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ORIGINAL ARTICLE

Serum levels of angiogenic growth factors in patients with thyroid gland tumors and parathyroid adenoma

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Abstract

OBJECTIVE: Angiogenic growth factors bFGF and VEGF ensure vascularisation of the growing tumor tissue. We decided to investigate their peripheral serum concentrations in patients with thyroid gland adenoma and papillary carcinoma and with parathyroid adenoma. We wanted to find the possible serum marker of these tumor diseases.

METHODS: 28 patients with thyroid gland tumor (14x adenoma, 14x papillary carcinoma) and 12 patients with parathyroid gland adenoma. Growth factors serum levels were measured by ELISA method.

RESULTS: We found significantly higher serum levels of bFGF in both groups of patients with thyroid adenoma (4.93 ± 3.42 ng/ml) and papillary carcinoma (5.69 ± 5.58 ng/ml) compared to the healthy population (1.47 ± 1.77 ng/ml). There were no significant differences of VEGF serum levels between all examined groups of patients (adenoma 213 ± 197, papillary carcinoma 210 ± 179, healthy 227 ± 231 pg/ml). We found significantly higher serum levels of bFGF in patients with parathyroid gland adenoma (7.59 ± 9.12 ng/ml) compared to those in healthy people (1.47 ± 1.77 ng/ml).

CONCLUSIONS: Higher bFGF serum concentrations in patients with thyroid and parathyroid tumors are in accordance with their immunohistochemical tissue levels described in the literature. Not so in VEGF. bFGF may be a serum marker of thyroid and parathyroid neoplasms.

Introduction

Vascularisation of the enlarging tumor mass is ensured by the higher production of angiogenic growth factors, like bFGF (basic Fibroblast Growth Factor), PDGF (Platelet Derivated Growth Factor), EGF (Epidermal Growth Factor) and VEGF (Vascular Endothelial Growth Factor). Their production may raise owing to a growing hypoxy in the middle of the tumor. Of course, there are also inhibitors of angiogenesis, for example TGFβ1 (Transforming Growth Factor β1), interferons, IL-6, trombospondin.

bFGF stimulates follicular cells growth, it has mitogenic and dedifferential effects. It's a very strong activator of angiogenesis, it activates fibroblasts and endothelial cells proliferation and migration. Higher production of bFGF was found in follicular cells of thyroid gland carcinomas [1, 2, 3]. bFGF is also produced by cells of parathyroid adenoma [4, 5].

VEGF is a strong mitogene for endothelial cells and it raises vascular permeability. It takes part in the neovascularisation if the tumor tissue [6, 7]. Owing to TSH, the VEGF production is activated in thyreocytes, that leads to the end of mitogenic TSH stimulation and to the initiation of angiogenesis [8, 9, 10, 11]. VEGF also takes part in the lymphatic vessels formation and affects tumor cells dissemination to the regional lymphatic nodes [12].

The aim of our study was to find serum concentrations of bFGF and VEGF in patients with thyroid gland adenoma and papillary carcinoma and bFGF serum levels in patients with parathyroid adenoma.

Patients and methods

All patients were operated on The Department of Otorhinolaryngology and Head and Neck Surgery in Faculty Hospital Motol from October 2000 until March 2001. The study involved 28 patients with thyroid gland tumor (14x adenoma, 14x papillary carcinoma) and 12 patients with parathyroid gland adenoma. In all cases total thyroidectomy or parathyroid adenoma exstirpation was carried out. There was anamnestically no other tumor disease and acute or chronic inflammation in these patients.

From every patient 20 ml of blood from cubital vein was obtained on the operating-room before the start of the operation. After 30 minutes this peripheral blood was centrifuged for 10 min. at 2600 turns/min. Thus obtained serum was freezed in liquid nitrogen and stored in a closed plastic tube at –80 °C. Measurements of serum concentrations of bFGF and VEGF were executed by ELISA method.

We also measured serum levels of bFGF and VEGF in the control group of healthy people.

Results

Differences in bFGF and VEGF serum concentrations in patients with thyroid gland tumors are shown in Figure 1. Results were statistically evaluated by Kruskal-Wallis test.

