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CPT1C deficient mice show increased hypothalamic 2-AG levels and impaired leptin and diet-induced thermogenesis

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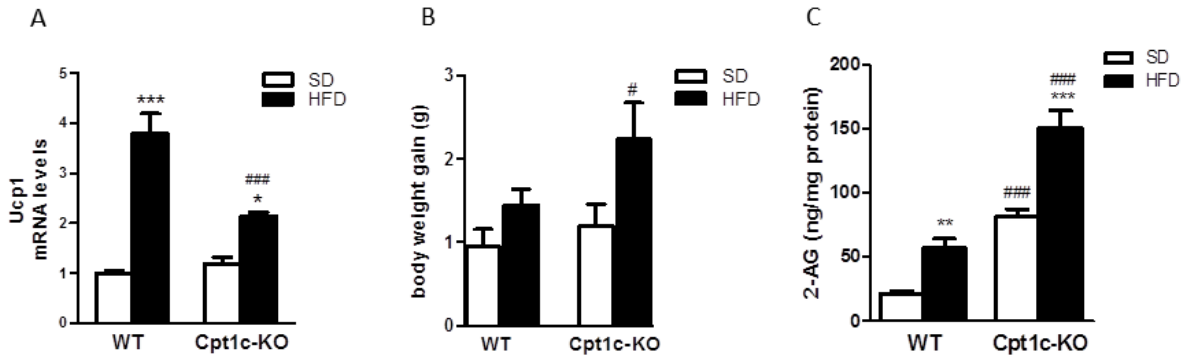
Introduction: Carnitine palmitoyltransferase 1 (CPT1) C is a brain specific isoform of the CPT1 enzymes family. CPT1C knock-out (KO) mice show an increased susceptibility to diet and leptin-induced obesity and impaired energy expenditure, although the molecular mechanisms underlying these effects are still unknown[1]. In relation to this, it has been described that administration of a high fat diet (HFD) changes hypothalamic levels of the endocannabinoid 2-arachidonoylglycerol (2-AG)[2] and that modifications in 2-AG levels regulates brown adipose tissue (BAT) thermogenesis[3]. Our objectives were to elucidate whether CPT1C is involved in the regulation of BAT thermogenesis through the modulation of hypothalamic 2-AG levels.

Methods: WT and CPT1C KO male mice were fed a standard (SD) or HFD for 7 days. Body weight and food intake were controlled. Hypothalamic 2-AG and AEA levels were measured by HPLC-MS/MS[4]. Thermogenesis activation of interscapular BAT (iBAT) was measured by infrared camera and BAT thermogenic gene markers (UCP1, PGC1a and PRMD16) were analyzed by real-time RT-PCR . BAT thermogenesis was also monitored after 4h-icv administration of leptin (0.1µg/µL) in WT and CPT1C KO mice.

Results: CPT1C KO mice showed an attenuated activation of iBAT temperature and thermogenic markers in response to central leptin or acute HFD. Moreover, CPT1C KO animals fed a HFD became hyperleptinemic and gained higher body weight than WT mice with HFD administration. Analysis of hypothalamic endocannabinoids revealed increased levels of 2-AG and AEA in CPT1C KO mice compared to WT animals either at basal condition or after HFD.

Fig. 1: Ucp1 mRNA relative levels in BAT (A), body weight gain (B), and hypothalamic 2-AG levels (C) after 7 days of HFD (*P<0.05 vs its corresponding strain with SD; #P<0.05 vs WT with its corresponding diet). Dara are media ± SEM (n=6-10) and statistical analysis was performed using One-Way ANOVA followed by a Bonferroni post-test.



Conclusions: Our data demonstrate that CPT1C is involved in the regulation of BAT thermogenesis and suggest that CPT1C could exert its effects through the modulation of hypothalamic endocannabinoid metabolism.

References:

1. N. Casals et al., 2016. *Progress in Lipid Research* **61**: 134-148

2. S. Higuchi et al., 2011. *Behavioural Brain Research* **216**: 477-480

3. Fisette A. et al., 2016. *Cell Reports* **17**, 1217-1226

4. Gong Y. et al., 2015. *J. Pharmaceutical and Biomedical Analysis* **111**: 57-63