

# Sex-dependent effect on mitochondrial and oxidative stress parameters in the hypothalamus induced by prepubertal stress and access to high fat diet

Ana Paula Toniazzo, Danusa Mar Arcego, Camilla Lazzaretti, Carina Mota, Carlos Eduardo Schnorr, Letícia Ferreira Pettenuzzo, Rachel Krolow, Jose Claudio Fonseca Moreira, Carla Dalmaz

## Abstract

Objective: Some factors related to lifestyle, including stress and high-fat diet (HFD) consumption, are associated with higher prevalence of obesity. These factors can lead to an imbalance between ROS production and antioxidant defenses and to mitochondrial dysfunctions, which, in turn, could cause metabolic impairments, favoring the development of obesity. However, little is known about the interplay between these factors, particularly at early ages, and whether long-term sex-specific changes may occur. Here, we evaluated whether social isolation during the prepubertal period only, associated or not with chronic HFD, can exert long-term effects on oxidative status parameters and on mitochondrial function in the whole hypothalamus, in a sex-specific manner. Methods: Wistar male and female rats were divided into two groups (receiving standard chow or standard chow + HFD), that were subdivided into exposed or not to social isolation during the prepubertal period. Oxidative status parameters, and mitochondrial function were evaluated in the hypothalamus in the adult age. Results: Regarding antioxidant enzymes activities, HFD decreased GPx activity in the hypothalamus, while increasing SOD activity in females. Females also presented increased total thiols; however, non-protein thiols were lower. Main effects of stress and HFD were observed in TBARS levels in males, with both factors decreasing this parameter. Additionally, HFD increased complex IV activity, and decreased mitochondrial mass in females. Complex I-III activity was higher in males compared to females. Conclusion: Stress during the prepubertal period and chronic consumption of HFD had persistent sex-specific effects on oxidative status, as well as on its consequences for the cell and for mitochondrial function. HFD had more detrimental effects on females, inducing oxidative imbalance, which resulted in damage to the mitochondria. This HFD-induced imbalance may be related to the development of obesity.

Keywords:

oxidative stress, Mitochondrial dysfunctions, Lipid peroxidation, Mitochondrial mass