We found significantly higher serum levels of bFGF ($p<0.01$) in both groups of patients with thyroid adenoma (4.93 ± 3.42 ng/ml) and papillary carcinoma (5.69 ± 5.58 ng/ml) compared to the healthy population (1.47 ± 1.77 ng/ml). There were no significant dif-

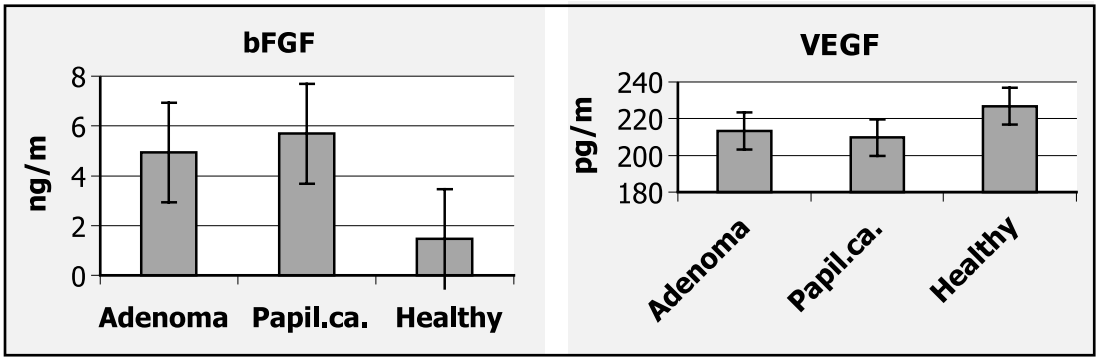

Figure 1. Graphs with average bFGF and VEGF serum concentrations in patients with thyroid gland tumors.

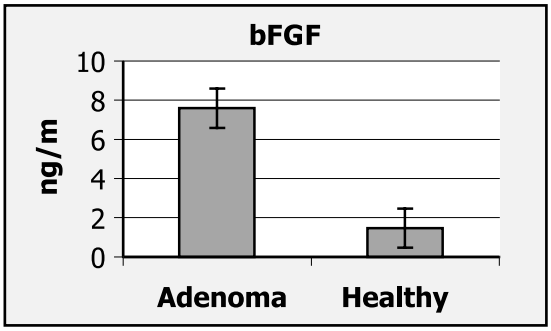

Figure 2. Graph with average bFGF serum concentrations in patients with parathyroid gland adenoma.

ferences of VEGF serum levels between all examined groups of patients (adenoma 213 ± 197, papillary carcinoma 210 ± 179, healthy 227 ± 231 pg/ml).

bFGF serum levels in patients with parathyroid gland adenoma are shown in Figure 2. Results were statistically evaluated by Kruskal-Wallis test.

We found significantly higher serum levels of bFGF ($p<0.01$) in patients with parathyroid gland adenoma (7.59 ± 9.12 ng/ml) compared to those in healthy people (1.47 ± 1.77 ng/ml).

Discussion

There are many works describing the level of particular growth factors production in thyroid gland tumors, but a little of those in parathyroid gland. In these works the expression or occurrence of growth factors is examined by their direct detection in the tissue, using PCR, immunohistochemical methods or in situ hybridization. We tried to find out, whether changes in the angiogenic growth factors production by the thyroid and parathyroid gland tissue are expressed by changes of their serum concentrations.

bFGF stimulates a proliferation of thyroid follicular cells, fibroblasts and endothelial cells. It has also dedifferential effects and it's a very strong activator of angiogenesis. Its production rises in the phase of a rapid goitre growth. In the literature, there is described higher bFGF production in thyroid adenomas and carcinomas, while this production is minimal in the normal thyroid gland tissue [1, 2, 3, 13]. We also found higher bFGF serum levels in patients with thyroid adenoma and papillary carcinoma compared to the healthy population.

Komatsu et al. 1994 describe higher bFGF expression in patients with MEN-1 syndrome [5]. bFGF has a mitogenic effect on the parathyroid tissue *in vitro* [4]. Our results confirm these facts. We found higher bFGF serum concentrations in patients with parathyroid gland adenoma compared to the healthy population.

The role of VEGF in thyroid gland tumors hasn't been quite cleared up yet. It inhibits follicular cells proliferation, but it also supports angiogenesis and tumor tissue vascularisation. It's proved, that VEGF is produced only in the isolated follicles in the normal thyroid gland. Its production rises in thyroid adenomas and especially in carcinomas (except for follicular carcinoma) [12, 14]. Our obtained VEGF serum concentrations aren't in accordance with these data. We can say, that VEGF serum levels negatively correlate with its levels detected directly in the thyroid tumor tissue (described in the literature). It can be explained by the higher growth factor consumption in the tissue, that is reflected by its lower serum concentration. This negative correlation may be dependent on the expression of VEGF receptors in the tissue.

