The role of palmitoylethanolamide (PEA) in the regulation of glucose homeostasis and central neuronal function in an animal model of diet-induced obesity

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Obesity is a complex, chronic disease and results from an imbalance between food intake, basal metabolism and energy expenditure (1). Fatty acyl ethanolamides are a class of endogenous lipid molecules and are generally referred to as N-acylethanolamines (NAEs) (2). Among NAEs, palmitoylethanolamide (PEA) is gaining ever-increasing interest not only for its anti-inflammatory and analgesic effects (3), but also for its novel metabolic activity mediated by peroxisome-proliferator activated receptor (PPAR)-Î± (4).
The aim of this project was to determine the pharmacological effects of PEA in an animal model of diet-induced obesity, feeding the animals with an high fat diet (HFD) and the mechanisms by which this lipid mediator could modulate central neuronal function involved in the storage and availability of energy sources, restoring lipid/glucose homeostasis. After weaning, C57BL/6J mice were randomly divided into four groups as follows: 1) control group (STD) receiving chow standard diet (12.1% fat); 2) STD group treated with PEA (30 mg/kg/die per os); 3) HFD group receiving high fat diet (45% fat); 4) HFD group treated with PEA (30 mg/kg/die per os). The treatment started after 12 weeks of feeding with HFD and continued for 10 weeks. During the experimental period body weight and blood pressure were monitored. One week before sacrifice, oral glucose tolerance test (OGTT) and insulin tolerance test (ITT) were performed. At the end of the experimental protocol, before sacrifice, bioelectrical impedance analysis was applied to determine fat body composition. Blood samples were collected and liver and hypothalamus were excised and frozen for following determinations.
Interestingly, PEA caused a reduction in body weight, improving glucose tolerance and preventing insulin-resistance induced by HFD feeding. Moreover, PEA restored the alterations of serum biochemical and inflammatory parameters underlined a marked reduction of ALT, AST, cholesterol and pro-inflammatory cytokines such as TNF-Î±, IL-1 and MCP-1. PEA also normalized serum levels of metabolic hormones and restored insulin sensitivity, as shown by HOMA index.
At hepatic level, PEA treatment significantly increased the phosphorilation of AMPK, stimulating fatty acid oxidation, compromised in obese mice. To evaluate tissue insulin-sensitivity, we determined the hepatic expression of the insulin receptor (IR), whose expression decreased in liver of HFD mice compared to that of STD animals, and increased in PEA-treated mice. Then, we evaluated the effectiveness of insulin signaling through the evaluation of AKT phosphorylated state and the expression of GLUT-2. PEA treatment restored the phosphorylation of AKT and expression of GLUT-2 in HFD animals. The evaluation of hepatic IL-6 and TNF-Î±, two cytokines related to liver inflammation and insulin-resistance, strengthened the protective effect of PEA, in reducing the upregulated transcription by HFD feeding.
To examine the arcuate (ARC) and ventromedial (VMH) neuronal activation, c-fos immunostaining was performed. In the ARC nucleus of HFD mice, a decrease in c-fos labeling was found. Interestingly, in the PEA-treated group, a trend of c-fos labeling increase was evidenced. Conversely, in the VHM of HFD mice a significant decrease in the neuronal activation was shown compared to STD mice. In this case, no differences were found between the HFD and PEA-treated mice.
Our data strengthened evidence on the metabolic activity of PEA, and showed the involvement of central and peripheral mechanisms. PEA clearly ameliorates glucose-tolerance and insulin-sensivity, indicating its therapeutic potential for the treatment of metabolic dysfunctions associated to obesity, such as insulin-resistance and type 2 diabetes.

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