INFLAMMATION AND ENDOPLASMIC RETICULUM STRESS PRECEDES MITOCHONDRIA DYSFUNCTION IN THE HYPOTHALAMUS OF DIET-INDUCED OBESE MICE

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Dietary fats are known to induce inflammation and dysfunction of the hypothalamus leading to increased caloric intake and reduced energy expenditure. Originally, TLR4 signaling and endoplasmic reticulum stress have been identified as potential triggers of this process. However, recently, hypothalamic mitochondrial dysfunction have been shown to occur in the hypothalamus of obese rodents suggesting that an additional mechanism could play a role as a trigger of the inflammatory response to dietary fats. Here, we evaluated the time course of events leading to the installation of dysfunction in the hypothalamus of mice fed on a high-fat diet. We used real-time PCR, immunoblot and transmission electron microscopy to evaluate changes in markers of inflammation, endoplasmic reticulum stress and mitochondria dysfunction. The chaperone, GRP78, and the chemokine, fraktalkine, were the first proteins undergoing a change, as early as six hours after introduction of dietary fats. Twelve hours after introduction of dietary fats we further detected the increases of IL10 and ATF6; and 24 h after introduction of dietary fats there were increases of IL1\textbeta, TNF\alpha, IL6 and mitofusin-2. Mitofusin-1 is changes only after three days on dietary fats. In the transmission electron microscopy experiments, changes in hypothalamic neuron mitochondria morphology, particularly swollen mitochondria with alteration in the aspect of the crests, were detected only after three days on dietary fat. We conclude that dietary fats induce a very early change in the expression of inflammatory and endoplasmic reticulum stress proteins, whereas changes in mitochondria proteins and mitochondria morphology are late events. Thus, dysfunction of hypothalamic neurons in diet-induced obesity may occurs as a consequence of an early activation of endoplasmic reticulum stress and inflammation. Acknowledgements: FAPESP. Keywords: Obesity, mouse, hypothalamus.