Effect of propranolol on various parameters of estrogen stimulation in the rat uterus[1]

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Summary. Pretreatment with propranolol does not modify the estrogen-induced uterine eosinophilia, the water imbibition effect, nor the increase in uterine RNA and protein content. This confirms the independence of these parameters from the estrogen-induced early increase in uterine cAMP, since, when observed, the latter is suppressed by propranolol pretreatment.

The role of adenosine 3′,5′-cyclic monophosphate (cAMP) in estrogen action in the uterus still remains unclear. It has been reported that the administration of estrogen to ovariectomized rats provokes an early increase in the uterine concentration of cAMP[2,3] and adenyl cyclase activity[4]. While there is controversy on this point[5,6], there is agreement to the fact that even when observed both responses can be prevented by the administration of DL-propranolol, a β-blocking and membrane stabilizing agent[3,4,7]. Exogenously administered cAMP produces estradiol-like induction of several uterine glycolytic enzymes[8,9] and an increase in the production of a specific, estradiol-sensitive cervicovaginal antigen[10,11]. Propranolol was found to inhibit the estrogen-induced increase in the production of this specific cervicovaginal antigen[11], but failed to inhibit other parameters of estrogen stimulation[7,11,12], suggesting that cAMP is involved in some but not all estrogenic responses.

Evidence has been published for the mediation of various estrogenic effects by 2 different and independent mechanisms[13–17]. 2 separate receptor systems for estrogens were found in the rat uterus: the cytosol-nuclear[18–20] and the eosinophil[13,14,21–24] receptor systems. The cytosol-nuclear receptor system is thought to be responsible, through a 2-step mechanism[18–20], for the genomic response, which involves an increased transcription of mRNA and increased protein synthesis in uterine cells. The eosinophil receptor system was proposed by one of us[13,15,17] 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.

To elucidate the possible role, if any, of cAMP in one or both of the above-mentioned mechanisms of estrogen action, and to determine whether or not one may dissociate from them a 3rd mechanism of estrogen action that would be mediated by cAMP, we studied the effect of propranolol on various parameters of estrogen stimulation.

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Effect of propranolol on the estrogen-induced uterine eosinophilia and other parameters of estrogen stimulation, 6 h after the administration of 30 μg estradiol-17 β/100 g b. wt

Parameter of estrogen stimulation	Experimental condition			
	Control	Propranolol	Estrogen	Propranolol + estrogen
Total number of uterine eosinophils	30 ± 11	127 ± 64	26333 ± 1825	31423 ± 3298
Uterine wet weight in percent of controls	100 ± 9.3	101.6 ± 11.2	203.9 ± 22.9	209.3 ± 14.1
Uterine protein/DNA in percent of controls	100 ± 2	101 ± 2	128 ± 7	121 ± 5
Uterine RNA/DNA in percent of controls	100 ± 5	103 ± 7	127 ± 9	127 ± 7
Uterine glycogen/DNA in percent of controls	100 ± 16	95 ± 15	134 ± 32*	102 ± 17*

*Not significant, as compared to controls.

Material and methods. Female immature rats, weighing 50 g, were used in the present experiments. A solution of estradiol-17β in 5% ethanol-saline was injected into the jugular vein under ether anesthesia, using a dosage of 30 μg/100 g b.wt. The control rats were similarly injected with equal amounts of the vehicle. The propranolol-treated animals were i.p. injected with 50 μg DL-propranolol (in saline)/100 g b.wt 20 min prior to the estrogen or vehicle injection.

The animals were killed 6 h after estrogen (or vehicle) administration and the uteri excized. The right uterine horn was used for biochemical studies and the left uterine horn was fixed in neutral formalin for subsequent histological studies[17].

