# Resistance to Diet-Induced Obesity is associated to selective epigenetic regulation of hypothalamic neuropeptides gene expression

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Feeding behavior and body weight are controlled by a complex and redundant system, in which hypothalamic orexigenic and anorexigenic neuropeptides play a key role. Excessive eating of high palatable energy dense food can imbalance such system and lead to obesity. Innate individual differences in obesity risk are well documented, but how environmental factors and diet manipulation can interact with the genetic background on individuals is still largely unknown. Epigenetic regulation of gene expression recently emerged as a potential important contributor [1]. In this study we investigated whether epigenetic regulation of the expression of genes encoding for key hypothalamic neuropeptides might be associated to obesity resistance in Sprague-Dawley rats placed on a high-fat diet to become obese (DIO). In particular, by Real-Time RT-PCR and Real-Time Methylation Specific PCR, respectively, we quantified the mRNA levels and the DNA methylation status of the promoter of genes encoding for neuropeptide Y (NPY), orexin (ORX), ghrelin (GHR) proopiomelacortin (POMC), prodynorphin (PDYN) and pronociceptin (PNOC) obtained from the hypothalamus (HY) of DIO rats, from DIO resistant rats (DR) [2] and from rats fed with a standard chow. Gene expression analysis revealed a significant increase of POMC and NPY in the HY of DR vs DIO rats and a significant decrease of GHR and PNOC vs both DIO and chow-fed rats. A consistent increase in DNA methylation was found at PNOC promoter in DR vs DIO rats. No other changes in DNA methylation status was observed for the other gene promoters studied.
These results suggest that specific modifications of hypothalamic neuropeptides involved in feeding control could be associated with resistance to obesity in DR rats. Moreover, they expand previous observations of a major role for PNOC in the control of body weight gain, showing that epigenetic regulation might affect its expression level upon diet manipulation. PNOC, as well as PDYN, is a precursor of opioid peptides and already considered as possible targets for obesity treatments [3]. Our findings open new perspectives for role of these peptidergic systems in obesity development and support the possibility of nutritional or pharmacological interventions that, by targeting their gene regulation, might be used to modify obesity risk.

[1] Campion J. et al. 2009 Obes. Rev. 10:383-392
[2] Sclafani A. et al. 1976 Physiol. Behav. 17:461-471
[3] Nogueiras R. et al. 2012 Obesity Facts 5:196-207