Short Communication

Plasma Levels of Cortisol, Leptin and an Expression of the Leptin Receptors in the Visceral Adipose Tissue in Case of Metabolic Syndrome

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Abstract

The systemic studies in the recent years have proved the understanding that neuroendocrine changes play a main role in the pathogenesis of central obesity, hypertension, insulin resistance, leptin resistance. These changes involve disorders of the hypothalamo-pituitary-adrenal axis activated after periods of prolonged stress and environmental stress factors.

Aim of this study is to look for the connection between the high plasma levels of cortisol, leptin and the expression of leptin receptors in the visceral adipose tissue in patients with metabolic syndrome. We have found positive correlation between the body mass index, the area of the visceral adipose and the plasma levels of cortisol and leptin in cases of increased expression of the leptin receptors.

INTRODUCTION

The adipose tissue is an endocrine organ with key regulatory function, also communicating with the brain and the peripheral tissues [1–3].

The adipose organ consists of two types of tissue - white and brown (visceral) adipose tissue, each of which is characterised by specific vascularisation, innervation and cell structure. All subcutaneous and visceral depots contain both white and brown tissue, whose relative quantity depends on the age, environmental temperature and the hormonal levels in the organism. The mature brown adipocytes show characteristic polyfacet lipid drops and typical mitochondria, however this happens only when they receive adequate beta-adrenergic stimuli. In case of lack of such stimuli, the brown adipocytes turn into cells, which are morphologically similar to the white adipocytes producing leptin. The stimulation of ventromedial hypothalamus leads to over-activation of the sympathetic nerves and the β3-adrenergic receptors, which leads to increased thermogenesis [4].

The abdominal (visceral, android, central) obesity is a characteristic feature of metabolic syndrome (MS). It is combined with increased activation of the hypothalamic-pituitary-adrenal axis with subsequent sympathicotony and increased secretion of cortisol from the adrenal [5,6]. Sympathicotony and hormonal imbalance are characteristic for chronic stress (emotional and/or chronic inflammatory), which are etiological factors for MS [7].

The increased plasma cortisol in the presence of hyperinsulinemia in MS leads to accumulation of masts in the visceral depot of the organism.

Visfatin could play an important role in the fast accumulation of visceral adipose tissue through autocrine and paracrine route [8].

With reduction of the visceral adipose tissue, the signal for fullness to the hypothalamus is reduced and this leads to hyperphagia. The intact thermogenesis in the visceral adipose tissue is important for the occurrence of the leptin anorexigenic effect on neuropeptide-tyrosine (NPY). Hypercortisolemia is found in patients with MS. It is found that glucocorticoids have stimulating effect on the expression of the ob-gene and increase the expression of leptin receptors [9,10].

Therefore we set the objective to search for a link between the high plasma levels of cortisol and the expression of leptin receptors in the visceral adipose tissue in patients with MS.

MATERIALS AND METHODS

23 patients with MS (20 women and 3 men) have been studied, who were diagnosed based on the criteria of the Adult Treatment...
Panel III of the American National Cholesterol Program and 10 controls (7 women and 3 men), respectively by gender and age, with no family history of diabetes mellitus or premature coronary atherosclerosis disease (documented cardiovascular disease in at least one immediate family member under 55 years of age for men and under 60 for women). The studies have been carried out based on the Helsinki Convention.

METHODS

Leptin and cortisol have been studied - radio-immunoassay:

Ten days before the blood and adipose tissue sampling, the medication treatment has been ceased. The blood samples have been taken between 8.00 and 9.00 in the morning from the antecubital vein and have been centrifuged immediately - 8500 g for 20 minutes at 4°C in order to remove the cells.

Plasma cortisol has been tested based on the radio-immunoassay method.

Plasma leptin was studied through radio-immunoassay. It has been studied with a kit for Alpha Diagnostics, San Antonio, TX, USA.

Histological study: Biopsy of abdominal, mesenteric adipose tissue, fixation in 4% paraformaldehyde, in 0.1 phosphate solution, pH 7.4 for 4 days at temperature of 4°C. Sections with thickness of 15 μm have been prepared by using cryomicrotome for histological evaluation.

Measurement of the visceral adipose tissue area in cm² and density in Hunsfield units through computer axial tomography (CAT) at the level of the third lumbar vertebra (L3).

Biopsy from the visceral adipose tissue (mesenteric) and immuno-histochemical definition of the expression of leptin receptors in this adipose tissue.

Statistical method - analysis of variance (ANOVA).

The data from the CAT of adipose tissue have been processed with software pack IAS 2000.47.

RESULTS

The body mass index in MS has an average value of 39.56±1.00 and 22±57 in the controls.

The plasma levels of cortisol in MS are 525.08±33.83 nmol/l and 368.00±14.89 nmol/l in the controls.

A suppressant test with 2 mg dexamethasone was performed - a suppression was achieved, which excluded Cushing’s syndrome.

Besides the high plasma levels of cortisol, the study of the 24-hour rhythm of cortisol in MS showed disturbed rhythm.

The plasma levels of leptin are significantly higher in MS - 6.76±2.95 ng/ml and 1.13±0.15 ng/ml in the controls.

