Novel insights on the central mechanisms mediating the hypophagic effects of oleoylethanolamide

J.B. Koczwara[1*], A. Romano[1*], C.A. Gallelli[1], F.E. Braegger[2], T.A. Lutz[2], S. Gaetani[1]

[1]Dept. of Physiology and Pharmacology 'V. Erspamer', Sapienza University of Rome, Rome, Italy
[2]Institute of Veterinary Physiology, Vetsuisse Faculty, University of Zurich, Zurich, Switzerland

* Equal contribution

The spread of 'obesity epidemic' and the poor efficacy of many anti-obesity therapies in the long-term highlight the need to develop novel efficacious therapy. This necessity stimulates a large research effort to find novel mechanisms controlling feeding and energy balance. Among these mechanisms a great deal of attention has been attracted by the endogenous lipid oleoylethanolamide (OEA).

OEA is a gut-derived satiety signal released from enterocytes upon the ingestion of dietary fat. The anorexigenic effect of OEA, which requires intestinal peroxisome proliferator-activated receptor-alpha (PPAR-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), the area postrema (AP), and the hypothalamic tuberomammillary (TMN) paraventricular (PVN) and supraoptic nuclei (SON). In the PVN and SON *c-fos* is induced in oxytocin (OXY) neurons; this activation is paralleled by increased OXY neurosecretion and 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). In the NST *c-fos* transcription is induced in specific subnuclei (Romano et al., 2014), especially those in close contact with the AP; 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).

The mechanisms responsible for NST activation remained poorly understood. Although previous reports suggested an involvement of visceral afferent fibres, contrasting novel findings (Azari et al, 2013) led us to hypothesize the activation of an alternative pathway through which OEA may exert its central effects. This pathway might involve the AP, a region of the hindbrain that lacks the blood-brain barrier, so that its receptors may be reached by circulating signals (Lutz et al., 1998).

To examine this hypothesis, we aimed to evaluate the relevance of AP in OEA-induced behavioural and neurofunctional effects. In particular, we subjected rats to a surgical lesion of AP, performed by aspirating the AP with a blunted cannula tip fixed to a tube attached to a vacuum pump (Lutz et al., 1998), and we evaluated the effects of peripheral OEA administration on feeding behaviour, and OXY immunoreactivity in the PVN, SON and in the pituitary gland.

In the behavioural experiment, we found that AP lesion prevented the anorexigenic effects of OEA, while these effects were maintained in sham-operated rats. Moreover, we found that in both PVN and SON the lesion of AP prevented the increase of OXY expression, which was maintained in sham-operated rats. Surprisingly, AP lesion did not have any influence on the increase of OXY immunoreactivity in the pituitary gland, an aspect that needs further investigation.

Altogether, these findings support the hypothesis that AP is involved in the activation of the NST that, in turn, leads to the activation of the hypothalamic OXY system, which is involved in mediating OEA's pro-satiety action.

Azari et al. (2013), *Am J Physiol Regul Integr Comp Physiol* 307, R167-R178.
Gaetani et al. (2010), *J Neurosci* 30, 8096-8101.
Lutz et al. (1998), *Peptides* 19, 309-317.
Provensi et al. (2014), *Proc Natl Acad Sci U S A.* 111, 11527-32.
Romano et al. (2013a), *Peptides* 49, 21-26
Romano et al. (2013b), *Am J Physiol Endocrinol Metab* 305, E1266-E1273.
Romano et al. (2014), *Physiol Behav* 136, 55-62