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Kidney-Specific CAP1/Prss8-Deficient Mice Maintain ENaC-Mediated Sodium Balance Through an Aldosterone Independent Pathway

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Background: The channel-activating protease 1 (CAP1/Prss8) is a glycoprophosphatidylinositol-anchored protein and is part of the membrane bound serine protease family. In vitro studies revealed CAP1/Prss8 as an activator of the epithelial sodium channel (ENaC). This channel, localized in the distal part and the collecting duct of the nephron, is involved in the maintenance of the electrolytic homeostasis by reabsorbing sodium from the lumen towards the blood. Na+ deprivation normally results in a rise of plasma aldosterone thereby increasing ENaC activity. It is hypothesized that ENaC is proteolytically cleaved by channel-activating proteases furin and CAP1/ prss8.

Methods: To test whether CAP1/Prss8 is required for renal ENaC activation, tubular nephron-specific CAP1/prostasin knockout mice (Prss8β-/-;Prss8rtTA Cre-TRE-Lox/Lox) and control mice were exposed to a low Na+ diet. Physiological parameters including urinary Na+ and K+, plasma electrolytes, aldosterone levels and renin activity were measured. ENaC activity was determined by benzamil-induced natriuresis.

Results: Upon Na+ deprivation, no changes in Na+ and K+ was observed in CAP1/ Prss8 knockout mice. α- or γENaC subunit cleavage pattern did not differ. Interestingly, although plasma aldosterone concentration was significantly decreased in CAP1/Prss8 knockout mice, ENaC activity was similar between the two groups, suggesting that the production of aldosterone is uncoupled from the renin-angiotensin system in CAP1/Prss8 knockout mice.

Conclusions: In summary, we were able to show that in vivo, CAP1/Prss8 was not required for ENaC proteolytic activation. Our experiments revealed that the lack of CAP1/Prss8 uncoupled ENaC activation from the classical renin-angiotensin-aldosterone stimulation on Na+ restriction. This study reveals a complex regulation of ENaC function including aldosterone-dependent and independent mechanisms.

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High Tissue Sodium Associates With Insulin Resistance in Prehypertensive Obese Individuals

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Background: High tissue sodium (Na+) accumulation plays a role in the development of hypertension by activation of inflammatory and metabolic pathways. We sought to determine if tissue Na+ content is associated with insulin sensitivity (IS) in patients with early hypertension, a known metabolic derangement commonly observed in patients with kidney and cardiovascular disease.

Methods: Tissue Na+ accumulation and IS were assessed in 83 participants with early hypertension (SBP 120 - 139 mmHg or DBP 70 - 89 mmHg) using 23NaMRI and hyperinsulinemic euglycemic clamp technique. Glucose disposal rate (GDR) was used as the marker of IS. High-sensitivity C-reactive protein (hsCRP) and interleukin 6 (IL-6) were used as markers of inflammation.

Results: GDR did not significantly associate with tissue Na+ in the entire cohort. In subgroup analysis according to obese vs lean, GDR significantly associated with muscle and skin Na+ among the obese (β=−1.11, 95% CI = −1.99, −0.24 and β=−0.45, 95% CI = −0.83, −0.07 for muscle and skin Na+, respectively) but not in lean participants. Among obese participants, there was significant effect modification by the inflammatory markers. The changes in GDR per unit changes in tissue Na+ were greater at higher levels of hsCRP (p=0.03 and 0.01 for muscle and skin Na+, respectively) and IL-6 (p=0.05 and 0.01 for muscle and skin Na+, respectively). This was not observed in lean participants.

Conclusions: Our data show a significant negative association between muscle and skin Na+ and IS in the obese, but not in lean individuals with early hypertension. Systemic inflammation may play a key role in the relationship between tissue Na+ and IS.

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Tissue Sodium Content and Intramuscular Adipose Tissue Accumulation in Individuals With Early Hypertension

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Background: High tissue sodium (Na+) accumulation has been associated with the development of hypertension through activation of inflammatory pathways. Hypertension is also linked with increased adiposity. Whether tissue Na+ plays a role in this relationship remains unknown. We hypothesized that excess tissue Na+ in the muscle could lead to intramuscular adipose tissue (IMAT) deposition and that pro-inflammatory characteristics of tissue Na+ mediate this effect in individuals with early hypertension.

Methods: IMAT and Na+ accumulation in the skin and muscle were measured using 1H- and 23Na-MRI imaging of the calf in 83 subjects with early hypertension (systolic blood pressure between 120 and 139 mmHg, or a diastolic blood pressure 70 and 89 mmHg). Blood samples were collected for high-sensitivity C-reactive protein (hsCRP) and interleukin 6 (IL-6) measurements.

Results: Median age was 48, with 68% female and BMI 27.5 kg/m². Median muscle and skin Na+ were 16.6 (IQR: 14.9-19) and 12.6 (IQR: 10.3-16.6) mmol/L, respectively. Median IMAT was 1.3 mL. IMAT was positively correlated with muscle and skin Na+ (r=0.38, p<0.001 and r=0.48, p<0.001, respectively). There was a significant effect modification of the relationship between IMAT and skin Na+ by the inflammatory markers hsCRP and IL-6. IMAT increased at high levels of inflammatory markers (p=0.03 and 0.01 for hsCRP and IL-6, respectively).

Conclusions: Our data show that high tissue Na+ concentrations in both skin and muscle associate with increased IMAT, suggesting an adipogenic effect. Systemic inflammation may play a key role in the relationship between skin Na+ and IMAT, potentially through high sodium-induced systemic inflammatory activation in the skin.

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