ONCOLOGY

Sex Steroids and Their Receptors in Patients with Tumors of the Pancreas

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A tendency toward an increase in serum content of sex steroid-binding globulin and a decrease in the total concentration of testosterone and its free and globulin-bound fractions and in the index of free androgens was observed in patients with pancreatic cancer. There were no statistically significant differences in baseline serum levels of hypophyseal hormones and prolactin in male patients and in the control. One or both types of steroid hormone receptors, the content of androgen receptors being higher than that of estrogen receptors, varying in a wide range were detected in 71% of the patients with malignant neoplasms. The occurrence of steroid hormone receptors was higher in adenocarcinomas, while their content was significantly higher in normal pancreatic tissues. The occurrence of androgen receptors was higher in male patients at the early stages of the disease, predominantly in highly differentiated adenocarcinomas located in the body of the pancreas. The content of androgen receptors was higher in male patients, in metastasizing tumors, in adenocarcinomas located in the body of the pancreas, and in patients without clinical and laboratory evidence of the mechanical jaundice syndrome. The content of androgen receptors positively correlated with the maximum size of the tumor.

Key Words: *pancreatic cancer; hormones; receptors*

The problems associated with the therapy of pancreatic cancer so far remain unsolved. Clinical methods are of limited application. On the one hand, this is due to insufficient knowledge about the mechanisms operating in the regulation of neoplasm growth in the pancreas and a small choice of pharmacological preparations. On the other hand, the majority of patients are admitted to the hospital with metastasizing tumors, when radical therapy is impossible [1,3]. This situation prompts improvement of diagnostic methods and search for new therapeutic approaches.

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There is evidence that sex steroids are involved in the regulation of the development and function of pancreatic cells and in blastomogenesis in humans and animals [9,17]. There are different opinions concerning the effects of steroids on malignant tumors of the pancreas [16]. Hormones have been used in the treatment of breast and prostate cancer. Recent evidence shows that steroid hormones are capable of stimulating and inhibiting malignant transformation of the cell and are involved in cancer progression.

Although the pancreas is not classical target organ of sex steroids, estrogen therapy affects its functional activity. Hormones have been used in the treatment of pancreatic cancer as a component not

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only of combined but also of complex therapy [16]. This therapy is based on experimental evidence that estrogens and prolactin influence the development of dimethylbenzanthracene-induced cancer of the pancreas and the conversion of estrone sulfate into biologically active estradiol-17β in pancreatic homogenate. This is typical of hormone-dependent organs such as the mammary gland, endometrium, and prostate [14]. It was reported that the pancreas contains androgen and estrogen receptors [2,6,9]. Since the presence of the receptor proteins in the target cells is an important stage in the mechanism of action of sex steroids, their identification in the pancreas is interesting from theoretical (better understanding of the role of steroids in the pathogenesis of pancreatic cancer) and practical (tumor sensitivity to endocrine therapy) viewpoints [4].

In the present study we compared basal levels of total testosterone, its albumin- and globulin-bound fractions, and hypophyseal hormones and analyzed the relationship between the occurrence androgen and estrogen receptors (AR and ER, respectively) in cytosolic fraction of the pancreas, on the one hand, with the main clinical manifestations of the disease and specific morphological parameters of the tumor, on the other.

MATERIALS AND METHODS

The study included 61 patient (36 men and 25 women, age 29-70 years) treated at the Clinic of Liver and Pancreatic Tumors of the Oncology Research Center in 1984-1992. Forty-one patient had primary pancreatic cancer and four patients had carcinoid. Controls were 16 patients with tumors of other location, in which normal pancreatic tissues were investigated, and 14 practically healthy subjects, in which blood concentrations of sex steroids and hypophyseal hormones was measured. Pancreatic cancer in all the patients was confirmed by morphological data. In 21 patient the tumor was located in the head and in 20 patients in the body of the pancreas. Four patients had the first stage of the disease (one patient $T_1N_0M_0$, three patients $T_2N_0M_0$), 14 patients had the second stage (all $T_3N_0M_0$), 8 patients the third stage (four patients $T_2N_1M_0$; and four patients $T_3N_1M_0$), and 15 patients had the fourth stage (one patient $T_2N_1M_1$, 5 patients $T_3N_0M_1$, and 9 patients $T_3N_1M_1$). Steroid hormones in the cytosolic fraction of the pancreas were determined by protamine sulfate precipitation of the hormone-receptor complex [8]. The index proposed by [7] was used to evaluate hyperandogenization the organism. Free and globulin- and albumin-bound fractions testosterone were calculated by the methods [5,15]. Serum concentrations of sex steroid-binding globulin, total testosterone, luteinizing and follicle-stimulating hormones, and prolactin were determined immunoradiologically using Farmos Diagnostica kits.

