Hyperphagia in children with craniopharyngioma is associated with hyperleptinaemia and a failure in the downregulation of appetite

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Abstract
Patients with craniopharyngioma frequently suffer from severe obesity. Leptin induces an inhibition of appetite via hypothalamic receptors. This study was undertaken to investigate whether a relationship exists between serum leptin levels and pituitary/hypothalamic lesions in craniopharyngioma patients. Serum leptin levels were evaluated by RIA in 14 patients (age 7–21 years; 7 females, 7 males) after they had undergone neurosurgical treatment for craniopharyngioma. Normal controls had a positive correlation between leptin levels and body mass index (BMI) with higher levels in the females than in the males. Significantly elevated leptin levels with respect to BMI were found in 11 craniopharyngioma patients who had been affected by a suprasellar tumour, whereas 3 patients with an intrasellar tumour had lower, almost normal serum leptin levels.

Our data suggest that craniopharyngioma patients develop hypothalamic obesity because their hypothalamic structures are insensitive to endogenous leptin. The elevated serum leptin concentrations found only in patients with a suprasellar tumour may be explained by a disturbed feedback mechanism from the hypothalamic leptin receptors to the adipose tissue.

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Introduction
Lesions of the hypothalamic–pituitary axis can lead to severe obesity, known as the Fröhlich syndrome. Craniopharyngioma is the most common neoplasm in the brain associated with hypothalamic–pituitary deficiencies. In patients suffering from craniopharyngioma, obesity associated with ravenous appetite is a well known but still unsolved problem. Leptin, the product of the ob(ese) gene, is a 167 amino acid protein secreted by adipose tissue. It induces a reduction of appetite by inhibiting the hypothalamic neuropeptide Y (NPY) resulting in controlled food intake (1). Hypothalamic receptors are directly involved in the action of leptin (2, 3). Whether the craniopharyngioma-associated obesity is caused by defective leptin signalling remains an unsolved question.

Subjects and methods
We evaluated serum leptin levels in 14 patients following neurosurgical treatment for craniopharyngioma. The tumour was located suprasellar in 11 patients, while 2 male patients and 1 female patient had an isolated intrasellar tumour. In all patients there were the characteristic histological findings of the cystic and solid components of craniopharyngioma. Four patients received postoperative cranial irradiation. The seven female (age 7–20 years) and seven male (age 9–21 years) patients had various pituitary hormonal deficiencies; all received adequate substitution therapy consisting of desmopressin, low dose hydrocortisone (5–15 mg/m² per day) and thyroxine (50–150 μg/day). On reaching the age of puberty, sex steroids were given if necessary. Three patients were on growth hormone treatment, 12–16 IU/m² per week. Normal probands (n = 53, 30 female, 23 male, age 7–23 years) with varying body mass index (BMI) and different pubertal stages served as controls. Blood samples were taken early in the morning. Serum leptin was measured by RIA (Linco, St Charles, MO, USA).

The leptin values and their covariable BMI were subjected to a two-way covariance analysis (ANCOVA) after logarithmic transformation. For the statistical analysis the program Statistica 5.0 (Statsoft of Europe, Hamburg, Germany) was used.
Results

Significantly elevated leptin levels with respect to BMI were found in the 11 craniopharyngioma patients who had been affected by a suprasellar tumour (females $P = 0.0007$, males $P = 0.0003$) with higher leptin levels in patients with a large tumour (Fig. 1). In contrast, the three patients with an intrasellar tumour had lower serum leptin levels comparable to those found in controls. In the normal controls, the leptin levels showed a positive correlation to BMI with higher levels occurring in the females than in the males as already found by Hassink et al. (4).

Discussion

The present study shows that the high endogenous leptin concentrations occurring in patients affected by craniopharyngioma are not sufficient for the correct feedback regulation of food intake. Obese suprasellar craniopharyngioma-operated patients had higher leptin levels than obese controls indicating a disturbed feedback control of leptin secretion. The control of energy intake is known to be influenced by several factors. Defective leptin signalling can be due to either leptin deficiency (e.g. obese ob/ob mice) or leptin resistance (e.g. diabetic db/db mice). Maffei et al. (5) found increased leptin gene expression in mice with both lesions of the hypothalamus and leptin receptor mutations. Leptin has been reported as being able to reduce the gene expression of NPY in the arcuate nucleus and to increase corticotrophin-releasing hormone (CRH) expression in the paraventricular nucleus in the brain of lean rats (3). NPY stimulates food intake and insulin secretion, and influences autonomic nervous system activity, whereas CRH inhibits food intake. If the craniopharyngioma has a suprasellar location, then it is highly probable that on both sides these nuclei or their connections are damaged either by the tumour itself or by iatrogenically induced operative lesions. The deficient leptin signalling associated with craniopharyngioma could result in the overexpression of hypothalamic NPY and a reduced hypothalamic CRH expression, both of which would cause increased appetite. A link is known to exist between the hypothalamus and the sympathetic innervation of adipose tissue. Leptin administration to ob/ob mice results in an increase in noradrenaline turnover in brown adipose tissue (6). Noradrenaline or a selective $\beta_3$-adrenergic receptor agonist inhibits the release of leptin from adipocytes (7). It is known that a reduced sympathetic tone caused by a deficient hypothalamic leptin transduction stimulates leptin synthesis in adipocytes via $\beta_3$-adrenergic receptors (7, 8). Therefore the elevated leptin levels seen in craniopharyngioma patients could result from a reduced $\beta_3$-adrenergic tone on the adipocytes caused by a deficient hypothalamic leptin signalling. Thus one possible role of leptin is the modulation of neurotransmitters and neuropeptides thereby closing the feedback loop from the brain to the adipose tissue.

The functions of this interesting molecule give a new insight into the clinical abnormalities of eating behaviour which might be caused by a defective feedback control system. Our data from craniopharyngioma patients suggest that patients with hypothalamic obesity are insensitive to endogenous leptin production and that their elevated serum leptin concentrations may be caused by a disturbed feedback mechanism.

References

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