BIOGERONTOLOGY

Expression of Melatonin and Serotonin in Human Prostate Tumors

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We present the results of immunohistochemical study demonstrating possible variants of neuroimmunoendocrine regulation of prostate tumor growth with serotonin, melatonin, and other hormones produced by neuroendocrine cells via paracrine and autocrine secretory mechanisms.

Key Words: *prostate; tumor growth; melatonin; serotonin*

More than half of men above 50 years have tumor diseases of the prostate, which impair sexual function and urination. Melatonin (MT) prevents the development of benign prostatic hyperplasia and decelerates atrophy of the male reproductive organs during aging [4,5]. However, little is known about structural and functional changes in the prostate as the extrapineal source of MT and on age-related variations in the secretion of extrapineal MT, which limits our understanding of the role of MT.

Selective serotonin reuptake inhibitors (serotonin antagonists) improve the prognosis of such diseases as cancer and benign prostatic hyperplasia [1,2]. Studying the disturbances of MT synthesis from serotonin will allow us to develop new methods of therapy for these diseases [3].

Here we studied the role of serotonin and MT produced by neuroendocrine (NE) cells of the prostate in tumor growth.

MATERIALS AND METHODS

Biopsy and surgical samples were obtained from 48 patients with benign prostatic hyperplasia and 32 patients with prostate cancer. The control group included prostate autopsy specimens from 22 men without prostate disease, who died from various causes.

The average age of patients with benign prostatic hyperplasia and prostate cancer and control subjects was 66.4 (50-74 years), 66.3 (58-84 years), and 34.1 years (25-65 years), respectively. Voluntary informed consent for the study of surgical and biopsy specimens was obtained from all patients of the treatment group.

The study was performed by histological and histochemical methods. Antigens were visualized in histological sections by the immunoperoxidase method. Electron microscopy was conducted under a JEM-100B electron microscope (Jeol). Morphometry was performed using a computer system of microscopic image analysis (Nikon) and microscopic image analysis software (Video Test-Morphology-4).

In each case 10 view fields were analyzed (×8400). The mean number of immunopositive cells (×200) was calculated per 1 mm^2 sectional area. Optical density of hormone expression was expressed in arbitrary units. The expression area was calculated as the ratio of the area of immunopositive cells to the total area of cells and expressed in percent. These parameters reflect the synthesis or accumulation of hormones.

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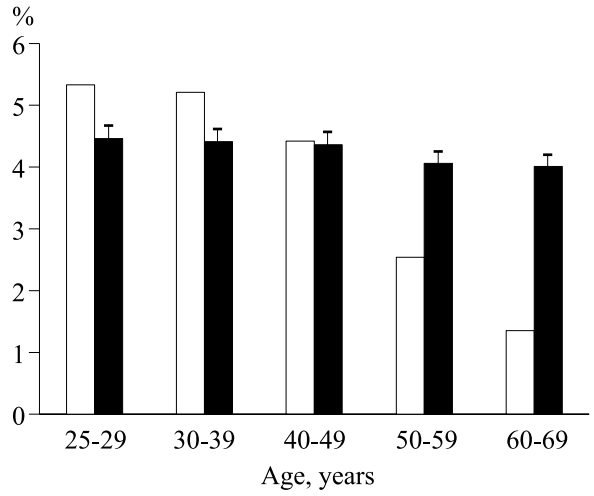

Fig. 1. Expression area for MT (dark bars) and serotonin (light bars) in the prostate of control patients as a function of age.

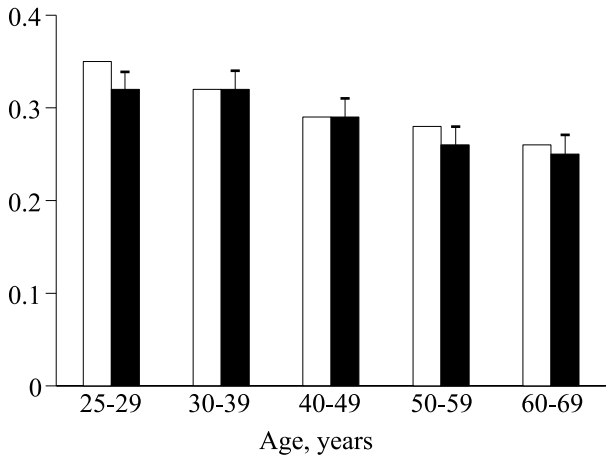

Fig. 2. Optical density for expression of MT (dark bars) and serotonin (light bars) in the prostate of control patients as a function of age.