In conclusion, we can say, that bFGF is possible serum marker of thyroid and parathyroid gland neoplasms. Its peripheral serum concentrations reflect the level of angiogenesis in the tumor tissue.

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REFERENCES

1 Eggo MC, Hopkins JM, Franklyn JA, Johnson GD, Sanders DS, Sheppard MC. Expression of fibroblast growth factors in thyroid cancer. J Clin Endocrinol Metab 1995; **80**(3):1006–1011.
2 Patel VA, Hill DJ, Eggo MC, Sheppard MC, Becks GP, Logan A. Changes in the immunohistochemical localisation of FGF-2, TGFβ1 and thrombospondin-1 are associated with the early angiogenic events in the hyperplastic rat thyroid. J Endocrinol 1996; **148**(3):185–199.
3 Shingu K, Fujimori M, Ito K, Hama Y, Kasuga Y, Kobayashi S, Itoh N, Amano J. Expression of fibroblast growth factor-2 and fibroblast growth factor receptor-1 in thyroid diseases: difference between neoplasms and hyperplastic lesions. Endocr J 1998; **45**(1):35–43.
4 D'Adda T, Amorosi A, Bussolati G, Brandi ML, Bordi C. Proliferation of endothelial component of parathyroid gland in multiple endocrine neoplasia type 1. Potential relationship with a mitogenic factor. Am J Pathol 1993; **143**(2):612–617.
5 Komatsu M, Tsuchiya S, Matsuyama I, Kaneko S, Suzuki Y, Ito N, Hanamura N, Seki T, Kobayashi S, Kuroda T. Expression of basic fibroblast growth factor in hyperplastic parathyroid glands from patients with multiple endocrine neoplasia type 1. World J Surg 1994; **18**(6):921–924.
6 Klener P. Cytokines in internal medicine. [In Czech] 1st ed. Prague: Grada Publishing; 1997.
7. Šterzl I. Cytokines – structure and function I., II. [In Czech] Diabetologie, metabolismus, endokrinologie, výživa 1999; **4**(2): 185–205.
8 Sato K, Miyakawa M, Onoda N, Demura H, Yamashita T, Miura M, Kasajima T, Yamazaki K, Obara T. Increased concentrations of vascular endothelial growth factor/vascular permeability factor in cyst fluid of enlarging and recurrent thyroid nodules. J Clin Endocrinol Metab 1997; **82**(6):1968–1973.
9 Sato K, Yamazaki K, Shizume K, Kanaji Y, Obara T, Ohsumi K, Demura H, Yamaguchi S, Shibuya M. Stimulation by thyroid-stimulating hormone and Graves' immunoglobulin G of vascular endothelial growth factor mRNA expression in human thyroid follicles in vitro and flt mRNA expression in the rat thyroid in vivo. J Clin Invest 1995; **96**(3):1295–1302.
10 Viglietto G, Romano A, Manzo G, Chiappetta G, Paoletti I, Califano D, Galati MG, Mauriello V, Bruni P, Lago CT, Fusco A, Persico MG. Upregulation of the angiogenic factor PlGF, VEGF and their receptors (Flt-1, Flk-1/KDR) by TSH in the thyroid gland of thiouracil-fed rats suggests a TSH-dependent paracrine mechanism for goiter hypervascularization. Oncogene 1997; **15**(22): 2687–2698.
11 Wang JF, Milosveski J, Schramek C, Fong GH, Becks GP, Hill DJ. Presence and possible role of vascular endothelial growth factor in thyroid cell growth and function. J Endocrinol 1998; **157**(1): 5–12.
12 Fellmer PT, Sato K, Tanaka R, Okamoto T, Kato Y, Kobayashi M, Shibuya M, Obara T. Vascular endothelial growth factor-C gene expression in papillary and follicular thyroid carcinomas. Surgery 1999; **126**(6):1056–1062.
13 Becks GP, Logan A, Phillips ID, Wang JF, Smith C, DeSousa D, Hill DJ. Increase of fibroblast growth factor (FGF) and FGF receptor messenger RNA during rat thyroid hyperplasia: temporal changes and cellular distribution. J Endocrinol 1994; **142**(2):325–338.
14 Katoh R, Miyagi E, Kawaoi A, Hemmi A, Komiyama A, Oyama T, Shibuya M. Expression of vascular endothelial growth factor (VEGF) in human thyroid neoplasms. Hum Pathol 1999; **30**(8): 891–897.