In patients with MS the area is 157.24±30.14 and it is 100.65±34.29 in the controls. The visceral adipose tissue with MS has density of 19109.68±3066.5 pixels and 13649.18±4099.6 pixels in the controls.

Summary: The visceral adipose tissue in MS is with statistically significantly higher area and density as compared to the controls (p<0.05).

DISCUSSION

The high levels of cortisol in case of MS, as well as the disturbed 24-hour rhythm of cortisol give the ground to assume hyperactivation of the hypothalamus-pituitary-adrenal axis in case of MS and disturbed hypothalamic feedback control mechanism. The high plasma levels of cortisol are an important factor for the increased lipogenesis in MC.

The increased plasma levels of leptin in MS (Figure 1) (Table 1), in combination with increased appetite of these patients also support the presence of disorder in the hypothalamic feedback control mechanism on appetite.

We have found positive correlation between the body mass index (BMI), the area of the visceral adipose tissue and the plasma levels of cortisol and leptin in cases of increased expression of the leptin receptors. This high expressions of the leptin receptors shows that the visceral adipose tissue is an important target for the action of leptin. The results confirm the important regulatory and metabolic role of leptin for increasing the thermogenesis in the visceral adipose tissue.

It is proven the leptin inhibits the preadipocyte differentiation and the lipogenesis in cell cultures through paracrine and autocrine mechanism of action. Leptin stimulates the lipolysis in adipocytes. On the other hand, the high cortisol levels in plasma have stimulating effect on the expression of leptin receptors [9]. This was confirmed by our results.

| Table 1: Clinical and laboratory characteristics of patients with MS - generalised stage (N=23) and healthy controls (n=10). |
|---|---|
| **Controls** | **MS generalised stage** |
| Age | 42.50 ±2.75 | 45.69 ±2.18 |
| Body mass (kg) | 64.80 ±1.98 | 100.47 ±3.43 |
| p<0.01 |
| Body mass index (kg m²) | 22.00 ±0.57 | 39.56 ±1.00 |
| Cortisol (mg/l) | 368.00 ±14.89 | 525.08 ±33.83 |
| p<0.01 |
| Leptin (ng/ml) | 1.13 ±0.15 | 6.76 ±2.95 |
| p<0.005 |
The high levels of plasma cortisol explain why the expression of leptin receptors in the visceral adipose tissue is significantly high in case of high plasma levels of leptin.

In summary – the visceral adipose tissue is characterised by high metabolic and lipolytic activity [11].

The high plasma levels of cortisol, in the presence of hyperinsulinemia, lead to increased lipogenesis in the visceral depot of the adipose tissue. Visfatin, which is a product of the visceral adipose tissue, also participates in the increased lipogenesis.

At the same time, hypercortisolemia in MS enhances the expression of the leptin receptors in the visceral adipose tissue and this leads to increased lipolysis and increased release of fatty acids in the portal vein. This is followed by increased synthesis of triglycerides and cholesterol from the liver, increased gluconeogenesis and the atherogenic lipid profile, which is characteristic for MS. It is controversial whether lipolysis is balanced by the respective storage of a large quantity of fat [12].

It is proven that for the presence of the regulatory effect of the white adipose tissue on appetite through the anorexigenic effect of leptin, presence of sufficiently large depot for visceral adipose tissue and preserved thermogenesis is necessary. This is probably cross-talk between adrenal glands, the white and visceral adipose tissue through the adipokines and under the control of the brain (hypothalamus).

The over-accumulation of visceral adipose tissue causes dysfunction of the adipocytes and imbalance of adipokines, which leads to metabolic and circulation diseases and atherosclerosis [13]. The participation of mastocytes in MS and the new adipose-immune link leptin-mastocytes was established [14].

The secretion of the adipose tissue constitutes a new target for pharmacology [15,16]. Recently, the metabotropic effect of neurotrophins and the participation of NGF and BDNF in the pathogenesis of obesity, type 2 diabetes mellitus and metabolic syndrome was proven [7,17-25]. Hyperneurotrophinemia in the early stages of MS and the subsequent hyperactivation of the hypothalamo—pituitary—adrenal axis leads to changes in the rhythm of cortisol secretion and changes in frequency and amplitude of the pulsations in cortisol and adrenalin secretion. This is likely to account for the reduced sensitivity of the leptin receptors in the hypothalamus. Glyco- corticoids are counterregulatory hormones for leptin. Probably all the above results in leptin resistance [27]. Cortisol has a permissive effect on NPY secretion by the paraventricular nuclei in the 35 hypothalamus. In hypercortisolemia the NPY secretion is increased irrespective of the high plasma levels of leptin. The feedback mechanism is also disturbed for hypothalamic control of the food intake and energy spending with subsequent central obesity. We can summarize that the appropriate therapeutic approach requires the recovery of the balance between the nervous, endocrine and immune systems. This can be achieved through the elimination of the chronic inflammatory and the chronic psychosocial stress (distress) and adequate control over hyponeurotrophinemia [28].

REFERENCES
3. Fain JN. Release of interleukins and other inflammatory cytokines by human adipose tissue is enhanced in obesity and primarily due to the nonfat cells. Vitam Horm. 2006; 74: 443-477.


