The role of leptin in breast cancer

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Summary

Leptin, the protein hormone produced mainly by adipocytes, placenta and mammary epithelium plays a significant role in, e.g., control of metabolism, reproductive processes, immune processes, angiogenesis, haemopoiesis and oxidation of lipids. Since some authors link leptin to mechanisms of mammary cancer development, the clinical data has been screened to allow evaluation of the hypothesis.

Key words: Leptin; Breast cancer.

Introduction

Leptin, or OB protein of 16 kDa in size, a product of ob genes, is produced mainly in adipocytes of the white adipose tissue and then secreted into the blood stream where it circulates in bound and free forms. It is regarded as an anorectic, anti-adiposity hormone.

Leptin not only decreases appetite and stimulates energy expenditure by inhibition of the hypophyseal neuropeptide Y function, it also participates in multiple processes, including immune processes, glucose metabolism, angiogenesis, control of blood pressure, haemopoiesis, oxidation of lipids and reproductive processes [1-3].

Leptin acts biologically through its specific receptor which manifests four isoforms (a long one and three short ones) differing in structure and function. Leptin mobilises two protein phosphorylation-based signalling pathways, including the JAK–STAT (just another kinase/signal transducer and activator of transcription) pathway and MAPK (mitogen activated protein kinase) pathway [4, 5].

Individuals of low body weight and low BMI (body mass index) carry low serum leptin levels while in obese individuals serum leptin concentrations are higher (mean 7.5 ± 9.3 and 31.3 ± 24 ng/ml, respectively). This apparent inconsistency can be explained by insensitivity or resistance of the majority of obese individuals to endogenous leptin. The phenomenon has been interpreted by some hypotheses formulated on the basis of studies performed on animals [6-8].

Serum leptin concentration is also influenced by age, sex, diet (zinc), levels of other hormones (insulin, glucocorticoids) and cytokines (TNF α, IL-1, IL-6), and by condiments (alcohol, cigarettes, amphetamines) [2, 4, 9, 10].

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Leptin and breast cancer

Since both leptin and breast cancer are associated with obesity, circulating levels of sex hormones and concentration of insulin-like growth factor-1 (IGF-I), several authors have examined relations of the above factors *in vitro* as well as *in vivo* in order to define the influence of leptin on the development of breast cancer.

Dieudonne *et al.* [11] tested the hypothesis by examining effects of leptin on the cell line of human breast cancer, MCF-7. The cells demonstrated expression of leptin receptor and responded by proliferation to recombined human leptin along both MAPK and STAT 3 signalling pathways. Similar results of studies were obtained by Laud *et al.* [12], who examined expression of leptin receptors (the long and the short isoform) in the tissues of 20 breast cancers and in two human breast cancer cell lines, T47-D and MCF-7. They found that both receptor types exhibited expression in all breast cancer tissues and that it was localised in proliferating cells. Supplementation of T 47 D cell line cultures with exogenous leptin exerted a significant stimulatory effect. A detailed analysis demonstrated that the cell proliferation took place due to activation of the MAPK pathway since MAPK-specific inhibitors blocked the leptin-induced cell proliferation. The authors suggested that leptin and its receptors may be linked to proliferation of breast cells and to pathogenesis of breast cancer.

Other studies performed on cell lines (human breast cancer cell line T-47 D and HBL 100) by Hu *et al.* [13] confirmed the proliferation-stimulating effect of leptin. In these studies, leptin was noted to activate not only the STAT-3 pathway but also the ERK (extracellular signal - regulated kinase) and AP-1 (activator protein 1) pathways. According to the authors, leptin may play some role in prevention and even in therapy of breast cancer.

O'Brien *et al.* [14] detected higher expression of leptin mRNA in three cell lines of human breast cancer: MCF-7; T 47 D and MDAM B 231, as compared to adipose tissue surrounding the gland. The authors found that leptin might be of significance in promotion of immunosuppression in breast cancer patients.