The following parameters were measured for each animal: uterine wet wt, DNA[25], RNA[26], protein[27] and glycogen[28] content, and total number of uterine eosinophils[16]. The increases in uterine wet wt, RNA per unit of DNA, protein per unit of DNA and glycogen per unit of DNA were expressed as percent change over the controls. The uterine eosinophilia were expressed as the total number of eosinophils in the uterus.

Results. DL-Propranolol, injected i.p. 20 min prior to the estrogen injection, does not block the estrogen-induced uterine eosinophilia, the uterine wet wt response or the estrogen-induced increases in uterine RNA and protein contents ($p < 0.001$, $p < 0.01$, $p < 0.025$ and $p < 0.05$ respectively as compared to controls without estrogen injection) (table). The differences in glycogen content between estrogen and estrogen+propranolol-treated animals, as well as those between control and estrogen-treated animals, are not statistically significant ($p > 0.05$) (table).

Discussion. Our results show that a pretreatment with propranolol does not block the estrogen-induced uterine eosinophilia, the water imbibition effect nor the increases in uterine RNA and protein contents. It was previously shown that a similar pretreatment with propranolol suppresses the estrogen-induced increase in uterine cAMP[3,7]. Therefore, it can be assumed that the estrogen-induced uterine eosinophilia and the water imbibition effect (proposed by one of us to be mediated by the eosinophil receptor system[13,15,17]), and the estrogen-induced increases in uterine RNA and protein contents (generally considered to be mediated by the cytosol-nuclear estrogen receptor system[18–20]) are independent of the estrogen-induced increase in uterine cAMP content.

The differences in glycogen content between estrogen and estrogen+propranolol-treated animals were not statistically significant in our experiments ($p > 0.05$). It was, however, previously shown that exogenously administered cAMP produces an estradiol-like induction of several glycogenolytic enzymes[8,9] and that theophylline, a drug that promotes cAMP accumulation by inhibiting phosphodiesterase, potentiates the action of submaximal doses of estradiol on several uterine glycogenolytic enzymes[29]. This suggests that cAMP is involved in this estrogenic effect, probably as a separate mechanism of estrogen action. Our previous studies with cortisol-treated animals have also demonstrated the independence of the glycogen effect from estrogen-induced uterine eosinophilia[30]; and our experiments with estradiol and estriol have suggested the possibility that the glycogen effect is independent of the cytosol-nuclear estrogen receptor system[31].

Our previous studies have shown that cortisol drastically decreases the estrogen-induced uterine eosinophilia and water imbibition responses[30]. It was suggested that the cortisol-induced blood eosinopenia limits the number of eosinophils entering the uterus after estrogen administration, thereby limiting all estrogen responses assumed to be dependent on the eosinophil estrogen receptor system (i.e. water imbibition effect)[30]. Alternatively, the lysosome membrane-stabilizing properties of cortisol could account for this antiestrogenic effect of cortisol[32]. Our present results permit us to discard the latter possibility since propranolol, a drug with lysosome membrane-stabilizing properties similar to cortisol[11], failed to inhibit both the uterine eosinophilia and the water imbibition estrogenic effects.

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Reversal of metamorphosis in mealy bugs treated with juvenile hormone-active insect growth regulator[1]

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Summary. Anal pore-plates are a typical adult characteristic of male mealy bugs. Nymphs treated with a juvenile hormone-active insect growth regulator moult several times into intermediary forms between nymph and adult. The number of the anal pores is reduced during each of these supernumerary moults.

The postembryonic development of the mealy bugs is a rather complicated process. The first 2 larvel stages of both sexes are similar; in the females even the 3rd and 4th instars – the latter may be regarded as being the neotenic adult – still retain the same basic form. The male larvae of the 3rd and 4th instars, called pronymph and nymph, develop the wing buds as the first adult characteristics. The ventral part of the anal segment remains, however, still smooth as in younger instars (figure 1). The nymph moults into the adult male which is, besides the fully developed wings, characterized by 2 plates on the ventral side of the anal segment with numerous pores (80–100) (figure 2).

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