THE ROLE OF LEPTIN IN THE DEVELOPMENT OF TUMOURS OF FEMALE GENITAL ORGANS

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Received May 19th, 2003; received in a revised form October 1st, 2003; accepted October 2nd, 2003

SUMMARY

Leptin concentrations in blood serum are significantly elevated in women suffering from endometrial carcinoma or from advanced breast carcinoma. Controversial results on the relations in other cancers of genital organs (ovary, uterine cervix, vulva) and in endometriosis require some further studies.

Key words: leptin, gynecological cancers, endometriosis.

INTRODUCTION

Leptin (OB protein), the product of *ob* gene is produced mainly by adipocytes of the white adipose tissue, from which it is secreted to the circulation in a free and a bound form. Leptin decreases appetite and stimulates energy expenditure by inhibiting hypothalamic neuropeptide Y (NPY), which stimulates appetite [1,2].

Even if leptin is regarded to represent an anti-obesity, anorexia-inducing hormone, its role is much broader: it participates in the control of blood pressure and of hemopoiesis, in immune functions, angiogenesis, oxidation of lipids, glucose metabolism, reproduction and apoptosis in adipocytes [1,3,4,5,6].

Serum leptin levels reflect the amount of adipose tissue in the body, age, sex, diet composition, levels of other hormones (insulin, steroid hormones) as well as levels of other cytokines, including TNFα - tumour necrosis factor α, interleukins 1 and 6 (IL-1 and IL-6) [7].

Persons characterized by a low weight and low body mass index (BMI) demonstrate low leptin levels whereas in obese individuals these levels are higher. In the studies of Considine et al. in the group of 136 individuals of a normal weight and in 139 obese persons, the leptin levels were found to be 7.5 ± 9.3 and 31.3 ± 24.1 ng/mL, respectively. This indicates that most obese individuals are insensitive to endogenously produced leptin [6]. This insensitivity is linked to resistance to leptin and it is suspected to result from a mutation of the leptin receptor or from an elevated serum leptin threshold (around 25-30ng/mL). Increased levels of leptin in the serum do not increase in parallel leptin concentrations in the cerebrospinal fluid and the brain [7,8,9].

Leptin acts through its receptor, coded by *db* gene, which exhibits 4 isoforms: the long OBR_L form and three short OBR_S forms differing from each other in the number and sequence of amino acids of the cytoplasmic portion of the receptor and therefore, in the function of the receptor [10]. The leptin receptor (OBR), mainly its long isoform, is expressed in the hypothalamus. Prevalent expression of short isoforms of the receptor has been detected in peripheral tissues: in the lungs, kidneys, liver, pancreas, suprarenal glands, ovaries, skeletal muscles and in the haematopoietic stem cells [1].

Praca w ramach grantu KBN pt.: Leptyna i jej receptory w mięśniakach macicy. Nr 3PO5A01622 nr. umowy 0371/P05/2002/22.

Leptin acts by binding to its specific receptors, which is followed by the activation of the JAK-STAT (just another kinase/ signal transducers and activators of transcription) system, linked to the activation of kinases, their phosphorylating activity and to stimulation of various cytokine receptors, regulation of gene expression and the resulting engagement of various signalling pathways [10,11].

The number of obese individuals the world over is on the increase. Statistical data indicate that around 80% of obese people suffer from at least one and 70% of them from two or more co-existing diseases. Obesity participates in the etiopathogenesis of certain diseases, such as diabetes, hypertension, cardiovascular diseases and also some malignant tumours [7,12].

Some types of tumours were found to be related to obesity:

Among 1245 patients with acute myeloid leukemia (AML) a group of 120 (9.6%) patients was distinguished in whom the acute promyelocytic leukemia (APL) was diagnosed. As compared to AML patients, the latter patients were more frequently obese ($p = 0.0003$). Increased BMI (> 50, body weight of 316 to 480 lbs) was found to predispose to APL [13,14].

Higher risk of colorectal carcinoma was noted in obese individuals of low physical activity. In *in vitro* studies leptin proved to act as a growth factor for cells of colorectal carcinoma [15]. In some clinical studies marked obesity was linked to accelerated progression of colorectal carcinoma [16].

