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Structural Characteristics of Antifibromatogenic Steroids: Experiments with Acetoxy-Pregnenolone.*

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Abdominal fibroids elicited by estrogens in the uterus[1] and in other parts of the abdominal cavity[2,3] have been shown to be prevented by 4 different steroids present in the body (testosterone, progesterone,[4] desoxycorticosterone,[5] dehydrocorticosterone[6,7]). Attention has been called to the fact that all these substances which possess antifibromatogenic activity are 3-keto-steroids.[8,9,10] Likewise dihydrotestosterone, a 3-keto-steroid not present in the body, was antifibromatogenic.[11,12] On the contrary, androsterone[13] and androstane-3-cis-17-trans-diol[12], steroids with an hydroxyl group at C_3, were not antifibromatogenic.

Since the side chain of two carbons at C_{17} apparently enhances the antifibromatogenic activity of a 3-keto-steroid,[8,9,10] the question arose whether a steroid with an hydroxyl group at C_3 might acquire antifibromatogenic faculty when a side chain of two carbons was added at C_{17}, Δ5-Pregnene-3,21-diol-20-one-21-monoacetate (21-acetoxypregnenolone)† offered the opportunity to study this question.

Tablets of estradiol and of acetoxypregnenolone (abbreviated A.O.P.) were implanted subcutaneously into 15 castrated female guinea pigs. One-half to 4 tablets of A.O.P. were used so as to vary the quantity absorbed. The tablets remained in the body for 90 days. The quantity absorbed was calculated from the loss of weight of the tablets washed and dried in vacuum. Results are given in Table I. The fibrous tumoral reaction was classified according to the system explained in former papers.

The average fibrous tumoral effect (F.T.E.) of A.O.P. acting simultaneously with estradiol was the same as with estradiol alone. The number of animals with abdominal fibroids of a diameter of about 3 mm or more, was also the same with A.O.P. as with estradiol alone. A.O.P. did not prevent other estrogenic or toxic actions of estradiol. The vagina was maintained open throughout the whole course of the experiment. There was genital bleeding and marked growth of the uterus. On the other hand these effects of estradiol are prevented by progesterone or desoxycorticosterone though not always with such small quantities of progesterone as in the present experiment.

The fibrous tumor reaction was still greatly pronounced when more than 300 μg of A.O.P.

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TABLE I.

Group	Estradiol absorbed per day, μg	Progesterone or A.O.P. absorbed per day μg	No. of animals	No. of animals with tumors classes 2 and 3	Avg fibrous tumoral effect F.T.E.†	Uterine wt, g
Estradiol alone*	16-46	0	15	12	5.1 (2-10.0)‡	5.7 (3.0-12.0)
Estradiol and progesterone*	28-56	Progester. 13-24	14	0	1.4 (1-2.5)	3.0 (1.7-5.1)
Estradiol and A.O.P.	21-63	A.O.P.§ 70-322	15	12	4.8 (1.5-8.0)	4.3 (2.5-8.2)
Estradiol and A.O.P.	26-63	A.O.P. 70-102	5	5	5.8 (2.5-8.0)	5.2 (4.0-8.2)
Estradiol and A.O.P.	30-40	128-202	5	4	4.8 (1.5-7.5)	4.2 (2.5-6.4)
Estradiol and A.O.P.	21-37	248-322	5	3	4.1 (1.5-6.5)	3.6 (2.5-6.2)

* From sets of experiments in 15.

† For an explanation of the units of F.T.E. see Lipschütz *et al.*, PROC. SOC. EXP. BIOL. AND MED., 1941, **46**, 164, and other papers.

‡ In parentheses—range.

§ Quantities calculated as free oxypregnenolone.

per day were absorbed. On the contrary, the antifibromatogenic threshold[14] of progesterone is about 13 μg per day;[12] that of desoxycorticosterone acetate is about 90 μg per day.[7,9] The difference between these two steroids and A.O.P. is striking.

A.O.P. is known to have corticoid activity[16,17] only slightly inferior to that of desoxycorticosterone acetate, but its progestational activity is about 25 times less than that of progesterone.[18] Antifibromatogenic activity was apparently concomitant with the progestational one;[9,15] the small progestational activity of A.O.P. would be in accord with the failure of the latter to prevent the fibromatogenic and other toxic actions of estradiol. The fact that A.O.P. has also some estrogenic activity[19] also might be relevant. Because of the great variations one meets in work with experimental fibroids we cannot state whether the diminished F.T.E. and uterine weight in the groups with greater quantities of A.O.P. (see second half of the table) indicate that A.O.P. had a slight antifibromatogenic activity.

Summary. Quantities of acetoxypregnenolone 10 to 20 times greater than the antifibromatogenic threshold of progesterone were unable to prevent the fibromatogenic and other toxic actions of estradiol. This gives new evidence in favor of the following 2 assumptions: first, that the ketonic oxygen at C_3 is essential, or highly important for the antiestrogenic and antifibromatogenic activity of steroid hormones; and second, that the antifibromatogenic activity is often concomitant with the progestational one.

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