Correlation of Estrogen-Induced Uterine Eosinophilia with other Parameters of Estrogen Stimulation, Produced with Estradiol-17β and Estriol

Two separate receptor systems for estrogens, thought to be involved in independent mechanisms of estrogen action, have been found to exist in vitro and in vivo in the rat uterus. These are the cytosol-nuclear receptor system and the eosinophil receptor system[1-4]. The cytosol-nuclear receptor system exists in the epithelial, stromal and muscular cells of the uterus[2,4] and is responsible for the genomic response of estrogens, i.e., the increases in uterine RNA and protein synthesis[5]. The eosinophil receptor system exists in the uterine eosinophils and is considered to be involved in some of the early estrogenic responses in the uterus, such as water imbibition, increase in vascular permeability, histamine releasing and estrogen priming effects[1-3].

The cytosol-nuclear and the eosinophil receptor systems have been shown to differ in their affinities for estradiol-17β and estriol[1]. To clarify the role of each receptor system in the mechanism of estrogen action, it is necessary to compare the affinities of estradiol and estriol for each receptor system with the potency of these estrogens for each parameter of estrogen stimulation. The present study intends to correlate, under identical experimental conditions, the potencies of estradiol-17β and of estriol for several parameters of estrogen stimulation with the change in the total number of eosinophils in the uterus and with the data available on the affinities of these steroids for the cytosol-nuclear and the eosinophil receptor systems.

Material and methods. Female immature Wistar rats, weighing 40 g, were used in the present experiments. A solution of estradiol-17β or estriol was injected into the jugular vein under ether anesthesia, using one of several dosages between 0.001 and 30 µg/100 g body weight. The

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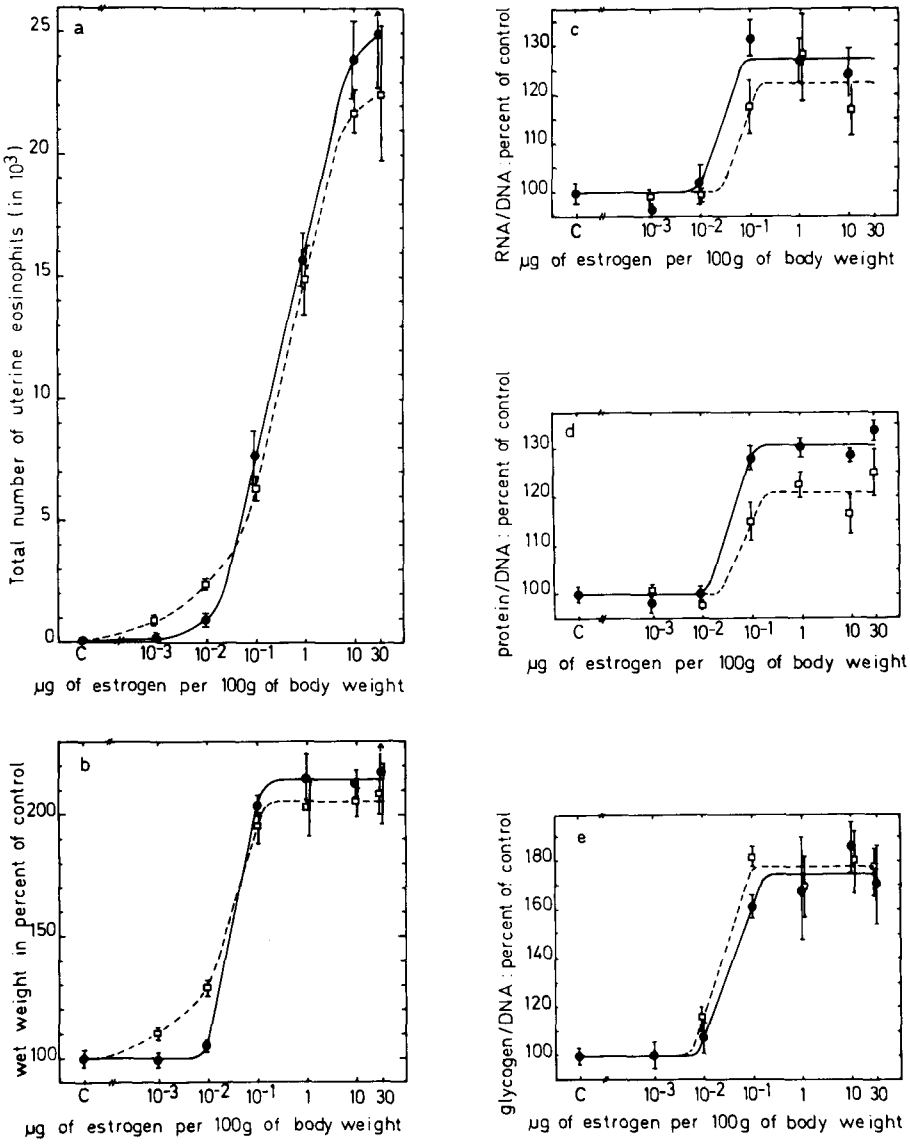

Dose response of estrogen-induced uterine eosinophilia and other parameters of estrogen stimulation. Estradiol-17β (●—●) or estriol (□---□) was given i.v. 6 h before the animals were sacrificed. The uterine eosinophilia (a) is expressed as the total number of eosinophils in the uterus. The uterine wet weight (b), RNA/DNA (c), protein/DNA (d) and glycogen/DNA (e) increases are expressed as Δ% of the controls.

control rats were similarly injected with equal amounts of the vehicle. The animals were sacrificed 6 h after the injection and the uteri excised. The right uterine horn was used for biochemical studies and the left uterine horn was used for histological studies.

