22. INTRAUTERINE INSTILLATION OF ESTROGEN: DISSOCIATION BETWEEN TWO GROUPS OF RESPONSES TO THE HORMONE

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To test whether estrogen-induced changes in the uterus are responsible for the massive migration of eosinophils to the organ after hormone administration, the effects on this response of intraluminal administration of estradiol into one uterine horn were measured in the injected and the controlateral horn. Genomic responses (hypertrophy and nucleolar enlargement of luminal epithelial cells) were measured as control for the absence of sufficient hormone recirculation to the non-injected horn. Intraluminal injection of 0.1 ng estradiol had no effect at all on either horn. With 10 ng, the genomic responses were present in the injected horn only while eosinophilia developed to the same extent in both horns. With 100 ng, the genomic responses and eosinophilia were identical in both horns. This is interpreted as eosinophil migration depends on systemic levels of estrogen. The finding that water imbibition (edema) showed the same pattern than eosinophilia lends further support to the hypothesis of the role of eosinophils in estrogen-induced uterine edema.

23. AN ENDOGENOUS INHIBITOR OF ^{3}H-ESTRADIOL BINDING IN RAT UTERINE NUCLEI

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The rat uterus contains two classes of specific nuclear estrogen binding sites which may be involved in estrogen action: the classical estrogen receptor type I (Kd$\sim$1nM) and nuclear type II sites (Kd$\sim$10-20nM) which are only activated or stimulated by estrogen under conditions which cause uterine hypertrophy and hyperplasia. Extraction of uterine nuclei with 0.4 M KCL or dilution of nuclear fractions prior to quantitation of estrogen binding sites by ^{3}H-estradiol exchange results in an "opening up" or increase (4-7 fold) in type II sites, whereas type I sites are not affected by this treatment. These increases in nuclear type II sites appear to be independent of protein concentration and may result from the extraction or dilution of a specific inhibitor of ^{3}H-estradiol binding to the nuclear type II site. We have isolated and purified this inhibitor and its molecular weight is 354. The inhibitor is present in cytosol preparations from rat uterus, liver, spleen, diaphragm, skeletal muscle and serum. Its uterine cytoplasmic levels are not affected by estrogen administration, ovariectomy or adrenalectomy. At present we do not understand the physiological significance of this inhibitor. However, if this material interferes with the type II sites in vivo, it may act to suppress estrogenic responses following hormone withdrawal by down-regulating nuclear type II estrogen binding sites.

24. THE ABSENCE OF BIOLOGICAL ACTIVITY OF PROGESTERONE AND ITS METABOLITES AND OF SYNTHETIC PROGESTINS APPLIED LOCALLY TO THE UTERI OF SPAYED MICE

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The extent to which extra- and intra- target tissue metabolism of progesterone and other progestins plays a role in their mode of action is obscure. To clarify it is necessary to show the relative direct action of these compounds and of progesterone on the uterus. Experiments were therefore done in an attempt to measure the biological activity after local application in oestrogen-primed spayed mice.

Oestradiol-17β stimulated mitosis in the luminal epithelium following intraluminal injection. Although progesterone inhibited this response when injected s.c. a relatively large dose of progesterone, its metabolites or synthetic progestins, failed to alter mitosis or epithelial morphology when injected locally. Thus a continuous penetration to a site of action may be necessary to elicit a response. Maybe progesterone occupies receptors briefly and only elicits full response when given in sufficiently high or frequent doses to occupy receptors for a sufficient time (Martin, 1969). In the spayed animal a depot would achieve this, such conditions being obtained by s.c. injection but not by local application.