PALMITOYLETAHNOLAMIDE ATTENUATES INSULIN RESISTANCE AND HEPATIC STEATOSIS IN DIET-INDUCED OBESE MICE.

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The relationship between obesity, insulin-resistance (IR) type 2 diabetes mellitus (T2DM) and MetS is well known (1). IR is defined as an inefficient glucose uptake and utilization in peripheral tissues in response to insulin stimulation. A potential link between inflammation and IR has been shown. Indeed, obesity is characterized by chronic low grade inflammation, where the release of adipose tissue-derived cytokines can block insulin action and cause systemic IR. It has been demonstrated a role of fatty acid ethanolamide in control of feeding behavior (2), in particular palmitoylethanolamide (PEA) has been demonstrated to reduce food intake and body weight, correcting leptin resistance at hypothalamic level, and increasing the catabolic pathway of fatty acids in white adipose tissue in model of mild obesity induced by ovariectomy in the rat (3).

Our study was focused on the pharmacological effect of PEA in an animal model of diet-induced obesity (DIO), feeding mice with a high-fat diet (HFD), and on the mechanisms by which this lipid mediator could modulate the storage and availability of energy sources, restoring lipid/glucose homeostasis. To this aim, mice were fed a standard chow diet (STD group) or HFD (DIO group). After twelve weeks, both STD or HFD mice were treated with PEA (30 mg/kg/day, o.s.) for ten weeks. At the end of the experimental period, body parameters were determined, and serum and tissues collected for following determinations.

Interestingly, PEA caused a reduction in body weight and fat mass, improved glucose tolerance and prevented IR, induced by HFD feeding. Moreover, PEA restored the alterations of serum biochemical and inflammatory parameters, inducing a marked reduction of ALT, AST, cholesterol, and pro-inflammatory cytokines, such as TNF-α, IL-1 and monocyte chemoattractant protein (MCP)-1. PEA also normalized metabolic hormone levels and restored insulin sensitivity. At hepatic level, PEA treatment significantly induced an increase in the activation AMPK/ACC pathway, stimulating fatty acid oxidation, compromised in obese mice. To evaluate tissue insulin-sensitivity, we determined the hepatic expression of the InsR, whose expression decreased in liver of DIO mice compared to that of STD animals, and increased in PEA-treated mice. Then, we evaluated the effectiveness of hepatic insulin signaling through the evaluation of InsR and Akt phosphorylated state and the expression of GLUT-2. PEA treatment restored insulin signaling. The protective effect of PEA was strengthened by the evaluation of hepatic IL-6 and TNF-α, whose transcription, upregulated by HFD feeding, was reduced.

To address the direct effect of PEA on hepatic insulin-sensitivity, we evaluated the restoration of insulin signaling, altered by the induction of IR, in HepG2 cells, a human hepatocarcinoma cell line. Therefore, we demonstrated in vitro that PEA increased the phosphorylation of Akt in insulin resistant cells, following insulin stimulation.

In vitro studies, using human SH-SY5Y neuroblastoma cell line, also indicated a modulation of glucose homeostasis at central level. When insulin-resistant cells were treated with PEA, the re-stimulation with insulin showed a restoration of Akt phosphorylation compromised in untreated insulin resistant cells, and therefore of insulin-sensitivity. These findings show that this acylethanolamide also displays a central effect on glucose homeostasis, reducing neuronal IR. Our data strengthened evidence on the metabolic activity of PEA, through the involvement of central and peripheral mechanisms. PEA clearly ameliorates glucose-tolerance and insulin-sensitivity, indicating its therapeutic potential for the treatment of metabolic dysfunctions associated to obesity, such as IR and T2DM.

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2. Mattace Raso et al (2014). Pharmacol Res. 86,32-41.

3. Mattace Rasoet al (2014). Endocrinology. 155(4),1291-301.