RESULTS

Baseline serum levels of hypophyseal hormones and sex steroids were determined 12 male patients before treatment and in 14 healthy subjects (control group). The average age of the patients and healthy subjects was 53.2±2.7 and 52.3±2.2 years, respectively. There were no differences in the levels of luteinizing hormone (patients 10.0±0.9, controls 12.5±1.7 mU/liter), follicle-stimulating hormone (patients 8.3±0.8, controls 10.4±2.9 mU/liter), and prolactin (patients 9.7±2.1, controls 10.6±1.7 ng/ml). However, we noted a tendency toward a decrease in serum concentration of total testosterone in the patients: 11.8±1.0 nM *vs.* 15.0±2.5 nM in the control. It should be noted that decreased serum concentrations of total testosterone in pancreatic cancer was reported by other researchers [12]. In patients, blood globulin concentration varied in a wider range than in healthy subjects: 27-188 *vs.* 25-89 nM. The content of free testosterone was lower in patients (1.64±0.22%), while that of globulin-bound testosterone was higher (65.4±4.6%) in comparison with healthy subjects (free testosterone 2.08±0.11%, globulin-bound testosterone 56.2±2.5%). In healthy subjects the index of free androgens was higher than in patients; however, the difference was statistically insignificant. In male patients with the mechanical jaundice syndrome the globulin concentration was the highest (110.4±22.8 nM) compared with that in the control (46.7±4.5 nM) and patients without this syndrome (59.6±22.2 nM). In patients with the syndrome, the concentration of testosterone decreased and plasma content of globulin-bound was higher than that of albumin-bound testosterone: 65.4±4.4 and 32.9±4.4%, respectively.

One or both types of sex steroid receptors were detected in cytosolic fraction of the pancreas in 71% of the patients, AR in 58.5% and ER in 26.8%. These findings are consistent with the data reported by others [11,14]. The mean levels of AR were higher than those of ER: 50.0±5.8 and 22.2±4.5 fmol/mg protein, respectively. High AR levels were revealed in three patients with carcinoids: 159, 180, and 183 fmol/mg protein. In one patient with carcinoid it was 189 fmol/mg protein. The occurrence of RA was higher than that of RE: 43.9 and 12.2%, respectively. Specific binding of sex steroids was not observed in 29.3% patients with pancreatic cancer.

