EFFECTS OF SUBDIAPHRAGMATIC DEAFFERENTATION ON OLEOYLETHANOLAMIDE-INDUCED FOS EXPRESSION IN BRAIN AREAS INVOLVED IN THE CONTROL OF FEEDING BEHAVIOR.

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Obesity is a worldwide public health issue. Research has focused on understanding the neurobiological mechanisms underlying the regulation of feeding behavior to discover new drug targets in this area. Visceral signals contribute to build a network of neural and hormonal signals that converge in the brain to control feeding. The endogenous lipid oleoylethanolamide (OEA), an agonist of the peroxisome proliferator-activated-receptor-alpha, plays 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 fat intake. OEA's effects are associated with c-fos transcription increase in 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), paralleled by increased OXY neurosecretion and elevated circulating OXY levels (Gaetani et al., 2010). Moreover, it has been demonstrated that the lesion of the noradrenergic projections from the brainstem to the hypothalamus prevents both behavioural and neurochemical effects of OEA on feeding (Romano et al.,2013).

The mechanisms responsible for NTS activation remained poorly understood. Although previous reports suggested an involvement of visceral afferent fibres (Fu et al., 2003), novel findings demonstrate that vagal afferent fibres are not strictly necessary to mediate OEA's pro-satiety effects (Azari et al, 2014). These findings suggest that OEA may exert its effects through the area postrema (AP), a region of the hindbrain that lacks the blood-brain barrier (Lutz et al., 1998). In this work, our aim was to investigate the role of abdominal vagal afferents in mediating OEA's effects on Fos expression in several brain areas involved in the control of feeding behaviour. To 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). Through immunohistochemical analyses of the brains of these rats, we evaluated Fos expression pattern in specific subnuclei of the NST, in the AP and in the hypothalamus. Moreover, we performed immunohistochemistry experiments to evaluate also the expression of dopamine-β-hydroxylase (DBH). The aim of these latter analyses was to assess weather the SDA could produce any alteration on noradrenergic neurones of the NST, which play a key role in the central effects of OEA. Sham-operated rats were used as controls.

As already found in the behavioural experiment, OEA decreases food intake by significantly increasing the latency to eat and the intermeal interval in both SDA and sham-operated rats.

Furthermore, consistently with the behavioural results, our neurochemical findings show that OEA increases Fos expression in the subnuclei of the NST and in the AP of both sham and SDA rats. As for the brainstem, OEA leads to the activation of different nuclei in the hypothalamus in both

sham and SDA rats. in keeping with the negative results obtained for Fos pattern, SDA did not cause any alteration of DBH expression in the areas analyzed.

Our findings indicate that vagal afferents are not strictly necessary for the satiety effect of OEA at both behavioural and neurochemical levels. 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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