Numerous authors have described higher levels of IGF-I in the blood of female breast cancer patients. The studies included women with *in situ* cancer or in early stages of cancer but in various age groups [15-17]. Mantzoros *et al.* [6] attempted to clarify the relation by means of anthropometric, demographic and hormonal analyses (estradiol, prolactin, IGF-I, IGF BP = insulin growth factor binding protein) in 83 women with breast cancer *in situ* and in 69 healthy premenopausal women. The authors could not link any significantly increased risk of in situ cancer with this group of women; yet, in the group of women with cancer serum leptin levels were lower than in the control group (13.69 ± 1.3 ng/ml and 16.03 ± 1.7 ng/ml, respectively). Still, the studies confirmed association of *in situ* cancer with elevated levels of IGF-I and IGF BP.

The same problem was the subject of the study by Petridou *et al.* [18], which provided a broad epidemiological analysis including age, domicile (urban or rural), education, BMI, menopausal age, age of delivering the first child and number of deliveries. Seventy-five women with breast cancer and 75 women in a control group were involved. However, the tested group included both premenopausal women (14 patients and 15 control women) and postmenopausal women (61 patients and 60 control women). Women with breast cancer were found to develop menarche earlier, to enter menopause later and to deliver their first child later. The authors found no associations between IGF-I and development of breast cancer in women before or after menopause, which the mentioned authors [15-17] noted.

On the other hand, in contrast to Mantzoros *et al.* [6], Petridou *et al.* [18] detected a significant relation ($p < 0.05$) between decreased serum leptin levels and development of breast cancer in women before menopause (leptin level in breast cancer patients: 14.7 ± 2.0 ng/ml and in the control group: 23.9 ± 4.1 ng/ml). The results are contradictory, but Mantzoros *et al.* [6] examined patients with *in situ* cancer while Petridou *et al.* [18] provided no data on advancement of the cancer. The authors of this latter study regard these results as impossible from a biological point of view and think that further studies on the problem should be performed.

In other studies, Ozet *et al.* [19] presented some interesting data, originating from studies on 58 obese women suffering from invasive ductal breast carcinoma of variable clinical stages; one group (30 women) was administered tamoxifen and the other was not given the drug (20 women). Detailed analysis demonstrated that there were no significant differences in serum leptin levels in women with breast cancer before or after menopause, in leptin levels and early or late clinical stages of the cancer, and no relations were marked between CA 15-3 serum levels and leptin levels. However, a statistically relevant difference in leptin levels was noted between the patients and healthy women (27.00 ± 2.71 and 17.65 ± 0.97 mg/ml, respectively). The authors analysed the data further and found that elevated leptin levels in breast cancer patients were detected only in the patients treated with tamoxifen (32.71 ± 4.06 ng/ml as compared to 19.39 ± 3.51 ng/ml). The authors think the mechanism responsible for the difference is unclear and suggest that the increased leptin expression may develop with mediation of estrogen receptors.

Augmented levels of leptin in serum and adipose tissue surrounding the breasts were detected by Tessitore *et al.* [20]. In 23 patients with breast cancer not only leptin but also tumour markers were assayed (CEA, CA 125) in serum as well as TNF-α, insulin, estrogen and progesteron receptors, indices of lipid metabolism (cholesterol, triglycerides, HDL) and total protein. Elevated levels of serum leptin in patients as compared to healthy women (10.4 ± 6.8 ng/ml against 2.8 ± 0.1 ng/ml) and elevated levels of leptin in breast-surrounding adipose tissue (leptin mRNA increased to 264% of the healthy control) paralelled elevated levels of biochemical and hormonal markers (CEA, CA 125, ER, PGR, TNF-α). The data indicates that leptin may represent a new marker of breast cancer and the authors believe it may be involved in the pathogenesis of neoplastic cachexia.

Even if the growing amount of evidence suggests a link between leptin and breast cancer development, Margot Cleary, a nutrition biochemist from Minnesota University, studying connections between the neuropeptide and etiology of metabolic disorders which result in obesity, maintains that "as for now, the leptin role in cancer is not yet clear". Christensen [21] hopes that future studies will confirm relations between leptin and breast cancer. Leptin will then represent yet another factor which, along with the patient's body weight, family history or also estrogen levels, can be accounted for in estimating the risk of breast cancer development in women.

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