

Caloric restriction increases the sensitivity to the hyperphagic effect of Nociceptin/Orphanin FQ limiting its ability to reduce binge eating in female rats

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Nociceptin/Orphanin FQ (N/OFQ) is a functional antagonist of corticotrophin-releasing factor, the main mediator of the stress response. Stress represents a key determinant of binge eating (BE) for highly palatable food (HPF). In relation to the antistress properties of N/OFQ, we evaluated its effect on BE. After the observation that episodes of food restriction increase the sensitivity to its hyperphagic effects, the function of NOP receptor and N/OFQ was investigated after cycles of food restrictions. In BE experiments, four groups were used: rats fed normally and not stressed or stressed, rats exposed to cycles of restriction/refeeding and then stressed, or not stressed [1]. In the other experiments, two groups were used: rats exposed or not to food restriction. Only restricted and stressed rats exhibited BE for HPF. Intracerebroventricular injections of N/OFQ of 0.5 nmol/rat significantly reduced BE. N/OFQ 1 nmol/rat did not reduce BE but significantly increased HPF intake following food restrictions. Cycles of food restriction increased animals' sensitivity to the hyperphagic effect of N/OFQ for HPF. In situ hybridization studies following food restrictions showed decreased ppN/OFQ mRNA expression in the bed nucleus of the stria terminalis (BNST) and increased expression of ppN/OFQ and NOP receptor mRNA in the ventral tegmental area (VTA) and in the ventromedial hypothalamus (VMH), respectively. Even though N/OFQ is endowed with pronounced antistress and anti-CRF properties and even though it inhibits the effects of several drugs of abuse, the results of the present study do not support the possibility of using NOP agonism as strategy for the control BE. In fact, if at low doses, possibly acting with anti-CRF mechanisms, N/OFQ prevents the expression of BE, at slightly higher concentrations, due to the sensitizing effect of food restriction history, it increases HPF consumption. In conclusion, the present study suggests that NOP receptor agonism may have limited potential in the treatment of binge-type eating disorders because yo-yo dieting associated with it, could increase the responsiveness to the hyperphagic effect of N/OFQ. Our results suggest that the increased hyperphagic response to N/OFQ is associated with upregulation of NOP receptor in the VMH, as well as with changes in ppN/OFQ in the BNST and VTA. Altered regulation of orexigenic systems in response to food restrictions might represent a very important event, which may account for failure of dieting as a strategy to reduce body weight in humans [2] and may predispose people to binge-type eating disorders.

[1] Cifani C. et al. 2009 *Psychopharmacology* 204(1):113-25

[2] Wing R.R., Phelan S. 2005 *Am J Clin Nutr* 82:222S-225S