Poster

Role of the cardiotrophin-1 in the physiological adaptation to fasting

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Keywords: Cardiotrophin-1; fasting; metabolic adaptions

ABSTRACT

Motivation: Cardiotrophin-1 (CT-1) is a member of the interleukin-6 (IL-6) family of cytokines. CT-1 is expressed in several metabolic tissues and it is a nutritionally regulated metabolic gene with a key role in glucose and lipid metabolism (1). CT-1 is expressed in white adipose tissue (WAT) and it has been reported to be upregulated in the metabolic syndrome. Our goal was to investigate the role of CT-1 in metabolic adaptations. We analysed the role of CT-1 in fasting, a physiological stress that elicits well-known metabolic adaptations (2, 3).

Methods: A differential study was carried out with wild type (WT) and CT-1 deficient animals. Mice were fed or fasted for 24 or 48 hours. Mice were males of 10-16 weeks of age. Glucose, free fatty acid (FFA) and ketone bodies were determined. WAT, liver and skeletal muscle were examined. Analysis of proteins was studied by Western-blot, mRNA levels were quantified by real-time PCR and histological studies were performed with H&E staining. We performed immunohistochemistry in WAT with tyrosine hydroxylase (TH) to determine sympathetic innervation. Adipocyte size was quantified using the software adiposoft.

Results: CT-1 mRNA expression in WAT increased markedly when mice were subjected to 48 hours fast. We did not observe any differences between WT and CT-1 null mice in fed state. However, by nutrient deprivation (24 and 48 hours) CT-1 knock-out mice exhibited less weight loss and a higher visceral adiposity compared to WT mice. The increase of FFA and ketone bodies in serum was reduced in CT-1 null mice as compared to WT animals. Analysis of WAT showed lower levels of phosphorylation (Ser-563 and 660) of the main lipase HSL (hormone sensitive lipase) in CT-1-/- mice at 48 hours as well as the levels of lysosomal acid lipase (Lipa), genes involved in lipophagy such as lysosome-associated membrane protein 1 (LAMP1), autophagy-related genes (ATG) and the LC3II/LC3I ratio. We analysed activation of AMPK (AMP-activated protein kinase) and the forkhead homeobox type O1 (FoxO1) transcription factor in WAT. In fasted animals, WAT from CT-1-/- mice showed higher number of increased adipocyte size with less expression of TH immunostaining as compared to WT animals. Analysis of the liver showed that fasting-induced lipid droplet formation was impaired in CT-1 null mice together with a higher LC3II/LC3I ratio.

Conclusions: Our findings suggest that CT-1 plays a relevant role in fasting adaptation.

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