Vagal afferents are not strictly necessary for the anorectic effect of the endogenous lipid oleoylethanolamide

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Obesity is currently a major worldwide public health issue. For this reason, during the last few years, research has focused on understanding the neurobiological mechanisms underlying the regulation of food intake and body weight to discover new drug targets in this area. Viscerosensory signals from the gut contribute to build a complex network of neural and hormonal signals that converge in the brain to control feeding behavior. The endogenous lipid oleoylethanolamide (OEA) appears to play a key role in this network by acting as a mediator of satiety. OEA is the monounsaturated analogue of the endocannabinoid anandamide that is released from enterocytes following the intake of dietary fat. These effects require the activation of peroxisome proliferator-activated-receptor-alpha (PPAR-alpha), and are associated with the activation of *c-fos* transcription in brain areas involved in the central control of satiety, such as the nucleus of the solitary tract (NST) and the hypothalamic paraventricular (PVN) and supraoptic (SON) nuclei. In both PVN and SON, *c-fos* mRNA is increased in neurons expressing oxytocin (OXY), whose activation is paralleled by increased OXY neurosecretion and elevated circulating OXY levels (Gaetani et al., 2010; Romano et al., 2013).
It has been recently demonstrated that OEA stimulates *c-fos* expression in specific subnuclei of the NST and strongly activates neurons of the area postrema (AP) (Romano et al., 2014).
Experimental evidence suggests that the anorectic effect of OEA is mediated by visceral afferent fibres, which are considered to play an important role in the transmission of many signals to the NST (Piomelli et al., 2013). This idea finds support in several studies, which have demonstrated that OEA's satiety effect is abolished in rats after treatment with the neurotoxin capsaicin or after a total subdiaphragmatic vagotomy (Fu et al., 2003; de Fonseca et al., 2001).
In this context we aimed to examine selectively the role of abdominal vagal afferents in OEA's hypophagic effect. For this purpose we subjected rats to a subdiaphragmatic vagal deafferentation (SDA), a surgical procedure that eliminates all abdominal vagal afferents but leaves about 50% of the vagal efferents intact (Norgren et al., 1994). We performed immunohistochemistry experiments to evaluate the *c-fos* expression pattern in specific subnuclei of the NST, in the AP and in the PVN; double immunofluorescence to test the co-expression of *c-fos* and OXY at PVN level and immunofluorescence experiments to evaluate OXY expression in the pituitary gland. In the behavioral experiment, we found that in both SDA and sham-operated rats OEA decreases food intake by significantly increasing the latency to eat and the intermeal interval. We observed, furthermore, an increase of *c-fos* expression in NST and AP in both SDA and sham-operated rats treated with OEA. Surprisingly, in the PVN OEA increases *c-fos* expression in sham-operated rats, but it seems to reduce this expression in SDA-operated rats. We also found that OEA induces an increase in the number of neurons co-expressing *c-fos* and OXY. Finally, at the level of the pituitary gland, we observed a decrease of OXY expression in both groups of SDA-operated rats, treated with vehicle and OEA, compared with sham-operated rats.
Our findings indicate that vagal afferents are not strictly necessary for the satiety effect of OEA. Moreover, the data obtained from the analysis of the AP seem to suggest that OEA can reach the central nervous system through a dual mechanism, which involves both vagal afferents and AP.

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