood glucose of greater than 300 mg/dl were salt-loaded (8% NaCl) for 10 days to induce hypertension. The mice were subject to metabolic cage studies for 24 hour urine collections in order to measure urinary electrolytes, albumin, and creatinine. Blood pressure was measured weekly by the tail-cuff method to assess the effect of metformin or vehicle given by oral gavage (dose of 60 mg/kg of body weight per day). At the end of the study the mice was euthanized and the left kidney was formalin-fixed and paraffin-embedded for immunohistochemistry while the right kidney was homogenized for Western blotting. Western blotting showed attenuation of total NCC and phospho-NCC in diabetic db/db mice given an oral gavage of metformin (Pearson correlation coefficient: 0.9470 +/- $2.52e^{-3}$) compared to vehicle (Pearson correlation coefficient: 0.9800 +/- $2.86e^{-3}$). Immunohistochemical analysis showed less co-localization of the actin cytoskeleton protein filamin and phosphorylated NCC in the metformin treated group compared to the control group. Taken together, we show metformin decreases sodium retention and blood pressure by reducing the density of renal NCC at the luminal membrane and the association between NCC and the actin cytoskeleton.

Diabetes Mellitus and Glucose Metabolism

LIPIDS, OBESITY AND METABOLIC DISEASE

Regulation of ENaC by Exosomal Lipids in the Diabetic Kidney

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Effective treatment of hypertension (HTN) in patients with diabetes may help to significantly reduce the risk of those patients developing additional complications including vascular disease and diabetic nephropathy. Blockers of the renin-angiotensin system including angiotensin converting enzyme inhibitors and angiotensin receptor blockers are not always effective in treating HTN in diabetic patients. Therefore, the aim of this study was to use an animal model of type 2 diabetes to investigate a novel mechanism of diabetes associated HTN involving exosomal lipids in the upregulation of epithelial sodium channel (ENaC) activity in the kidney. We performed metabolic cages studies using male and female hypertensive (salt-loaded induced) diabetic db/db mice and healthy age-matched wild-type control mice in order to isolate and characterize urinary exosomes from each group by nanoparticle tracking analysis, Western blotting, and transmission electron microscopy. Our mass spectrometry based lipidomic studies identified key lipids that were differentially expressed in the kidney derived exosomes from the hypertensive diabetic mice compared to control mice. Sphingomyelin quantification assays showed total sphingomyelin content was elevated in the exosomes from the hypertensive diabetic mice compared to the control group. Single channel patch clamp studies showed urinary exosomes enriched in sphingomyelins from hypertensive diabetic mice compared to controls increase ENaC activity (at the level of channel density and open probability) in cultured distal tubule renal epithelial cells. Moreover, exogenous application of sphinomyelin-6 to cultured mouse cortical