THE BIOLOGICAL ROLE OF ESTRIOL

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Experiments on the human and guinea pig uterus showed that the activity of steroid-receptor interaction of estriol in vitro is 9.4% for the guinea pig and 17% for the human uterus relative to the activity of estradiol. Injection of estriol into guinea pigs in vivo in a dose of 0.25-5 mg sharply reduced the estriol-binding capacity of the uterine receptor system. The existence of competition between estradiol and estriol for binding with the active centers of the receptor proteins of the uterus is postulated.

KEY WORDS: estrogenic receptors of the uterus; estriol (biological role); binding of steroids with receptors (mechanism).

The effect of steroid hormones is known to take place through complex formation with the receptor systems of target organs [6, 10, 14].

Estradiol has the greatest affinity for the estrogenic receptor system of the uterus, and at the same time it is the most active natural estrogen [9, 11]. Estriol, the other natural estrogen, can also bind in appreciable amounts with the receptors of the uterus [9, 11]. However, it has no biological action, and it can accordingly be regarded as an inactive metabolite of estradiol [2]. In this case the biological significance of changes in the ratio between estradiol and estriol toward accumulation of the latter during pregnancy remains obscure [1, 5, 12, 15].

In this investigation an attempt was made to discover the biological role of estriol by studying the character of its interaction with the uterine receptors.

EXPERIMENTAL METHOD

Female guinea pigs weighing 100-130 g were decapitated and the uterus was removed and treated in the cold. Uterine tissue from women obtained at hysterectomy for complete prolapse also was used. It was considered that the properties of the estradiol-binding system of the human uterus remain unchanged with age [7]. The estradiol-binding system was isolated from the uterus by the method described previously [4]. 17β-Estradiol-6,7-H^3 (specific activity 56 Ci/mmole; Radiochemical Centre, Amersham, England), preliminarily purified by chromatography on paper in the B_3 system of Bush, and a number of natural and synthetic steroids (Table 1) were used. The specificity of steroid binding was determined by the method described previously [4] and expressed as a percentage relative to the binding of estradiol. In some experiments the animals received two injections (20 h and 1 h before sacrifice) of estriol in doses of 0.25, 0.5 1, and 5 mg in 0.1 ml propylene glycol or 0.2 ml peach oil. The binding system was incubated with increasing quantities (from 100 to 450 pg) of labeled estradiol.

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TABLE 1. Affinity of Steroids of the Estrone Series to the Estradiol-Binding System of the Human and Guinea-Pig Uterus

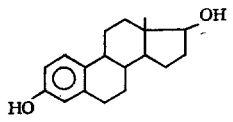
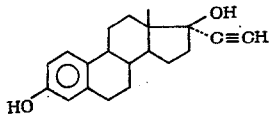
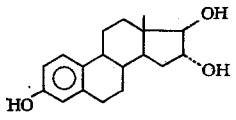
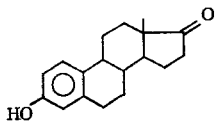
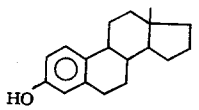
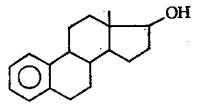
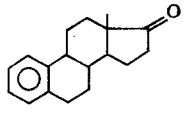
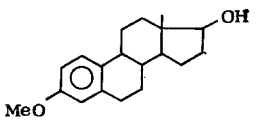
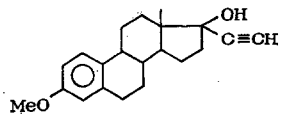
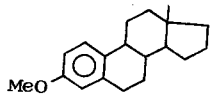
Name of steroids	Formula	Binding (relative affinity (in %)	
		human uterus	guinea pig uterus
Estradiol		100	100
Ethinylestradiol		91,7	81,0
Estriol		17,0	9,4
Estrone		12,4	24,8
17-Deoxyestradiol		33,3	1,37
3-Deoxyestradiol		3,66	0,45
3-Deoxyestrone		1,66	0,2
3-Methoxyestradiol		1,35	0,45
3-Methoxyethinyl-estradiol		1,3	0,9
17-Deoxy-3-methoxy-extradiol		1,1	0,016

TABLE 2. Change in Binding of Labeled Estradiol by Receptor System of Guinea-Pig Uterus after Injection of Different Doses of Estriol in Vivo

Character of experiment	Binding of labeled estradiol) (in %)	
	injection in oil	injection of propylene glycol
Control	100	100
Injection of estriol (in mg)		
0,25	32,4	—
0,5	28,8	18,1
1	23,4	16,4
5	—	15,8

[1]Animals of control groups received injections of oil or propylene glycol and binding of labeled estradiol by receptor system of uterus of these animals was taken as 100%.

EXPERIMENTAL RESULTS

As Table 1 shows, 17β-Estradiol, 17β-ethinylestradiol, estrone, estriol, and 17-deoxyestradiol had the greatest affinity for the uterine estradiol-binding system. All these estrogens have an unsubstituted hydroxyl group in the third position of the A phenol ring of the steroid molecule, which is evidently decisive for interaction with the estrogenic receptor of the uterus. A similar pattern was found by Hähnel et al. [9]. Removal or substitution of the phenolic hydroxyl group almost completely abolished binding, as was observed in the case of 3-deoxy- and 3-methoxysteroids (Table 1). However, modification of position 17 also plays an important role. Estrone, 17-deoxyestradiol, and estriol, in which the hydroxyl group at C_{17} forms a cyclic arrangement with the hydroxyl group at C_{16}, possessed much less affinity for the binding system. Attachment of the steroid molecule to the active center of the receptor evidently takes place initially through the phenolic hydroxyl group. This may perhaps facilitate attachment of the hydroxyl group in the β-position of the 17th carbon atom of the steroid D ring to the receptor. Only interaction with two points of the active center of the receptor can lead ultimately to the manifestation of biological activity of the estrogen.

It can accordingly be postulated that steroids with modified oxygen function in position 17 bind with the active center of the receptor only through the phenolic hydroxyl group and, with no biological effect themselves, prevent the binding of other steroids. A similar blocking effect has been postulated for 17α-estradiol which, as a biologically inactive estrogen, can form complexes with the uterine receptors [13]. Estradiol also, which binds with only one point of the active center of the receptor, may perhaps also have a blocking action and prevent binding of estradiol and the manifestation of its biological effect.

The experiments actually showed that estriol, if injected into guinea pigs in doses of 0.25-5 mg, sharply inhibits binding of labeled estradiol with the receptor system of the uterus of these animals (Table 2). These results suggest that estradiol and estriol compete for binding with the active centers of the receptor proteins of the uterus.

The results to some extent explain clinical observations indicating changes in the ratio between estradiol and estriol toward accumulation of the latter during pregnancy, a decrease in the estriol level with the development of threatened abortion, and the use of estradiol and other active estrogens for the induction of labor in cases of delayed onset of labor and postmaturity [3, 8, 15].

The biological role of estriol can be considered to be the protection of pregnancy by limiting or abolishing the action of estradiol on the uterus through its blocking effect on the estrogenic receptors of the uterus.

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