The results were analyzed by means of Excel and Statistica 5.0 software (Statsoft). Intergroup differences were evaluated by Student's *t* test. Statistical processing also included correlation analysis and calculation of the correlation coefficient (*k*).

RESULTS

Examination of all specimens revealed high expression of MT and serotonin in NE cells. The area of MT expression significantly decreased with age (Fig. 1): in young patients this parameter 4-fold surpassed that in patients of 60-69 years ($p<0.05$). The area of serotonin expression also decreased with age. A positive correlation was revealed between the age of patients and area of MT expression ($k=0.06$).

Optical density of MT and serotonin was maximum in patients of 25-29 years. This parameter significantly decreased in elderly patients ($p<0.05$, Fig. 2).

Our results indicate that expression of serotonin and MT in NE cells of human prostate significantly decreases with age ($p<0.05$).

A certain level of hormone expression (serotonin, MT, *etc.*) in healthy subjects is necessary for normal function of the prostate. The average area of expression is 3-5%. Unfavorable factors (experimental model of premature aging, age, *etc.*) impair the regulatory mechanisms, which results in an increase in the number of NE cells, stimulation of serotonin production and, therefore, development of benign prostatic hyperplasia and adenocarcinoma.

Normal expression of MT was more often observed in intact prostate than in adenocarcinoma. MT expression in adenocarcinoma and normal gland did not differ in 33% specimens. Examination of 59% specimens showed that MT expression in adenocarcinoma is higher than in normal prostate ($p<0.05$, Table 1). A similar pattern of expression was typical of serotonin ($p<0.05$, Table 2). Expression of MT and serotonin in adenocarcinoma was higher than in benign prostatic hyperplasia ($p<0.05$ and $p<0.02$, respectively).

Nonendocrine differentiation in prostatic adenocarcinoma is usually manifested in the appearance of isolated islets with NE cells, which express

TABLE 1. MT Expression in the Prostate of Practically Healthy Men and Patients with Benign Hyperplasia and Adenocarcinoma

Group	Total	Within normal	Increased
Intact prostate	22	20 (90.9)	2 (9.1)
Benign prostatic hyperplasia	48	42 (87.5)	6 (12.5)
Adenocarcinoma	32	13 (40.6)	19 (59.4)

Note. Here and in Table 2: percent of the total number of men in the group is shown in brackets.

TABLE 2. Serotonin Expression in the Prostate of Practically Healthy Men and Patients with Benign Hyperplasia and Adenocarcinoma

Group	Total	Within normal	Increased
Intact prostate	22	21 (95.5)	1 (4.5)
Benign prostatic hyperplasia	48	45 (93.7)	3 (6.3)
Adenocarcinoma	32	11 (34.3)	21 (65.7)

serotonin and MT. Increasing the degree of nonendocrine differentiation is accompanied by a rise in the number and volume of these islets. This type of cell distribution can be considered as a possible focus of nonendocrine differentiation in the subpopulation of epithelial tumor cells. The first change in local tumor homeostasis can be induced by malignant epithelial cell, which gained the postmitotic nonendocrine phenotype due to the effect of an oncogene.

A large body of evidence exists that products of NE cells have the paracrine effect on adjacent epithelial cells in normal and tumor tissue [3-7]. NE cells are arranged in small immature hyperplastic nodules during benign prostatic hyperplasia.

We conclude that normal expression of MT and serotonin is more often observed in intact prostate than in adenocarcinoma. Expression of MT and serotonin in adenocarcinoma is higher than in benign prostatic hyperplasia. The results of immunohistochemical study and published data suggest that serotonin, melatonin, and other hormones of NE cells regulate prostate tumor growth by the paracrine and autocrine secretory mechanisms.

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