PHARMACOLOGY AND TOXICOLOGY

Relative Binding Activity of New Antigestagens with Progesterone Receptors in Human Hyperplastic Endometrium

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We determined the content and binding capacity of progesterone receptors in the endometrium of patients with adenomatous and fibroid polyps, adenocystic hyperplasia, and atypical hyperplasia before and after gestagen therapy. Hyperplasia of the endometrium was accompanied by changes in affinity of cytosolic progesterone receptors for antigestagens, which provides the possibility of individual correction of hormone therapy.

Key Words: *progesterone receptors; antigestagens; endometrial hyperplasia*

Malignant processes in the endometrium are often preceded by endometrial hyperplasia (EH). Clinical observations indicate that the incidence of uterine cancer progressively increases and ranks fourth among malignant neoplasms in women [1,3,5]. In light of this studies of the pathogenesis, early diagnostics, and optimal therapy of EH are of considerable importance.

The main forms of EH include adenomatous and fibroid polyps (AFP), adenomatous hyperplasia, adenocystic hyperplasia (ACH), and atypical hyperplasia (AH). AH characterized by structural changes and intensive proliferation of glands is associated with high risk of cancer. This disease is transformed into endometrial cancer in 10% patients (according to different reports the incidence of transformation varies from 2 to 50%) [5,7,10].

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Recent studies showed that the sensitivity of endometrial receptors to steroids plays an important role in the development of EH. The efficiency of hormone therapy depends on the state of receptors on target cells [2,4]. Conservative therapy of patients with EH includes various hormonal preparations: gestagens, complex estrogen-gestagen drugs, antiestrogens, gonadotropin antagonists, and agonists of luteinizing hormone-releasing hormone.

Gestagens and antiestrogens are used for the therapy of EH because gestagens act as physiological antagonists of estrogens, while antiestrogens block the effect of estrogens at the receptor level. From this standpoint successful therapy of leiomyoma and endometriosis with antigestagens suppressing the effect of progesterone on target cells via blockade of its receptors seems to be paradoxical [6,8]. The effect of these preparations is probably associated with blockade of progesterone-dependent biosynthetic processes in target cells.

Here we studied binding properties of endometrial progesterone receptors for antigestagens for individual correction of hormone therapy in patient with various forms of EH.

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MATERIALS AND METHODS

We studied the relative binding capacity (RBC) for new modified pregna-D'-pentaranes 16α,17α-cyclohexanoprogesterones (derivatives of progesterone with the additional carbocycle D') synthesized at the N. D. Zelinskii Institute of Organic Chemistry (laboratory of Prof. A. V. Kamernitskii): 16α,17α-cyclohexane-5α-pregnane-3,20-dione (5α-pentarane), 16α,17α-cyclohexane-5β-pregnane-3,20-dione (5β-pentarane), and mifepristone (RU-486).

Clinical samples were obtained from the Department of Obstetrics and Gynecology (Therapeutic Faculty, Russian State Medical University). We studied samples from patients with AFP (n=16, control group), ACH (n=39), and AH (n=19) obtained before and after progestin therapy with 17-hydroxyprogesterone capronate.

The age of patients was 33-45 years. The associated extragenital diseases included anemia, disorders of the gastrointestinal tract, liver, biliary tract, and kidneys, type I-III hypertension, and type I-II obesity. Most patients had combined extragenital diseases.

In patients with EH, 71% of associated diseases were presented by inflammation of the reproductive organs. EH was often accompanied by leiomyoma and adenomyosis (40 and 29%, respectively). It should be emphasized that 24% patients had leiomyoma associated with adenomyosis. This indicates that proliferative changes in the endometrium and myometrium are mediated by the same pathogenetic mechanisms. In 50% patients EH was associated with diseases of the uterine cervix, which suggests indirect structural damage to the endometrium. In 36% patients anamnesis included diagnostic uterine curettage; repeated curettage was performed in 50% these patients and followed by hormone therapy.

The samples were examined immediately after surgery or stored at -25°C for no more than 3 days. Protein content and binding of ^{3}H-estradiol (E_2) and ^{3}H-progesterone (P_4) to receptors for E_2 (RE) and P_4 (RP), respectively, were assayed in the cytosolic endometrial fraction.

RBC for pentaranes at RP in human hyperplastic endometrium was estimated by the method of M. Schneider *et al.* [9].

The data were processed with standard statistical methods. Between-group differences were evaluated by Student's t test.

RESULTS

RBC for test preparations depended on the type of pathological processes in the endometrium (Fig. 1). EH was associated with changes in binding characteristics of cytosolic RP. Progestin therapy also affected these parameters.

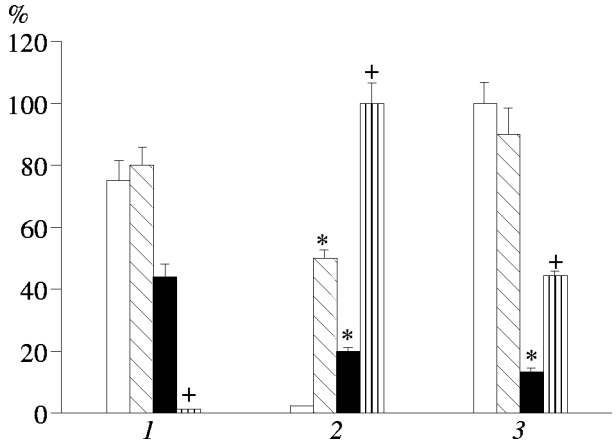

Fig. 1. Relative binding capacity for mifepristone (*1*), 5α-pentarane (*2*), and 5β-pentarane (*3*) with progesterone receptors in the cytosolic fraction of human endometrium. Light bars: adenomatous and fibroid polyp. Oblique shading: adenocystic hyperplasia. Dark bars and vertical shading: atypical hyperplasia before and after gestagen therapy, respectively. p<0.05: *compared adenomatous and fibroid polyp; +compared to atypical hyperplasia before gestagen therapy.

In patients with AH receiving gestagens for 3 months RBC for 5α-pentarane increased by 5 times (Fig. 1). In AFP samples this compound did not displace progesterone from the progesterone-RP complex. The maximum RBC for 5β-pentarane was found in AFP and the minimum RBC for this compound was detected in AH before therapy (however, this parameter increased during progestin therapy, Fig. 1). RBC for the reference drug mifepristone was similar in AFP and ACH, while in AH this parameter was 2-fold lower and sharply decreased during therapy (Fig. 1).

Our findings suggest that gestagen therapy not only decreased the number of RP in the cytosolic endometrial fraction, but also modified affinity of these receptors for the ligands. RP lost the ability to bind mifepristone. A unique property of the test compounds was their ability to displace progesterone from the progesterone-RP complex in the endometrium after hormone therapy. These data indicate that pentaranes hold much promise for conservative therapy of patients with AH.

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