Liver Mitochondria Isolated from Nicotinamide Nucleotide Transhydrogenase Deficient Mice ($NNT^{-/-}$) are More Sensitive than Controls to Disfunction Induced by High- Fat Diet

Navarro, C.D.C[1]; Dal'Bó, G.A.[1]; Ronchi, J.A.[1]; Figueira, T.R.[1]; Rovani, J.C.[2]; Oliveira, H.C.F.[2]; Castilho, R. F. [1]; Vercesi, A.E.[1]

[1]Departamento de Patologia Clínica, Faculdade de Ciências Médicas, Universidade Estadual de Campinas, Campinas, SP, Brasil; [2] Departamento de Biologia Estrutural e Funcional, Instituto de Biologia**,** Universidade Estadual de Campinas, Campinas, SP, Brasil.

High fat diet (HFD) may induce obesity and fatty liver diseases, which are associated with mitochondrial dysfunction and redox imbalance. Nicotinamide nucleotide transhydrogenase (NNT) is a mitochondrial source of NADPH and plays a role in redox homeostasis and may be associated with obesity. Thus, the aim of this study is to investigate whether NNT modifies adiposity and liver mitochondria responses to chronic HDF. Previously, *Nnt* wild-type (C57BL/6/JUnib) was used as control and compared to *Nnt* mutant (C57BL/6J) mice fed with HDF. Here, we submited NNT-mutated ($NNT^{-/-}$) and wild-type ($NNT^{+/+}$) congenic mice to a chow or HFD for 20-weeks. We observed higher adiposity (36-51%) and content of hepatic triglycerides (43%) in $NNT^{-/-}$ compared to $NNT^{+/+}$ on HFD. In isolated liver mitochondria, no alterations were found in mitochondrial respiration but HFD increased by 22% the H_2O_2 release from $NNT^{-/-}$ mitochondria compared with $NNT^{+/+}$ on a HFD. In addition, compared to chow, HFD reduced the ability of mitochondria from $NNT^{-/-}$ to metabolize peroxide by 52%, which was reversed in the presence of ADP or ADP plus oligomycin A. HFD did not impair peroxide metabolism by $NNT^{+/+}$ mitochondria. Taken together, NNT displayed a protective role against the deleterious effects of HFD on liver mitochondria redox balance. The disruption in redox homeostasis due to NNT loss seems to favor steatosis development and body adiposity.

Keywords: Nicotinamide nucleotide transhydrogenase (NNT); high fat diet (HFD); C57BL/6J.

Supported by: CAPES. CNPq and FAPESP.