EFFECT OF PROGESTERONE ON THE MITOTIC ACTIVITY OF THE EPITHELIUM OF THE REPRODUCTIVE ORGANS

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The stimulant action of progesterone on the mitotic activity of the uterine epithelium of rabbits has been known for a relatively long time [7]. These findings have been confirmed in mice [1]. It has been shown that progesterone, besides estrogens, is capable of stimulating the mitotic activity of the epithelium of the mammary glands of castrated female mice [2]. Biochemical methods of analysis have shown that progesterone, if injected into rats together with estradiol, depresses the growth-stimulating action of the latter, but if injected before the animals receive estradiol, it subsequently increases the action of the latter [5]. If the uterine cornua of guinea pig embryos are cultivated in a nutrient medium with the addition of progesterone in doses of 1 and 2 μg/ml, the mitotic activity of uterine epithelium is substantially depressed by the influence of the progesterone [6].

On the basis of data in the literature and personal observation, the author earlier concluded that estrogens, in small doses, stimulate and in large doses, given repeatedly, depress the mitotic activity of the epithelium of the reproductive organs. The epithelial cells of the uterine glands are most sensitive to estrogens, followed by the epithelium of the uterus, the vagina, and the mammary glands [3,4].

The object of the present investigation was to determine whether the same general rules govern the action of progesterone on the mitotic activity of the epithelium of the reproductive organs.

EXPERIMENTAL METHOD

Pilot experiments showed that the most suitable dose of progesterone for demonstrating its action on the mitotic activity of the epithelium of the mammary glands is 0.5 mg per diem on the castrated female mouse weighing 20-25 g. The corresponding dose for the uterus and vagina is 0.2 mg.

The experiments of series I were carried out on 41 noninbred sexually mature female albino mice weighing 20-25 g. On the 20th day after castration, the mice received daily subcutaneous injections of 0.5 mg progesterone in 0.1 ml apricot oil in the dorsal region. The mice were sacrificed at 11 A.M. 24 h after receiving the last of 2, 4, and 7 injections. The control group of castrated mice received 7 injections, each of 0.1 ml of apricot oil, daily, after which they were sacrificed. The histological treatment of the material and determination of the mitotic activity were carried out as in the previous investigations [2].

The animals of series II received daily subcutaneous injections of 0.2 ml progesterone in apricot oil 20 days after castration. The mice were sacrificed after 2, 3, 4, and 6 injections of progesterone. The controls were castrated mice receiving 6 injections, each of 0.1 ml apricot oil. The second series of experiments was carried out on 30 animals.

EXPERIMENTAL RESULTS

The results of the experiments of series I are shown in Table 1, from which it is clear that no mitoses were present in the mammary gland epithelium of the control castrated animals. After the administration of progesterone, mitoses appeared. Their number reached a maximum after 4 injections, amounting on the average to 4.55 ‰. After 7 injections, the mean mitotic index fell to 0.63 ‰. The difference between these results is statistically significant ($P < 0.01$).

In the animals used in the experiments of series II (Table 2), after the second injection of progesterone, the mitotic activity of the vaginal epithelium increased by a statistically significant degree from 1 ‰ in the controls to

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TABLE 1. Action of Progesterone on Mitotic Activity of the Epithelium of the Mammary Glands of Castrated Female Mice

Number of injections of progesterone	No. of animals	Mean value of MI in ‰	P
2	6	0.39	0.002
4	9	4.55	
7	8	0.63	0.01
7 injections of oil (control)	8	0.00	

Note: Here and in Table 2, MI stands for mitotic index.

2.61 ‰ in the experimental animals (P = 0.0001). After the third injection of progesterone, the mitotic activity of the vaginal epithelium reached a maximum, 11 ‰. In the mice sacrificed after the fourth injection of hormone, the mean mitotic activity was 8.94 ‰, and after 6 injections it fell to 3.28 ‰ (P = 0.001).

In the epithelium lining, the uterine cavity, after 2 and 3 injections of progesterone, the mitotic activity remained the same as in the control animals. However, after the fourth injection of progesterone, the mitotic activity of the uterine epithelium increased from 2.17 to 6.50 ‰ (P = 0.001). In the animals sacrificed after 6 injections, the mitotic activity fell to 2.22 ‰ (P = 0.001).

In the epithelium of the uterine glands, the mitotic activity was lower after injection of progesterone than in the control series throughout the experiment. Hence, in these experimental conditions, progesterone did not stimulate the mitotic activity of the epithelium of the uterine glands, but instead, inhibited it. Possibly a smaller dose of progesterone is required for stimulating the mitotic activity of the epithelium of the uterine glands.

It follows from these results that progesterone, when injected repeatedly into castrated female mice, at first causes an increase in the mitotic activity of the epithelium of the mammary gland and vagina and of the epithelium lining the uterine cavity, and then, after 3-5 injections, it depresses mitotic activity. Consequently, progesterone, like the estrogens, is at the same time a stimulator and an inhibitor of the mitotic activity of the epithelium of the reproductive organs and mammary glands.

As was shown previously [3], the sensitivity of the vaginal epithelium to estrogens is lower than that of the uterine epithelium and, in particular, of the uterine glands. With respect to progesterone, slightly different relationships are observed. The mitotic activity of the vaginal epithelium in the present experiments increased immediately after the first injections of progesterone, whereas to bring about an increase in the mitotic activity of the uterus, four injections were needed (Table 2). In addition, the maximal level of mitotic activity induced by progesterone was much higher in the epithelium of the vagina than in the uterus.

Hence, the vaginal epithelium is most sensitive to the action of progesterone, and next follows the epithelium of the uterus. The epithelium of the mammary glands reacts to larger doses of progesterone than the epithelium of the vagina and uterus. Further experimental investigations are needed to determine the role of progesterone in the regulation of the mitotic activity of the epithelium of the uterine glands.

Evidently in female mammals, the proliferative processes in the epithelium of the different reproductive organs may be stimulated or depressed independently by different concentrations of ovarian hormones. The effect of the combined action of estrogens and progesterone on the mitotic activity of the epithelium of the reproductive organs may be either stimulating or inhibitory, depending on the concentration of these hormones and the sensitivity of the particular organ to them. This may go a long way towards explaining the contradictions in the reports published in the literature.

TABLE 2. Action of Progesterone on Mitotic Activity of the Epithelium of the Vagina and Uterus of Castrated Female Mice

Number of injections of progesterone	Number of animals	Vagina		Uterine cavity		Uterine glands	
		MI in ‰	P	MI in ‰	P	MI in ‰	P
2	6	2.61	0.0001	2.72	0.500	0.61	
3	6	11.00	0.223	1.94	0.001	0.61	0.223
4	6	8.94	0.001	6.50	0.001	1.83	
6	6	3.28		2.22	2.72	1.22	
6 injections of oil (control)	6	1.00		2.17		2.72	0.001

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of the first issue of this year.
