Activation of browning in white adipose tissue during chronic kidney disease

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INTRODUCTION AND AIMS: In patients with chronic kidney disease (CKD), protein energy wasting (PEW) is characterized by an increased resting energy expenditure (REE), although the underlying mechanisms remain poorly understood. Browning corresponds to the activation of inducible brown adipocytes in white adipose tissue (WAT) and participates in cachexia associated with hypermetabolic diseases such as cancers. The objective of this study was to highlight a phenomenon of browning associated with CKD and to study the potential role of uremic environment in the activation of this phenomenon.

METHODS: ST31L1 mouse adipocytes were incubated for 24h (i) with plasma (20% v/v) from healthy volunteers or chronic haemodialysis patients, (ii) with two major uremic toxins (p-Cresyl sulfate and Indoxyl-sulfate) or (iii) with cardiac natriuretic peptides at concentrations found in CKD patients. We quantified the content of uncoupling protein 1 (UCP-1) recognized as a hallmark of browning and studied the adipocytes differentiation. In vivo, study was carried out on 5/6 nephrectomy mice with measurement of indirect REE, WAT UCP-1 expression and content after 3 weeks of uremia.

RESULTS: The incubation of ST31L1 adipocytes with plasma from uremic patients led to an increase of UCP-1 protein (+ 153%, p < 0.05) compared to the control plasma and inhibited by cycloheximide, a potent protein synthesis inhibitor. Incubation of adipose cells with uremic toxins failed to alter UCP-1 synthesis or adipocytes differentiation. ST31L1 exposure to atrial natriuretic peptides (ANP) led to a significant increase of UCP-1 content (+ 47%, p < 0.05). Consistent with these findings, elevation of NT-pro BNP (brain natriuretic peptide) is positively correlated to protein energy wasting (PEW) criteria in a cohort of 149 haemodialysis patients without cardiovascular history (r=0.22 (0.054-0.37), p<0.05). CKD mice exhibited an increase in REE compared to sham mice consistent with a possible transformation of WAT into brown adipose tissue (BAT) and activation of thermogenesis. Moreover, UCP-1 content is significantly higher in CKD WAT compared to sham mice (p = 0.02) with an increase in the expression of several thermogenesis genes in the WAT of CKD mice (such as UCP-1, PGC1α and PRMD16).

CONCLUSIONS: Taken together, these data suggest the activation of a browning phenomenon during CKD. Uremic toxins do not appear to participate in this phenomenon although p-Cresyl sulfate was previously shown to induce adipocyte dysfunction in vitro. The activation of browning in WAT could contribute to PEW associated with CKD through an increase in thermogenesis and REE. Our data suggest that accumulation of cardiac natriuretic peptides during CKD could contribute to the browning of WAT, and their accumulation seems to be linked to nutritional status among dialysis patients. These observations open interesting perspectives to better understand the mechanisms involved in browning in CKD and to confirm this phenomenon in human.