SATIETY FACTOR OLEOYLETHANOLAMIDE PREVENTS BINGE-LIKE PALATABLE FOOD CONSUMPTION INDUCED BY STRESS IN FEMALE RATS WITH A HISTORY OF FOOD RESTRICTION

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Introduction: Several observations suggest that the lipid-derived satiety factor oleoylethanolamide (OEA) might represent a novel pharmacological target for the treatment of binge eating disorder. OEA inhibits food intake with a mechanism that appears behaviourally selective and associated to the activation of selected brain areas. These include the hypothalamic oxytocinergic neurons. The central administration of a selective oxytocin (OXY) receptor antagonist is able to prevent OEA effects, thus suggesting a role of the oxytocinergic system in mediating OEA's action of feeding behaviour. The role played by OXY in feeding is well characterized and patients affected by eating disorders often display abnormalities in OXY receptors functions. In addition to their expression in the paraventricular (PVN) and supraoptic nuclei, OXY receptors are also found in many brain areas where the dopaminergic neurotransmission regulates motivation and reward, such as prefrontal cortex, nucleus accumbens (NAc) and caudate putamen (CPu). OEA treatment re-establishes a normal sensitivity to the rewarding properties of fat in diet-induced obese mice and exerts anti-depressant-like effect in different animal models, by regulating serotonin (5-HT) and norepinephrine (NA) levels in the brain. In the present work we investigated the anti-binging effects of OEA in a well-characterized animal model and analysed the neurobiological bases of these effects by focusing on the brain pattern of c-Fos expression and on monoamine concentrations in selected brain regions. Moreover, we investigated the effect of OEA administration on hypothalamic OXY mRNA levels and on OXY receptor expression.

Material and methods: We used a well-characterized animal model of binge eating (Cifani et al., 2009) to evaluate the dose-dependent effects of an acute treatment with OEA (2.5, 5, 10 mg/kg intraperitoneally) on feeding behavior. Thereafter, we examined the effects of OEA on the brain pattern of c-Fos immunostaining by focusing our attention on the amygdala (AMY) and the PVN (involved in the control of stress and hedonic/homeostatic feeding), the NAc, the CPu, the ventral tegmental area (VTA) and the substantia nigra (SN) (involved in the reinforcement and motivational aspects of feeding). Moreover, by HPLC analyses we measured the tissue concentrations of dopamine (DA), NA, 5-HT and their main metabolites in selected brain regions to evaluate possible OEA effects on monoaminergic systems.
Finally, we investigated OXY mRNA levels by in situ hybridization of the PVN and OXY receptor expression by immunostaining of the medial prefrontal cortex, NAc and CPu to evaluate the effects of OEA on the oxitocinergic system.

Results: OEA treatment selectively prevented binge-like eating in a dose dependent manner with the strongest and long-lasting effect observed at 10 mg/kg. By analysing c-Fos expression we found that OEA treatment to binge eating rats prevented the activation of NAc, CPu and SN, and stimulated PVN and VTA, as compared to the activation observed in the same areas of control rats, where OEA was ineffective. These effects were associated to an increase of NA in the CPu, no effect on monoaminergic tissue concentration in the SN, and to an increase of 5-HT and to a decrease of DA tissue levels in the NAc.
Finally, we found that OEA increased OXY mRNA at the PVN level and restored a normal pattern of OXY receptor expression in the CPu and NAc of bingeing rats.

Discussion and conclusions: These results support the hypothesis that OEA might represent a novel potential pharmacological target for the treatment of binge-like eating disorders, and open new perspective on the role of the oxytocinergic system in these pathologies.