In six patients (14.6%), both AR and ER were identified. In normal pancreatic tissue AR and ER were found in 50% of cases, their levels being significantly higher than in pancreatic cancer 102.8±13.0 and 50.0±5.8 fmol/mg protein, respectively. In normal and diseased pancreatic tissues, both the occurrence (26.8 and 35.7%, respectively) and levels of AR (22.2±4.5 and 27.0±5.0 fmol/mg protein, respectively) were similar. In contrast to pancreatic tumors, in normal pancreas the occurrence of ER and AR was 2-fold higher (28.5 %). In patients, the RA content tended to increase with age. In patients aged 30-49 years the mean RA content in pancreatic tumor was 46.0±7.2 fmol/mg tissue, RA occurrence being 6%; in patients aged 50-59 years RA content was 49.5±7.9 fmol/mg protein and RA occurrence was 58%, in patients aged 60 years these parameters were 51.4±14.4 fmol/mg protein and 54%. In male patients the occurrence of AR was 60.9% and that of ER was 39.1%. The AR content in them was higher than that of ER: 55.7±7.9 and 26.8±6.0 fmol/mg protein, respectively. The occurrence of AR was similar in female and male patients 55.5 and 60.9%, respectively; ER (12 fmol/mg protein were detected in 2 out of 18 patients with adenocarcinomas (11%). In males, the mean levels (55.7+7.9 and 39.3±7.0 fmol/mg protein, respectively) and the occurrence of AR (3-fold) were higher than in females. Androgen receptors were detected only in 4 out of 14 patients (28.6%) with a 10-90-day long mechanical jaundice syndrome. A tendency toward a decrease in the AR level in the cytosolic fraction was revealed in patients with and without the mechanical jaundice syndrome: 51.3±16.8 and 84.7±15.5 fmol/mg protein, respectively. A positive correlation was established between the maximum size of pancreatic tumor and its RA content (r=0.57, n=24, p<0.05). In male patients with an AR content of 10-50 fmol/mg protein the tumor was significantly smaller (6.1±1.0 cm) than in patients with an AR content of 51-200 fmol/mg protein (8.8±0.5 cm). Pancreatic adenocarcinomas containing no AR had the maximum size: 6±1 cm. Although the AR content in the cytosolic fraction of pancreatic tumor was lower in patients with the first or second stage of the disease (43.2±6.4 fmol/mg protein) than in patients with the fourth stage (72.8±13.0 fmol/mg protein), the occurrence of AR was higher at the early stages of tumor growth (46.6 and 66.7%, respectively). Estrogen receptors were detected in six patients with the first or second stage of the disease, the ER content being 12-136 fmol/mg protein (mean content 36.8±20.3 fmol/mg protein). It tended to decrease in comparison with that in patients with the third or fourth stage of pancreatic cancer (61.6±37.8 fmol/mg protein). The highest level of AR was revealed in pancreatic tumors of the patients with liver metastases (78.9±14.2 fmol/mg protein); it differed significantly from the same parameter in patients without metastases (43.2±8.0 fmol/mg protein, p<0.05). The occurrence of AR was higher in male patients with tumors located in the body of the pancreas than in patients with tumor located in the head of the pancreas (80 and 50%, respectively); the AR content was significantly higher in the body of the pancreas (p<0.05). In female patients, the occurrence of AR was also higher in tumors located in the body (64%) than in the head (43%) of the pancreas; however, the AR content was higher in adenocarcinomas located in the head of the pancreas. These findings point to the sensitivity of adenocarcinomas located in the body and head of the pancreas to steroid hormones.

In highly differentiated pancreatic tumors, the occurrence of AR was 68.7%, in moderately differentiated tumors it was 57.1%, and in poorly differentiated tumors 55%. The RA content significantly increased with the degree of tumor differentiation: in highly differentiated tumors it was 35.3±4.5, in moderately differentiated 47.4±8.0, and in poorly differentiated 81.0±12.3 fmol/mg protein. The occurrence of RA was practically independent of the degree of tumor differentiation: 31.2, 25.0 and 22.2% in highly, moderately, and poorly differentiated tumors, respectively, which agrees with the data of others [14].

Our findings indicate that in pancreatic cancer the concentrations of total testosterone, hypophyseal hormones, globulin, free and bound testosterone, and sex steroid receptors are related to the major clinical and morphological characteristics of the disease and imply a higher sensitivity of pancreatic adenocarcinomas to androgens than to estrogens. Since surgical treatment in most cases of pancreatic cancer is palliative, alternative approaches, including hormone therapy, have been developed [10,13,16]. It should be noted that it was demonstrated that antiestrogens block the growth of pancreatic tumors both in experiment and in clinical practice [17,18]. The presence of AR in pancreatic tumors in the majority of patients confirm the data of Greenway *at al.* [12]. These researchers have hypothesized that androgens and estrogens are involved in the development of pancreatic tumors and that the low serum levels of total testosterone in patients are associated with high activity or aromatase in the tumor. It can be suggested that increased activity of 5α-reductase promotes the formation of a more active androgen in the cells of pancreatic tumor, thus maintaining the synthesis of the receptor pro-

tein at a high level. The fact that ER are not present in pancreatic tumors seems paradoxical if the effectiveness of antiestrogen therapy in the this disease is considered [18]. It should be remembered, however, that the absence of free binding sites for estradiol-17β in the cytosolic fraction of pancreatic tumors does not slash the synthesis of ER in tumor cells. The possibility that the majority of ER is occupied by endogenous estrogens cannot be ruled out. It was reported that the synthesis of these estrogens from testosterone is more intensive in pancreatic tumor than in normal tissue. The possibility that the effect of estrogens on tumor cells in the pancreas is mediated by polypeptide growth factors and prostaglandins cannot be excluded.

Thus, our findings open new prospects in the development of endocrine therapy of pancreatic tumors. The effectiveness of the this therapy should be confirmed by clinical observations.

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