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THE EFFECT OF ESTROGEN AND ANDROGEN ON THE SEBACEOUS GLAND TURNOVER TIME*

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ABSTRACT

The effect of estrogens on sebaceous gland cell turnover time was measured in four adult male volunteers administered 1 mg of ethinyl estradiol daily for six weeks. Two of the subjects were continued on ethinyl estradiol for an additional six weeks during which time 100 mg of methyl testosterone was administered orally per day together with the estrogen. Biopsies were obtained from the non-hairy area of the cheek 40 minutes subsequent to the intradermal injection of 10 microcuries of tritiated thymidine. During the administration of 1 mg of ethinyl estradiol, a decrease of approximately 50% in the labeling index of the human sebaceous gland and its germinative layer was observed. When 100 mg of methyl testosterone was administered concomitantly with the estrogen, the labeling indices returned toward normal. The changes in the labeling indices were accompanied by corresponding changes in sebum production.

It has been well established that human sebaceous glands are influenced by sex steroids. The administration of methyl testosterone to prepuberal males has been shown to result in both an increase in sebaceous gland size, as determined by histologic examination of serial sections, and an increase in glandular activity, as measured by the gravimetric determination of sebum production (1). The administration of estrogen in high doses to adult males has been shown to decrease both sebaceous gland size and sebum production levels. However, smaller doses of estrogen, which do not produce a histologically recognizable reduction in glandular size, may still significantly reduce the secretion of sebum (2). Such a descrepancy is somewhat difficult to explain since the sebaceous gland is a holocrine structure in which size would be expected to parallel secretory rate. The difference may lie in the possibility that the gravimetric determination of sebum production is a more sensitive method than the estimation of glandular size by histologic observation. It also may be due to alterations in cellular activity in the sebaceous gland. For example, planimetric measurements of sebaceous gland size in rats have shown that estrogens decrease gland size without decreasing mitotic activity (3). In fact, it was found in immature rats that estrogen administration increased the incidence of mitosis. In this study, we have investigated the effect of estrogens on sebaceous gland cell turnover utilizing the technic of tritiated thymidine nuclear tagging. We have also studied the effect on cell turnover from the concomitant administration of estrogen and androgen. The turnover studies have been compared with sebum production levels determined gravimetrically.

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MATERIALS AND METHODS

Four adult male volunteers were administered 1 mg of ethinyl estradiol orally per day for six weeks. During an initial control period, and at the end of six weeks of ethinyl estradiol administration, a 4 mm punch biopsy was obtained from the non-hairy area of the cheek, 40 minutes subsequent to the intradermal injection of 10 μc of tritiated thymidine (6.7C/mM; obtained from New England Nuclear Corporation, Boston, Mass.) according to the method described by Epstein and Epstein (4). Two of the subjects were continued on 1 mg of ethinyl estradiol orally per day for an additional six weeks during which time 100 mg of methyl testosterone daily was administered orally together with the estrogen. Additional biopsies were obtained from these two subjects at the end of the experiment. Radioautography was performed on serial sections of each specimen utilizing Kodak NTB-2 photographic emulsion. The tritiated thymidine labeling index (the number of labeled nuclei per 1000 total nuclei) was determined for both the germinative layer and for the whole gland. A minimum of 1500 germinative cells

and 5200 total gland cells were counted for each subject. Sebum production was measured approximately once weekly according to the method of Strauss and Pochi (5). The values for sebum production given in this paper represent a mean of the last three values during each observation period.

RESULTS

The results are given in Table I. Tests for statistical significance were determined by the method of paired comparisons. The labeling index, calculated both for the germinative layer and for the whole gland, is shown for each subject during the control period, during the period of ethinyl estradiol administration, and during the period of ethinyl estradiol plus methyl testosterone administration for the two subjects so treated. During estrogen administration, the labeling index as determined for both the whole gland and the germinative layer fell to approximately 50% of the respective control values. When methyl testosterone was administered with ethinyl estradiol, the labeling indices returned toward the control level. The decrease of about 50% in the labeling indices during estrogen administration was accompanied by a decrease in sebum production which varied from 30% to 58% in the four subjects. When methyl testosterone and ethinyl estradiol were administered together, sebum production returned toward the control level, roughly paralleling the changes in the labeling indices.

Histologic examination showed no recognizable decrease in gland size in any of the four subjects during estrogen administration.

DISCUSSION

The daily dose of 1 mg of ethinyl estradiol was chosen because this level had been previously shown to produce a consistent decrease in sebum production in most adult males without a detectable histologic decrease in gland size. The studies reported here reveal that this dose also produces a significant decrease in the labeling indices of the sebaceous glands.

The turnover time of a constantly renewing population of cells such as the sebaceous gland can be calculated if the DNA synthesis time is known and if the labeling index is determined by direct counting (6, 7). The relationship between turnover time and labeling index can be expressed by the following formula:

$$T = \frac{t_s}{n_s/N}$$

Where:

T is the turnover time

t_s is the DNA synthesis time and

n_s/N is the labeling index, that is, the number of labeled nuclei per total nuclei present

Therefore, as the labeling index decreases, the value for the turnover time increases. If the DNA synthesis time of the proliferating cells of the sebaceous glands is not altered by the administration of estrogen, then the observed decrease in the labeling index would be indicative of an increase in the turnover time.

Ebling (3) utilized the colchicine arrest method to study the effect of estrogen on the proliferation of rat sebaceous glands. From his studies it appeared that exogenous estrogen decreased the turnover time of the sebaceous glands in rats. However, both Ebling's study and ours have not taken into account the possibility that estrogens may alter various phases of the cell cycle. For example, Ebling's finding

TABLE I

Effect of hormonal administration on labeling indices of the germinative layer and of the whole sebaceous gland, and on sebum production

Subject		Germinative layer labeling index	Whole gland labeling index	Sebum production (mg/10 cm²/3 hr)
1.	Control	75.4	42.3	4.23
	Ethinyl estradiol*	44.4†	12.8‡	2.92‡
2.	Control	69.8	28.0	2.20
	Ethinyl estradiol	46.8†	13.5‡	1.56‡
3.	Control	79.6	35.2	1.69
	Ethinyl estradiol	41.4†	13.4‡	0.71‡
	Ethinyl estradiol plus methyl testosterone	73.1	29.3	1.29
4.	Control	60.8	33.8	3.74
	Ethinyl estradiol	35.7†	17.6‡	1.60‡
	Ethinyl estradiol plus methyl testosterone	59.3	30.0	2.05

* See text for dosages.

† $P < .01$.

‡ $P < .05$.

of an increased incidence of mitoses in immature rats could result from a prolongation of mitosis under the influence of estrogens. Our findings of a decreased thymidine labeling index could result from a shortening of DNA synthesis time.

This study showed a correlation between labeling indices and sebum production levels. Such a correlation indicates that the decreased sebum production levels resulted from effects on the gland itself, either directly or indirectly, and not from other factors such as impeded delivery of sebum to the skin surface, etc. With the administration of estrogen, there was a consistent decrease in the labeling index to about 50% of the control value. A corresponding but more variable decrease was found in the sebum production level. These values also correlated well when testosterone was administered concomitantly with estrogen, both showing a return toward the control level. Furthermore, these results show that estrogens alter the cellular activity of the sebaceous glands even though visible changes in gland size were not detectable. Human sebaceous glands do not readily lend themselves to accurate planimetric measurements because of the marked variability in size between glands and the irregular shape of the individual glandular acini. However, if accurate planimetric studies were feasible, changes in gland size might have been detectable.

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