The following parameters were measured in the uterus of each animal: wet weight, DNA[6], RNA[7], protein[8] and glycogen[9] content, and the total number of uterine eosinophils[10]. The effects of the estrogen stimulation were assessed individually in each animal. The mean value ($\pm$ SEM) of each parameter of estrogen stimulation were calculated by pooling the results obtained in each of the 8 to 12 animals used for each experimental condition. The uterine wet weight ,RNA/DNA, protein/DNA and glycogen/DNA increases were expressed as percent change over the controls. The uterine eosinophilia was expressed as the total number of eosinophils in the uterus.

Results. The Figure shows the increases in the total number of uterine eosinophils, in the uterine wet weight and in the uterine RNA, protein and glycogen content 6 h after the i.v. injection of estradiol-17β or estriol. Estriol is a stronger estrogen than estradiol for the uterine eosinophilia and the uterine wet weight responses (Figure a and b). Estradiol is a stronger estrogen than estriol for producing increases in the uterine RNA and protein content (Figure c and d). Both hormones present similar potencies to induce the increase in the uterine glycogen content, except at a dose of 0.1 µg/100 g body weight, dose at which estriol produces a slightly stronger response than estradiol (Figure e).

Discussion. The present investigation shows that estradiol-17β is a stronger estrogen than estriol for the genomic response of estrogens, that is, the 6 h increases in the uterine RNA and protein contents. It is well established that estradiol-17β has a higher affinity than estriol for the uterine cytosol-nuclear receptor system[11]. Comparing the affinity data of estradiol-17β and estriol for the cytosol-nuclear receptor system with the dose-response of these estrogens, it is clear that the genomic response of estradiol-17β and estriol correlates with the affinities of these estrogens for the cytosol-nuclear receptor system. This correlation provides further support of the evidence for the mediation of the genomic response of estrogens by the uterine cytosol-nuclear receptor system.

A different situation occurs with the estrogen-induced uterine eosinophilia and the 6 h increases in the uterine wet weight. Estriol is a stronger estrogen than estradiol-17β for inducing these two parameters of estrogen stimulation. We have previously shown that estriol has a higher affinity than estradiol-17β for the receptors in the uterine eosinophils[1]. Comparing the affinity data of estradiol-17β and of estriol for the eosinophil receptors with the dose-response data of these estrogens, it is clear that the uterine eosinophilia and the 6 h wet weight responses produced by estradiol-17β or estriol correlate with the affinities of these estrogens for the eosinophil receptors. This correlation supports the hypothesis of the mediation of the uterine eosinophilia and the 6 h wet weight responses by the eosinophil receptors[1,3,12].

Summary. Estradiol-17β is a stronger estrogen than estriol for the genomic response of estrogens. Estriol is a stronger estrogen than estradiol-17β for the estrogen-induced uterine eosinophilia and the 6 h increase in the uterine wet weight[13].

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Time-Dependence of Estradiol Effects on Protein Synthesis in the Rat Neurohypophysis

The participation of estrogens in the modulation of the oxytocin-releasing reflex is now well documented[1,2]. Estrogens can alter this reflex by acting at any of several sites along the arc. One of possible sites of action is the neurohypophysis itself, i.e., estrogens could modify the responsiveness of the posterior lobe to nervous signals triggering oxytocin release. In a recent work we have observed that the neurohypophysis of the spayed female rat is able to concentrate and retain estradiol from the blood stream, and contains a cytoplasmic macromolecular component that binds estradiol with high affinity[3]. Estradiol uptake varies diurnally and seems to be dependent upon melatonin secretion from the pineal gland[3]. The present experiment was undertaken to examine the time-dependency for estrogens effects on the posterior lobe by measuring changes in ^{3}H-leucine incorporation into neurohypophyseal proteins as a function of time of injection of estradiol.

Material and methods. Wistar female rats were kept in the light from 07.00 to 21.00 daily and were given access to food and water ad libitum. Rats castrated 3 weeks earlier received a single dose of 0.3 µg estradiol or vehicle at 06.00 or 14.00 h. 24 h later the rats were sacrificed and pools of 2 neurohypophyses were incubated for 1 h at 37 °C in Krebs-Ringer bicarbonate buffer containing 1.5

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