NOCICEPTIN/ORPHANIN FQ AND FOOD INTAKE IN DISEASE-PRONE WOKW AND DISEASE-RESISTANT DA RATS

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Nociceptin/orphanin FQ (N/OFQ) an opiod peptide that binds to the NOP receptor has been show to increase food intake in normal rats (1). The present study evaluated the effect of N/OFQ on feeding behaviour of two different strains of rat: the Dark agouti (DA) and the Wistar Ottawa Karlsburg W (WOKW) rats which present a feature of remaining lean and becoming obese respectively. Lateral brain ventricle (LV) injection of N/OFQ (2.1, 4.2 and 8.4 nmol/rat) increased significantly food intake in DA rats leaving unaltered WOKW feeding behaviour. This difference in response is also observed when other two major feeding controlling systems are activated: the melanocortin and the corticotropin system. Indeed, LV injection of the melanocortin receptor MCR3/4 antagonist SHU9119 (1nmol/rat) did increase feeding behavior in both rats but the WOKW strain responded with a longer (more than four hour) latency to initiating feeding behaviour compared to the two hours significant hyperphagic effect elicited in DA rats. Further, LV injection of the corticotropin releasing factor (CRF) (0.5μg/rat) in overnight food deprived rats produced a significant reduction of food intake in DA rats compared to WOKW rats. Corticosterone levels were also measured in both strains after LV injection of N/OFQ (8.4 nmol/rat). Plasma corticosterone levels resulted higher in WOKW rats compared to DA animals.
To understand the mechanism underlying the different response to LV N/OFQ injection, DNA sequencing of *Nop* receptor (*Oprl1*), Cocaine-amphetamine related transcript peptide (*Cart*) and pre-nociceptin peptide (*Pnoc*) were performed. Further, total RNA was isolated from hypothalamus and adipose tissue of 7 WOKW and 7 DA rats of 4 weeks, transcribed in cDNA and used for real-time PCR. Target cDNA was amplified by primer sets of *Oprl1, Cart* and *Pnoc*. These data have shown that WOKW have a higher relative gene expression of *Cart* in the hypothalamus. *Cart* is coding an anorectic peptide, which might explain their different feeding response. Differences in DNA sequence have been also observed between both strains that might further explain their difference in feeding response.
The present data show that DA and WOKW rats do respond differently to N/OFQ and that the nociceptin, but also the melanocortin and corticotropin system, are somehow altered in these strains.

[1] Pomonis JD, Billington CJ, Levine AS. Neuroreport. 1996; 8:369-371.