Sex-dependent changes of hypothalamic neuropeptides in response to a prolonged high-fat diet

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Introduction

The hypothalamus plays a major role in the regulation of food intake [1]. The hypothalamic neuropeptides with actions on the feeding behavior can be divided into two classes: orexigenic and anorexigenic (stimulate or inhibit food intake, respectively). Two types of neurons in the hypothalamus are of major importance for the control of these processes: neurons co-expressing neuropeptide Y (NPY) and agouti-related protein (AgRP), and neurons coexpressing pro-opiomelanocortins (POMC), the molecular precursor of alpha-melanocyte stimulating hormone (α -MSH) and cocaineand amphetamine-regulated transcript (CART). These neuropeptides exert opposing effects on food intake and fuel homeostasis.

Leptin, an adipocyte-secreted hormone that plays an important role in the regulation of energy balance, acts on specific receptors in the hypothalamus inhibiting orexigenic peptides and activating anorexigenic peptides [2].

It is well known that the intake of a high-fat diet induces obesity, but the susceptibility to diet induced obesity seems to be different between sexes. According to previous studies, female rats are more prone to gain weight when offered a palatable cafeteria diet [3] showing gender-linked differences in body weight regulation.

The aim of this study was to investigate whether the intake of a high-fat diet might differentially alter the

expression of leptinregulated hypothalamic genes involved in food intake control in male and female rats.

Materials and methods

Male and female Wistar rats were divided into two groups: normalfat (NF) group-fed on a standard chow diet (15.9 kJ/g) with 10% calories from fat; and seven high-fat (HF) group-fed on a chow diet (19.7 kJ/g) with 45% calories from fat (Research Diets, Inc., NJ, USA). Body weights and food intake were recorded three times a week from weaning until the age of 6 months when rats were killed by decapitation.

Leptin concentration in serum was measured with a mouse ELISA kit (R&D Systems, Minneapolis, Min, USA).

Hypothalamic gene expression of orexigenic (NPY, AgRP) and anorexigenic (POMC, CART) neuropeptides were examined by real-time PCR using the LightCycler System with SYBR Green I sequence non specific detection (Roche Diagnostic GmbH, Mannheim, Germany).

Results and discussion

The intake of a high fat diet resulted in higher overweight in female than in males rat (7% in males and 11% in females vs. respective controls, $p < 0.05$, Student's t test). The increase in serum leptin levels after a high-fat diet feeding was also higher in females than in male rats (24% in males and 76% in females vs. respective controls, $p < 0.05$, Student's t test). However, in female but not in male rats, the intake of high-fat diet was associated with higher hypothalamic NPY expression and higher NPY/POMC ratio

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($p < 0.05$, Student's t test). Gender differences in brain concentrations of peptides have been previously described [4] and seems to be due to the different hormone environment. The increase in NPY expression despite of the increase in leptin serum levels seems to indicate a central leptin resistance induced by high-fat diet feeding. Similarly other authors have also shown a marked suppression of leptin signaling in the hypothalamus of mice fed with a high fat diet for 19 weeks [5]. We did not find significant differences in the other neuropeptides studied.

In conclusion, these data suggest that the increased expression of NPY in female rats under a high-fat diet could indicate central leptin resistance and can contribute to explain the higher susceptibility of female rats to high-fat diet induced overweight compared with male rats.

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