Palmitoylethanolamide prevents metabolic alterations and restores leptin sensitivity in ovariectomized rats

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Recently it has been suggested a role of fatty acid ethanolamides in control of feeding behavior (Hansen and Diep, 2009). Among these, palmitoylethanolamide (PEA) has been described as a well known anti-inflammatory compound, but it has not been directly implicated in appetite regulation and weight gain.
The aim of the present study was to investigate whether a chronic treatment with PEA modulates feeding behavior and weight gain through the modulation of hypothalamic leptin signaling and orexigenic or anorexigenic peptides.
To this purpose, we used a rat model of mild obesity induced by ovariectomy. Five weeks after surgery, a group of ovariectomized rats (OVX) were treated with palmitoylethanolamide (PEA; 30 mg/kg/daily s.c.). Control sham operated rats (SHAM) and OVX rats received the vehicle. All treatments continued for five weeks.
Here, we showed that in ovariectomized rats chronic administration of PEA causes a time-dependent decrease of food intake and body weight, accompanied by a reduction of fat mass. Moreover, PEA lowered plasmatic leptin levels, that were up-regulated in ovariectomized rats. In order to investigate the modifications of leptin signaling induced by PEA and its capability to restore hormone sensitivity, we evaluated the expression of the functional isoform of leptin receptor (Ob-Rb) in the hypothalamus and several modulators of its activation. We found not only an increase in Ob-Rb expression in PEA treated OVX rats, but also a reduction in the suppressor of cytokine signaling 3 (SOCS3) and in the protein tyrosine phosphatase 1B (PTP1B), two inhibitors of receptor signaling. The restoration of central leptin sensitivity was also shown through an increase of signal transducer and activator of transcription (STAT)-3 phosphorylation in the hypothalamus of OVX rats treated with PEA. Accordingly with the restoration of leptin signaling transduction, we found a reduction of Agouti related peptide and an increase in proopiomelanocortin transcription, a typical hypothalamic expression pattern associated to improvement of feeding behaviour.
Hystological analysis of white adipose tissue revealed a hypertrophic phenotype in OVX animals, which was reverted by PEA treatment. Moreover, we found an increase in AMP-activated protein kinase (AMPK)-α phosphorylation and CTP1 transcription, suggesting an increase in ATP-producing catabolic pathway. Furthermore, the expression of several cytokines and adipokines suggested a shift in the activation state of adipose tissue macrophages (ATM) from an anti-inflammatory M2 state to an inflammatory M1 state following PEA treatment. The above findings suggest that several interactions take place between PEA and leptin, resulting in reduction of food intake and body weight and involving leptin sensitivity at hypothalamic level. The reduction of weight gain induced by PEA is also accompanied by a reduced inflammatory state of the macrophagic infiltrate in white adipose tissue and cytokine production responsible of the metabolic dysfunctions associated with obesity-linked disorders.

Hansen HS, Diep TA N-acylethanolamines, anadamide and food intake. Biochemical Pharmacology 2009; 78:553-560