PHYSIOLOGY

Role of Sex Hormones in Development of Pituitary Adenoma

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Role of sex hormones in the development of pituitary adenomas was investigated by analyzing the content of nuclear estradiol and testosterone receptors in different tumors of the anterior pituitary: prolactinomas, meningiomas, growth hormone-producing adenomas, astrocytomas, neurinomas, and ependymomas. The concentration of nuclear estrogen and androgen receptors in prolactin-secreting pituitary adenomas was much higher than in growth hormone-producing adenomas and other pituitary tumors.

Key Words: *sex hormones; pituitary adenoma; feedback regulation*

Reception of extracellular regulators occupies a special place in complex mechanisms of biological recognition. According to modern concepts, hormones regulate activity of competent cells via specific receptor proteins. These receptor proteins are responsible for discriminatory reception of the signal and initiation of the corresponding reactions in the cell.

There are two types of receptors differing by their location. Receptors of polypeptide hormones, prostaglandins, and neurotransmitters are located on the plasma membrane, and the effects of these substances are mediated by intracellular messengers cAMP, Ca^{2+}, and cGMP. Steroid and thyroid hormone receptors are located inside the cells and hormone-receptor complexes can directly regulate gene activity. Specific ligand-receptor binding ensures selectivity at the stage of initial recognition of the hormone by the cell; this binding is characterized by very high interaction energy, high affinity, and limited binding capacity. The main principle underlying selectivity of effects of steroids at the level of interactions of hormone receptor complexes with cell nucleus remains unknown.

Studies of steroid reception and cell reactivity to these hormones will extend our views on mechanisms of programming and regulation of vital activity in health and disease, in particular, during development of pituitary adenoma. Hormonal activity of pituitary adenomas depends on functional state of higher CNS compartments and hormonal status (or imbalance). It is now acknowledged that the development of pituitary adenomas is characterized by two stages: first, spontaneous or induced mutations appear in pituitary cells and second, endogenous and exogenous activating factors promote extensive tumor growth. Sex hormones belong to such factors, specifically, estrogens which are important regulators of prolactin (PRL) and gonadotropin secretion. Clinical and experimental data suggest that long-term treatment with high estrogen doses can induce prolactin-secreting pituitary tumors [10].

Here we studied the role of sex hormones in the pathogenesis of pituitary adenomas. To this end we measured the concentrations of nuclear estradiol and testosterone receptors in pituitary adenomas of different structure.

MATERIALS AND METHODS

Experimental material was obtained during surgery from 19 patients (16 women and 3 men) with PRL-

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secreting adenopituitary tumor, 9 patients with meningioma, 3 with astrocytoma, 3 with neurinoma, 2 with somatotropinoma, and 1 with ependymoma. Tumor tissue was homogenized in 0.01 M TEM buffer (0.01 M Tris-HCl, 0.0015 M EDTA, 0.01 M 2-mercaptoethanol, pH 7.4) and centrifuged at 800*g* for 10 min. For isolation of nuclear fraction, the precipitate was homogenized in 0.01 M TEM buffer (0.01 M Tris-HCl, 0.0015 M EDTA, pH 6.8) and centrifuged in 2.2 M sucrose at 13,000*g*. Under these conditions nuclei precipitated after 60 min, while other cell elements floated to the surface [2]. The number of specific binding sites in the nuclear fraction of tumor tissues was evaluated by competitive radioligand binding assay [6]. Labeled hormones were 17-β-2,4,6,7-^{3}H-estradiol (^{3}H-E2, specific activity 90 Ci/mmol, St. Petersburg) and 1,2,6,7-^{3}H-testosterone (^{3}H-T, specific activity 75 Ci/mmol, Amersham). Aliquots of nuclear fraction were incubated with saturating concentrations of ^{3}H-E2 (6×10^{-9} M) and ^{3}H-T (40×10^{-9} M) at 32°C for 60 min, twice washed from free hormone with TEM buffer (pH 6.8), and the precipitate was transferred to scintillation vials with 1.5 ml ethanol. Radioactivity was measured in a SL-30 liquid scintillation counter (Intertechnique). The number of binding sites in nuclei was estimated in fmol/mg DNA and the content of DNA was measured as described previously [7].

RESULTS

The maximum concentration of nuclear estradiol receptors was found in PRL-secreting pituitary tumors (Fig. 1, *a*), it 3.7- and 5.0-fold surpassed receptor concentration in meningioma and astrocytoma, respectively. The concentration of estradiol-binding sites in neurinoma was also decreased, while in somatotropinoma this parameter was virtually the same as in PRL-secreting pituitary adenomas.

Similar relationships were revealed for nuclear testosterone-binding sites : the number of nuclear testosterone receptors in tumor cells secreting PRL and GH (Fig. 1, *b*) 2-fold surpassed that in meningioma and astrocytoma and was 3.7-fold higher than in neurinoma.

