High dietary fat intake influences the central effects of the satiety factor oleoylethanolamide: possible implications for obesity management

A. Romano, S. Gaetani

Dept. of Physiology and Pharmacology 'V. Erspamer', Sapienza University of Rome, Rome, Italy

The adaptation to particular dietary regimens can alter the mechanisms through which the central nervous system (CNS) senses nutrient availability. These alterations might alter the homoestatic mechanisms involved in the regulation of food intake and energy balance and might contribute to the development of aberrant eating patterns and/or obesity, as suggested by several experimental observations on the effects of the chronic exposure to high amounts of dietary fat (HFD).
In this study we investigated whether increasing the fat content of the diet can affect the CNS response to the anorexigenic factor oleoylethanolamide (OEA).
OEA is a gut-derived satiety signal released from enterocytes upon the ingestion of dietary fats. The anorexigenic effect of OEA, which requires intestinal peroxisome proliferator-activated receptor alpha and is supposedly mediated by vagal afferents, is associated with the induction of c-fos in several brain areas involved in the control of food intake, such as the nucleus of the solitary tract (NST) and the hypothalamic tuberomammillary (TMN) paraventricular (PVN) and supraoptic nuclei (SON). In the PVN and SON *c-fos* is induced in oxytocin (OXY) neurons and this activation is paralleled by increased peptide neurosecretion, elevated circulating OXY levels (Gaetani et al., 2010; Romano et al., 2013a) and appears to be regulated by the histaminergic projections from the TMN (Provensi et al., 2014). Moreover, noradrenergic projections from the NST to the TMN and to the PVN are likely involved in mediating the effects of OEA in the hypothalamus (Romano et al., 2013b).
In the present study, we aimed to investigate whether the exposure to a HFD alters the hindbrain and hypothalamic responses to OEA. To this purpose we evaluated the effects of OEA, administered at a dose able to inhibit eating (10mg/kg i.p.), on the induction of c-fos in the NST, area postrema (AP), PVN and SON in rats maintained either on standard chow or a HFD. Furthermore, we evaluated whether the exposure to the HFD could modify the effects of OEA on OXY mRNA expression in the PVN and SON.
The results showed that i.p. OEA, at a dose and at a time-point that cause a significant inhibition of eating, stimulates *c-fos* expression in specific subnuclei of the brainstem and hypothalamus with a pattern that differed markedly between rats fed a HFD and rats fed the standard chow. In fact, we observed for the first time that HFD exposure attenuated the neuronal activation induced by OEA in all areas of the brainstem analysed (central (SolC), medial (SolM), dorso-medial (SolDM), lateral (SolVL) NST and the AP) and mostly at -13.80 mm from bregma, where the AP reaches its maximum extension. Interestingly, the exposure to the HFD altered the neuronal response to OEA also at the hypothalamic level. In fact, the PVN of HFD-fed rats showed a greater sensitivity to OEA, with an increase of *c-fos* levels. The altered OEA neuronal responses in HFD rats are paralleled by altered behavioral effects, thus HFD-fed rats were also more sensitive to the immediate hypophagic action of OEA than chow-fed rats. In fact OEA's inhibitory effects on eating were greater in HFD-fed rats than in chow-fed rats. Finally OXY mRNA expression within the PVN and SON after i.p. OEA, was not significantly affected in either brain areas of either diet group.
Our results indicate a cause–effect link between prolonged consumption of fat-enriched diet and an altered central responsiveness to peripherally administered OEA. The present study further expands our knowledge on the relationship between ingestion of dietary fat and the activation of brain areas involved in the homeostatic control of food intake.

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