Some studies indicate that leptin increases the risk of prostate cancer development [17,18]. In the studies on 149 men in the population of Northern Sweden an intermediate but not high leptin levels correlated with the development of cancer [17]. Other studies indicate, in turn, that elevated leptin concentrations are insignificant in the development of prostate cancer or even in benign hypertrophy of the gland [19].

The expression of leptin and that of its receptor varies in tumours of different histological origin or even in tumours of the same origin. In some cases of the ovarian, renal or testicular carcinomas the expressions of both the leptin and its receptor were likely to point to autocrine action of leptin, and in other tumours (leukemias) the expression of the leptin receptor without expression of leptin was found, suggesting a systemic or paracrine effect of the cytokine on tumour cells [20].

In some studies, leptin was linked to the anorexia – cachexia syndrome in some cancer patients [21,22] but, according to Simons et al. [23], leptin does not participate in the development of cachexia due to lung cancer [21,22].

BREAST CANCER

Obese women were found to carry a higher risk of developing breast cancer [24]. In the studies of Tessitore et al. [25] on 23 women with breast cancer plasma leptin and insulin levels were higher than in controls. The elevated leptin levels correlated with augmented levels of estrogen and progesteron receptors and elevated levels of breast cancer markers, CA 15.3, CEA. The authors suggest that leptin should be treated as a clinical marker of the disease.

In the studies of Ozet et al. [26] leptin was estimated in 58 women with breast cancer and in 58 healthy women, serving as a control group. Serum leptin levels were significantly higher in the breast cancer patients than in the control group (27.00 and 17.65 ng/mL, respectively). The analysis included also BMI, the age of women, the stage of the disease, the concentration of CA 15.3 and the hormonal status (pre- or post-menopausal). Some patients received tamoxifen, some did not.

No correlation could be detected between leptin concentration and the early or late stages of the cancer, or between leptin concentration and CA 15.3 levels. Pre-menopausal and post-menopausal women did not differ in BMI or leptin levels.

Women with breast cancer who received tamoxifen manifested a significantly higher leptin levels than those who received no tamoxifen (32.71 and 19.39 ng/mL, respectively). Thus, high leptin levels in breast cancer patients showed no relation to the stage of the disease but were related to tamoxifen administration,

although the mechanism of the relation remained unclear.

In other clinical observations [24], 83 pre-menopausal women with *in situ* carcinoma demonstrated lower leptin levels than 69 healthy women of the control group (13.69 ± 1.3 ng/mL and 16.03 ± 1.7 ng/mL, respectively). According to the authors, leptin does increase the risk of breast cancer development.

In *in vitro* cultures [27] of breast cancer cells, expression of leptin mRNA was more pronounced than in the adipose tissue. This pertained to three cell lines (MCF-7, T470 and MDAMB).

It has been suggested that leptin may play a role in the development of immunosuppression in females with breast cancer.

ENDOMETRIAL CARCINOMA

Its development is related to obesity, early menarche, late menopause and to high levels of unbalanced estrogens [28].

Controlled clinical investigations of Petridou et al. [29] were performed on 84 women with endometrial carcinoma and on 84 healthy women of the control group with respective BMI values of 29.2 ± 5.72 and 26.5 ± 3.43. Serum leptin levels in women with endometrial carcinoma were found to be 36.7 ± 25.7 ng/mL and those in the control group were 26.9 ± 19.8 ng/mL. The difference was significant at p = 0.006.

Leptin levels were found to be strongly related to endometrial cancer.

UTERINE CERVIX CARCINOMA

Leptin was detected to induce angiogenesis [30]. Obermair et al. [31] are of the opinion that, apart from the effects of the vascular endothelial growth factor (VEGF), the angiogenesis factor, neoplasia in the form of uterine cervix carcinoma is being modulated also by leptin. Lebrecht et al. [32] by measuring the levels of leptin and of VEGF have examined the role of the two factors in the development of uterine cervix carcinoma in 84 women with cervical cancer, 28 patients with CIN I – III and in 35 healthy women.