These results attest to a relationship between the concentrations of estradiol and testosterone receptors in PRL-secreting pituitary tumors (in particular, in prolactinomas). It seems that disturbed receptor binding in brain structures regulating gonadotropic function of the pituitary and PRL secretion impairs the feedback mechanism in the hypothalamus-pituitary-gonadal system. This is confirmed by clinical symptoms: prolactinomas are associated with sexual dysfunction (amenorrhea, galactorrhea, sterility in women, decrease or loss of libido, impotency, and azoospermia in men). At present some problems in the etiology, pathogenesis, strategy of examination, and therapy of patients with tumor-induced hyperprolactinemia are solved [1,3-5], but the role of sex hormones in the pathogenesis of PRL-secreting tumors remains unclear. According to one theory, the principal role is attributed to impairment of the hypothalamic regulation, while in another theory the key mechanism is a primary gene defect in pituitary cells. These concepts reflect two consecutive stages in the formation of pituitary adenomas. Phase I consists in appearance of spontaneous or induced mutations in pituitary cells, while during phase II the primary role is played by endogenous and exogenous activating factors, in particular, sex hormones promoting tumor growth. Estro-

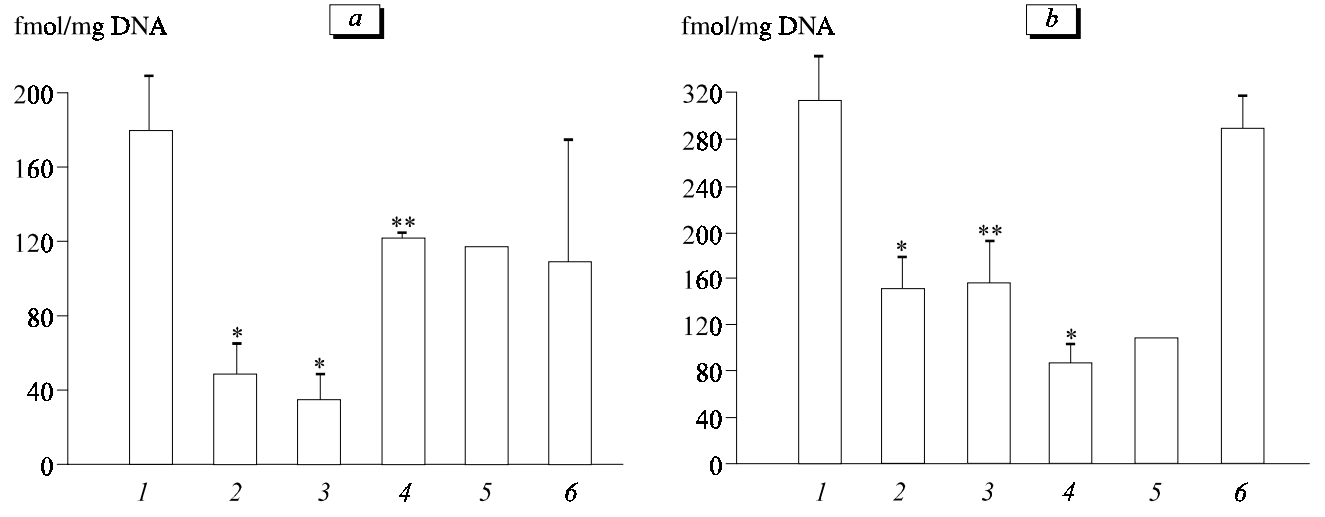

Fig. 1. Concentration of nuclear estradiol (*a*) and testosterone (*b*) receptors in tumors. *1*) prolactin-secreting pituitary adenoma (n=17), *2*) meningioma (n=9), *3*) astrocytoma (n=3), *4*) neurinoma (n=3), *5*) ependymoma (n=1), and *6*) GH-secreting tumor (n=2). *p<0.001, **p<0.05 *vs.* prolactin-secreting pituitary adenoma.

gens regulate PRL secretion in the pituitary and increase PRL concentration in the blood [8,9]. This stimulatory effect of estrogens was observed *in vitro* in pituitary explants [13], adenohypophyseal tumor cells [11], and primary culture of intact rat adenohypophysis [15]. During menstrual cycle, blood concentration of PRL changes synchronously with estrogen level; the concentration of both hormones peaks in the middle of the cycle [3]. Long-term treatment with high doses of estrogens can induce PRL-secreting pituitary tumors both in rats and humans [10]. Estrogens stimulate the proliferation of lactotrophs and cause the development of PRL-producing tumors in some inbred rat strains.

These data indicate that estrogens stimulate or modulate PRL secretion in humans and rats, but the target and mechanism of their effects in PRL-secreting cells are unknown. Little is also known on the role of androgens in the regulation of PRL secretion. Injection of testosterone to castrated rats of both sexes increased blood concentration of PRL [12,14].

Our data on specific binding of androgens in tumor cells and differences in the concentration of testosterone receptors in tumors of different structure and location agree with published data. Moreover, it seems that endocrine therapy can be used in pituitary PRL-secreting tumors. Elucidation of the target, mechanisms, and role of sex hormones in this process will contribute to the solution of fundamental problem of pituitary PRL-secreting tumors.

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