ROLE OF BROWN FAT IN INCREASED ENERGY EXPENDITURE IN UREMIA-ASSOCIATED CACHEXIA

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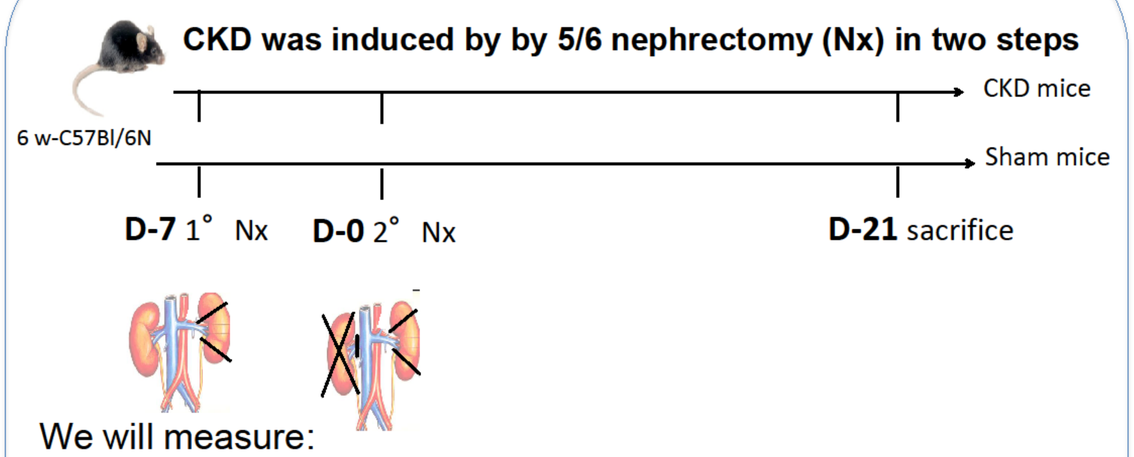
Introduction

Wasting is common in chronic kidney disease (CKD) and is associated with high mortality. One key characteristic of cachexia is higher resting energy expenditure levels (REE) which has been linked to greater thermogenesis in brown fat. Brown fat is composed of adipocytes similar to classical interscapular brown adipocytes (iBAT) and white adipocytes converted into brown, a phenomenon called browning. However, studies on REE have provided inconsistent results in CKD and the underlying mechanisms are still poorly understood.

The purpose of this study was
1-to examine whether REE is increased in a mouse model of CKD induced by 5/6 subtotal nephrectomy.
2-to ascertain whether CKD is associated with an activation of brown fat (BAT) and a browning of white adipose tissue (WAT).

Methods



We will measure:
- Indirect calorimetry with metabolic cages
- Biometry
- Expression of thermogenes genes by RT-PCR in brown adipose tissu (BAT) and in white adipose tissue (WAT)

