Oleoylethanolamide mitigates cardiac metabolic alterations secondary to obesity induced by high-fat diet in C57/BL6J mice

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Background: It is well known that high-fat diet (HFD) feeding causes cardiac inflammation, remodeling, and dysfunction, and that increased fat intake, especially saturated fat, is a major driver of cardiometabolic diseases. Oleoylethanolamide (OEA) is a member of acylethanolamides recognized for its metabolic and anti-inflammatory properties due to the high affinity for different receptors and to its role as a modulator of the endocannabinoid system. OEA effects on the cardiovascular alterations caused by fat overnutrition are still unknown.

Purpose: The aim of this study was to evaluate the impact of OEA treatment on cardiac metabolic changes induced by HFD in obese mice.

Methods: Male C57Bl/6J mice were divided into 3 groups: control group (STD) receiving standard chow diet; mice fed with HFD for 20 weeks; HFD group treated with OEA (HFD+OEA 2.5 mg/kg/die i.p.) from week 12 to week 20.

Results: In HFD mice, OEA treatment reduced body weight measured throughout the experimental period. Before sacrifice, we performed the oral glucose tolerance test (OGTT), where HFD+OEA mice showed an improvement of insulin sensitivity, altered by HFD. HFD feeding led to a significant increase in the production of inflammatory cytokines and chemokines, such as interleukin (IL)-1β, IL-6, the monocyte chemoattractant protein (MCP)1 and the pro-fibrotic marker fibrillin in the cardiac tissue. Conversely, OEA normalized the transcription of the above-mentioned pro-inflammatory mediators in the heart of obese mice. OEA treatment also reduced the gene expressions levels of cardiac fatty acid transporter CD36, that were significantly induced in the heart of HFD-fed mice, and that have been found to be linked to myocardial lipid accumulation. We also evaluated the gene expression levels of the adipokines adiponectin and meteorin-like protein (Metrnl), finding that the increased ventricular expression of both in HFD mice were significantly reduced by OEA. Moreover, OEA treatment induces an increase in AMPK and AKT phosphorylation, whose pathways converge towards the phosphorylation of AS160, a kinase implicated in the translocation of the glucose transporter (GLUT) 4 to the cardiomyocyte membrane, a mechanism involved in the modulation of cardiac glucose metabolism.

Conclusions: Taken together, our results indicate a potential cardioprotective effect of OEA as a molecule able to reduce body weight and body weight gain, to ameliorate glucose disposal improving blood glucose, to restore cardiac metabolic alterations related to obesity, and to decrease proinflammatory and profibrotic markers at cardiac level, induced by HFD.