LIVER MITOCHONDRIA ISOLATED FROM NICOTINAMIDE NUCLEOTIDE TRANSYTHROGENASE DEFICIENT MICE (C57BL/6J) ARE MORE SENSITIVE THAN CONTROLS TO DISFUNCTION INDUCED BY HIGH-FAT DIET


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Obesity is known to increase the incidence of hepatic diseases including nonalcoholic steatohepatitis (NASH) which evolution is associated with mitochondrial dysfunction and redox imbalance. In this regard, it is known that mitochondrial nicotinamide nucleotide transhydrogenase (NNT) has a role in redox homeostasis and may be associated with obesity. Thus, the aim of this study is to investigate a possible role of NNT activity in liver mitochondria disturbances caused by high-fat diet (HDF) induced obesity. For this purpose, Nnt mutant (C57BL/6J) was compared to Nnt wild-type (C57BL/6/JUnib) mice fed a HFD. Mitochondrial parameters as oxygen consumption, calcium ion uptake and retention capacity, \( \text{H}_2\text{O}_2 \) production rate and organic peroxide metabolization were evaluated in liver mitochondria isolated from Nnt wild type and Nnt mutant mice after 18-week on a chow or HFD treatment. We observed higher weight gain in Nnt mutant mice up to 40% compared with Nnt wild-type under HFD. No alterations were found in mitochondria respiration but HFD increased \( \text{H}_2\text{O}_2 \) production by 41% in Nnt mutant and 32% in wild type mice (p < 0.05). In addition, HFD reduced both organic peroxide metabolization and \( \text{Ca}^{2+} \) retention capacity by 50% in Nnt mutant mice compared with chow diet. Such a HFD effect was not seen in wild type mitochondria. Taken together, these results show that an association between the lack of NNT and HDF leads to redox homeostasis disruption, higher susceptibility to \( \text{Ca}^{2+} \)-induced mitochondrial permeability transition and exacerbated weight gain. Furthermore, redox state regulation by NNT seems to have a protective role on the deleterious effects of by HFD. These may be relevant for NASH development in C57BL/6J mice model.

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

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