Indirect calorimetry

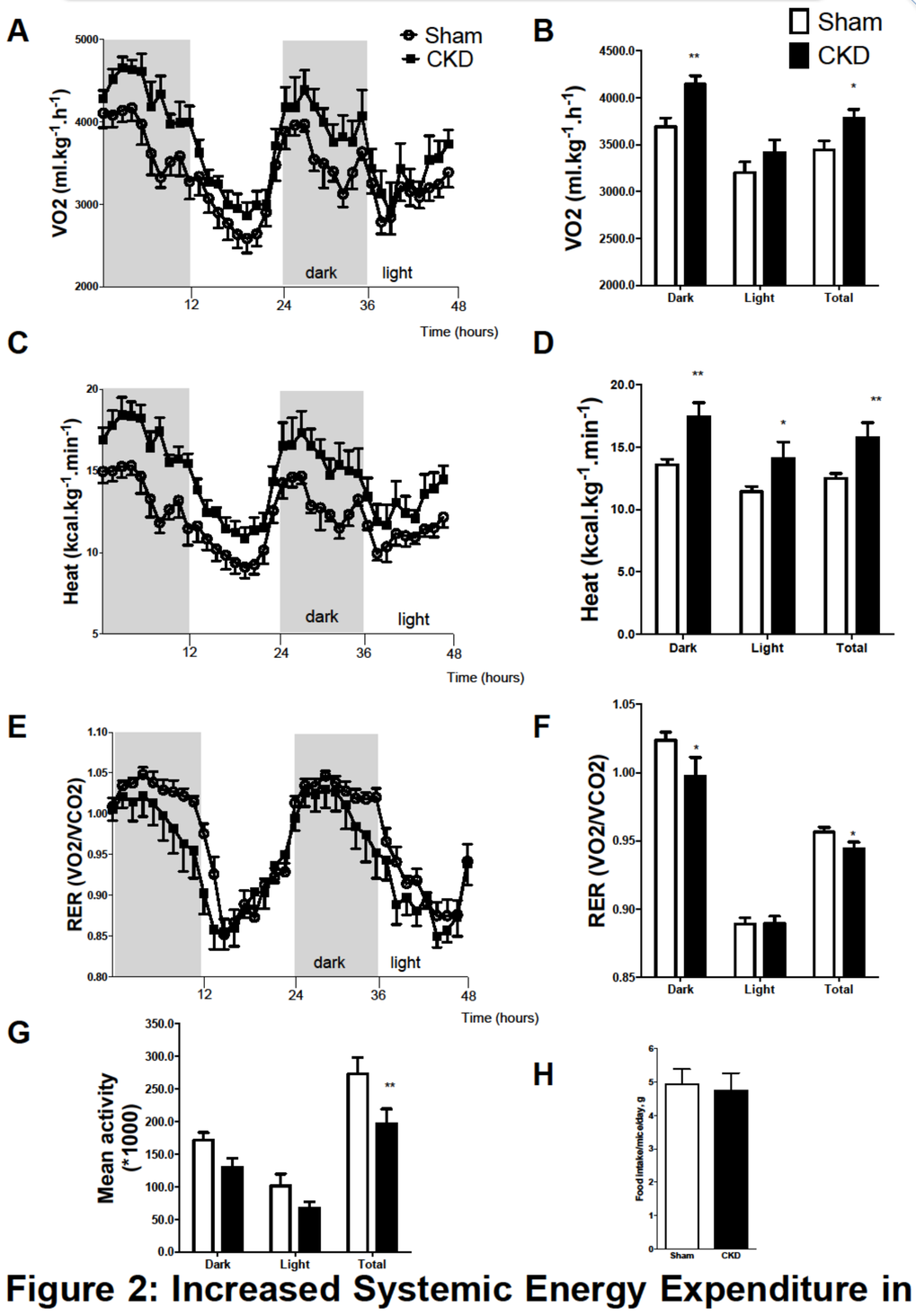


Figure 2: Increased Systemic Energy Expenditure in 5/6 nephrectomy mice without increase food intake or activity.

Sham and CKD were housed individually in metabolic cages. **A**-Oxygen cunsumption (VO_2) at each time point and **B**-Average of VO_2 over the last 2 days; **C**-Heat production at each time and **D**-average of heat production over the last 2 days; **E**-Respiratory exchange ratio (RER) at each time point and **F**-average RER over the last 2 days; **G**-Overall motility; **H**- Food intake. N=6 per group. Data are presented as mean ± SEM. Statistical analysis was conducted using the two-tailed t-test. *p < 0.05; **p < 0.01.

Biometry

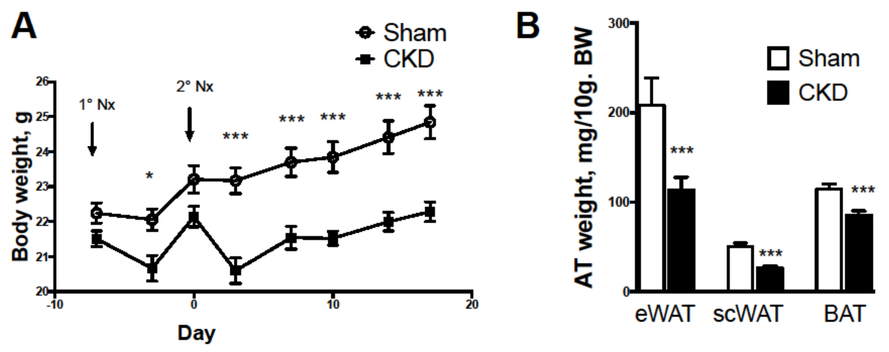
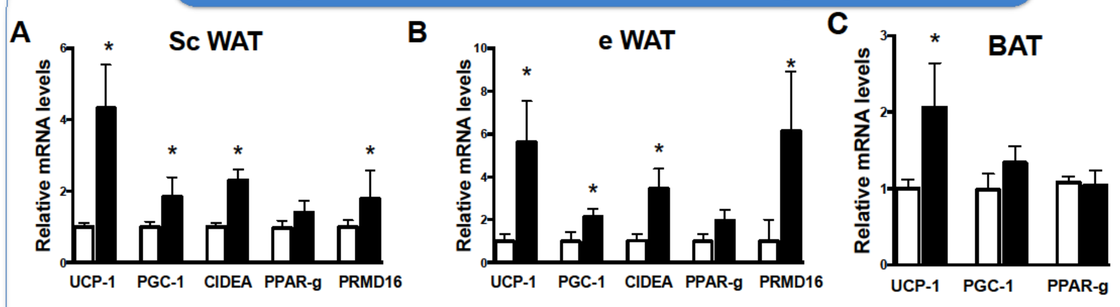


Figure 1: CKD cause cachexia.

A-Evolution of body weight (Nx: Nephrectomy); **B**-Weight of fat (eWAT: epididimal; scWAT: subcutaneous; BAT). The values are mean ± SEM. Statistical analysis was conducted using the two-tailed t-test. N=6 *p<0.05; ***p < 0.001 compared with the sham group.

Expression of genes implicated in thermogenesis



UCP-1: uncoupling protein 1; PGC-1:Peroxisome proliferator-activated receptor-gamma coactivator 1; CIDEA: Cell death activator CIDE-A; PPAR-g: Peroxisome Proliferator-Activated Receptor Gamma; PRMD16: PR domain containing 16.

Figure 3: CKD stimulates thermogenic gene expression WAT and BAT

mRNA levels in scWAT (**A**), eWAT (**B**), BAT (**C**). The values are mean ± SEM. N=3-5 Statistical analysis was conducted using the two-tailed t-test. *p<0.05; compared with the sham group.

Conclusion

CKD is associated with a **hypermetabolic state**, presumably resulting from **activation of brown adipose tissue and browning** of white adipose tissue. Further studies are needed to explore the mechanisms of brown fat activation and his role in increased REE in CKD. Inhibition of browning could represent a new therapeutic approach to prevent cachexia in CKD patients.

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