

ROLE OF THE AREA POSTREMA IN THE HYPOPHAGIC EFFECTS OF OLEOYLETHANOLAMIDE

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Oleoylethanolamide (OEA) is a naturally occurring lipid that acts as a satiety signal generated in the intestine upon the ingestion of fat. The pro-satiety effects evoked by systemic OEA administration are mediated by the activation of the peroxisome proliferator-activated receptor- α (PPAR- α) (Fu et al., 2003) and have been associated to the involvement of selected brain areas, such as the nucleus of the solitary tract (NST) in the brainstem and the tuberomammillary (TMN) and paraventricular (PVN) nuclei in the hypothalamus, where noradrenergic, histaminergic and oxytocinergic neurons play a necessary role (Romano et al., 2013; Provensi et al., 2014; Gaetani et al., 2010).

How OEA signal can reach the brain remained to be fully elucidated. Although visceral ascending fibers were hypothesized to mediate OEA's effects (Fu et al., 2003), recent findings demonstrated that the hypophagic action of peripherally administered OEA does not require intact vagal afferents (Azari et al., 2014) and is associated to a strong activation of the area postrema (AP) (Romano et al., 2014), a circumventricular organ that displays a weak blood brain barrier (BBB) and is located in close contact with the cerebral ventricles. These properties allow the direct access to the brain for circulating peptides and other peripheral signals (Lutz et al., 1998), which do not readily reach other areas of the brain parenchyma across the BBB. Therefore, we hypothesized that the AP might represent a receptive region for circulating OEA and that AP neurons might be the first central target of this lipid signal.

To test this hypothesis, we subjected rats to a surgical lesion of the AP (APX rats) and evaluated the effects of intraperitoneal OEA administration (10 mg kg⁻¹) on food intake, on Fos expression, on oxytocin immunoreactivity at the level of PVN and pituitary gland and on the expression of dopamine beta hydroxylase (DBH) within the brainstem and PVN. Further, we aimed to assess the phenotype of neuronal populations activated by OEA in the brainstem; to this aim, we assessed, also, whether OEA induced Fos expression co-localized with DBH as marker for noradrenergic neurons. Finally, as last step of our study, we investigated PPAR- α expression within the AP. SHAM-operated animals were used as controls.

The results obtained from the present study showed that the AP lesion completely prevented OEA's behavioral and neurochemical effects in the brainstem and in the hypothalamus. Moreover, OEA increased DBH expression in AP and NST neurons of SHAM rats while the effect in APX rats was absent, thus suggesting the possible involvement of noradrenergic AP neurons. We also found that OEA induced an increase of Fos expression in DBH-expressing positive neurons at the level of AP and NST, while this effect was completely prevented by the AP lesion. Interestingly, PPAR- α immunofluorescence in the AP clearly showed the expression of this receptor at this site.

Altogether, the results from the present study support the hypothesis of a necessary role of the AP in mediating OEA's central effects that sustain its pro-satiety action.

Azari et al. (2014), *Am J Physiol Regul Integr Comp Physiol* 307, R167-178.

Fu et al. (2003), *Nature* 425, 90-93.

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, 11527-11532.

Romano et al. (2013), *Am J Physiol Endocrinol Metab* 305, E1266-E1273.

Romano et al. (2014), *Physiol Behav* 136, 55-62.