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

David Careros (1), José M. Vélez (1), Matilde Bustos (1*)

(1) Oncohematología Genética. Cirugía oncológica, Terapia celular y Transplante de órganos. Instituto de Biomedicina de Sevilla (IBiS). CSIC-US-HUVR. Sevilla

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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.

REFERENCES


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