Serum VEGF levels were significantly elevated ($p<0.001$) in patients with cervical carcinoma and in patients with CIN I-III as compared to healthy women. Serum VEGF was significantly elevated ($p=0.02$) in women with cervical carcinoma as compared to women with CIN. Serum VEGF showed a significant correlation with the stage of the tumour but showed no such relation to lymph node involvement, survival time or the period in which the patients were free of the disease.

Leptin concentrations did not differ in patients with uterine cervix carcinoma (10.9; range: 1.0 to 49.9 ng/mL), those with CIN I-III (8.6; range: 1.9 to 42.3 ng/mL) and healthy women (10.1; range: 2.4 to 53 ng/mL). They did not correlate with the survival time or the time in which the patient was free of the disease. No correlation was demonstrated between concentrations of VEGF and leptin in patients with uterine cervix carcinoma, patients with CIN I-III and healthy women.

VULVAR CARCINOMA

Angiogenesis was demonstrated to play a significant role in the progression of vulvar intraepithelial carcinoma to the invasive cancer [33] whereas overexpression of VEGF was detected in patients with vulvar carcinoma (34). Since angiogenesis and adipogenesis are linked to each other, it has been advanced that leptin plays a role in the development of new vessels (leptin-dependent angiogenesis) [4].

At the University of Vienna department 37 patients with vulvar carcinoma and 37 healthy women were examined. Serum leptin levels were higher in the patients (15.8; range: 1.1 to 45.6 ng/mL) than in healthy women (10.1; range: 2.4 to 53.5 ng/mL). The authors did not consider leptin to be an angiogenic factor since its levels did not reflect clinical advancement, histological diagnosis or lymph node involvement. Leptin levels also failed to correlate with less favourable prognosis [35].

OVARIAN CANCER

Pilot studies of Szenajch et al. [20] on cell lines of the ovarian cancer (OVCAR3, OVP10) did not detect leptin, its receptors being noted only in the former cell line.

In tissues of the ovarian cancer, the expre-

ssion of the receptor was detected and in some of them, the expression of leptin was noted. In tissues of benign tumours of the ovary, neither leptin nor its receptor expression was detected. The authors suggest a link between the expression of leptin receptor and malignancy.

However, in the studies of Karlsson et al. [36] the expression of the receptor (more pronounced in the short forms) and the expression of leptin were observed in the vesicular liquid. Clarification of this phenomenon requires some further studies.

MEIGS' SYNDROME

Leptin levels showed a reverse correlation with Meigs' syndrome. Following surgery, in the absence of a tumour, with receding ascites and pleural fluid, when CA 125 concentrations (from 354 to 14.2) decrease, leptin levels increase. The authors have suggested a role of leptin in the pathogenesis of Meigs' syndrome [37].

ENDOMETRIOSIS

This disease is thought to be associated with elevated production of pro-inflammatory cytokines, such as interleukins (IL-1 and IL-8), TNF α and VEGF. Moreover, in the development of endometrial implants, significant role is played by inflammatory mediators and neoangiogenesis. Theoretically, a certain role could be ascribed also to leptin: inflammatory cytokines such as IL-1 and TNFα stimulate leptin secretion while leptin, in turn, induces some increase in the levels of certain cytokines and plays the role of angiogenesis-promoting factor [5, 30, 38].

In their multicentre studies only two years ago, Matarese et al. [39] noted some higher serum and ascitic fluid levels of leptin (30.3 ± 14.8 ng/mL and 35.9 ± 17.4 ng/mL, respectively) in 13 women with various clinical stages of endometriosis as compared to 15 women of the control group. The authors suggest that pro-inflammatory and neoangiogenetic effects of leptin may play a role in the pathogenesis of endometriosis.

In 2002, results of some studies, including multicentre studies on leptin in endometriosis have turned out to be completely different from those discussed above [40]. These studies were carried out on 42 women with various clinical stages of endometriosis and on 25 women of the control group. Serum leptin levels were similar in the two groups of women (2.1 ± 8 ng/mL and 12.5 ± 9.4 ng/mL, respectively). No differences were revealed in leptin concentrations in the analysis of the disease stages, number of implants, cysts, depth of endometriosis or its signs/symptoms.

Some further studies seem to be required for the clarification of the problems.

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