Steroid Compounds, Vasodilation, and Vasoconstriction in the Mouse[1] (36749)

THOMAS R. FORBES AND GAIL GLASSEN

Department of Anatomy, School of Medicine, Yale University, New Haven, Connecticut 06510

An earlier investigation (1) has demonstrated that the administration of some steroid compounds is followed by significant increases in the diameter of the ovarian and uterine veins of the ovariectomized mouse. The effects of continuous administration of eight additional steroid substances on the diameters of those and other veins in the ovariectomized mouse are now to be reported.

Materials and Methods. Segments of cylindrical and uniformly compressed pellets of single crystalline steroids without excipient were prepared (2). The compounds were estriol, androsterone, androstenedione (androst-4-ene-3, 17-dione), Δ^5-pregnenolone (5-pregnen-3β-ol-20-one), 11α-OH-progesterone (11α-hydroxypregn-4-ene-3,20-dione), 5α-pregnanedione (5α-pregnan-3,20-dione), 5β-pregnanedione (5β-pregnan-3,20-dione), and etiocholanolone (3α-hydroxy-5β-androstan-17-one). Adult virgin Jackson Laboratory B6D2F$_1$ (C57BL/6-J $\times$ DBA/2-J) mice were ovariectomized. One week later by a previously described technique (1) a 3.5–4.5 mg segment of pellet was attached by a ligature to the right uterine horn. Care was taken not to obstruct or touch major blood vessels. Glass pellets similar to those made of steroid compounds were implanted by an identical technique in ovariectomized control mice. There were 10 animals in the 7-day control group, in the 21-day control group, and in each of the 16 experimental groups. Each control and experimental group was killed by ether inhalation 7 or 21 days after implantation of pellets. The abdomens were opened and seven major veins (Table I) were carefully exposed without touching them. The diameter of each vein at the point indicated in Fig. 1 was measured in the arbitrary units of an ocular micrometer, and the measurements for a given vein in a given control or experimental group were averaged. Next, the 10 individual measurements for a given vein in an experimental group were compared with the 10 corresponding measurements in the appropriate control group, and the Wilcoxon rank sum test (3) was applied to determine whether the difference in the two groups was significant ($p < .05$). It was realized that comparing the various 7-day experimental groups with the single 7-day control group and comparing the 21-day experimental groups with the single 21-day control group, although it simplifies statistical analysis, has the effect of producing more significant differences than is strictly appropriate at the 0.05 significance level. Differences which were significant at this level were therefore regarded as borderline.

Results. Observations 7 and 21 days after pellet implantation are reported in Table I in terms of percentage increase or decrease in average diameter of experimental veins as compared to their controls, but only if such values differed significantly by the rank sum test. A blank space in Table I indicates that the individual values of the corresponding experimental group did not differ significantly from those of the controls.

Discussion. Exogenous progesterone and estrogens have been shown to produce dilation in the uterine, coronary, and internal mammary vessels of rats and mice (4–9). Uterine hyperemia is a feature of pregnancy and the estrous cycle in the same species (10, 11). The present study measures the relative effect of eight compounds on seven major veins. Of the latter, the right uterine,

[1] This research was supported by Grant GB 16749 from the National Science Foundation.

TABLE I. Percentage Increase or Decrease[a] When Significant[b] in Average Diameter of Veins after Treatment with Steroid Pellets Compared to Averages for Corresponding Veins in Control Mice with Glass Pellets.

	Ovarian		Uterine		Common Iliac		
	Left	Right	Left	Right	Left	Right	Inf. vena cava
7-Day treatment							
Estriol	28***	32***	40***	42***			
Androsterone		12*	23***	34***		10*	
Androstenedione	26**		13*	34***			
Δ5-Pregnenolone	12*	37***	8*	35***			—10**
11α-OH-Progesterone[c]	28*	25**		35***			
5α-Pregnanedione		17**	13**	26***			
5β-Pregnanedione	21**	20*	32***	35***			
Etiocholanolone		20*	21***	32***			
21-Day treatment							
Estriol	30**	23***	59***	61***			10***
Androsterone	18*	16*	25**	28**			11**
Androstenedione		14**	15**	31***			15***
Δ5-Pregnenolone		18*		9***		—4**	7**
11α-OH-Progesterone[d]						—11**	9**
5α-Pregnanedione			12*	15*			
5β-Pregnanedione						—4*	
Etiocholanolone					—5*	—9*	

[a] Minus values.

[b] $*p < .05$; $**p < .01$; $***p < .001$.

[c] Pellets almost totally absorbed at autopsy.

[d] Pellets completely absorbed before autopsy.

left uterine, right ovarian, and left ovarian veins appeared to be most responsive. It will be recalled that the segment of pellet was attached to the *right* uterine horn; presumably, the greatest amount of steroid was absorbed into the right venous tributaries.

All pellets were subjected during preparation to the same amount of compression. It is known that uniformly made pellets of some steroid compounds are absorbed much more rapidly than others (12). Such differences presumably influenced the present results. If, for example, 11α-OH-progesterone had not been absorbed so rapidly (Table I), its effect might have been greater.

Whereas ovarian and uterine veins when they responded significantly usually did so by increasing in diameter, the iliac veins, which receive the blood from the uterine veins, either were essentially unresponsive or actually underwent moderate decreases in diameter. The inferior vena cava, measured at a point just beyond that where the blood from the right ovarian vein enters, after 21 days usually showed a modest but undeniable dilation.

These data support our earlier conclusion that the administration of some steroid compounds is associated with significant increases in diameter in the ovarian and uterine veins of the ovariectomized mouse (1). It can now be added that under the conditions of the experiment the iliac veins, which receive the blood from the uterine veins (Fig. 1), showed no positive response, while the inferior vena cava, measured at a point after it had received the drainage from the ovarian, uterine, and iliac veins, showed modest increases in diameter after 21 although not after 7 days. On the basis of present evidence, it appears that in the ovariectomized mouse the response of a vein to a given steroid depends on the steroid, its concentration in the vein, the duration of treatment, and, very likely,

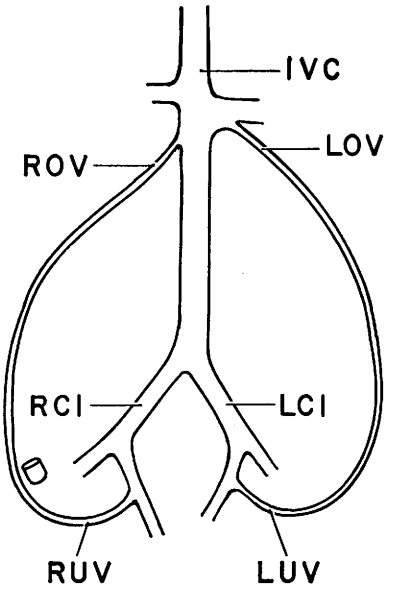

FIG. 1. Diagram of mouse veins studied. Inner ends of leaders indicate points at which veins were measured. Note position of pellet. LOV, left ovarian vein; ROV, right ovarian vein; LUV, left uterine vein; RUV, right uterine vein; LCI, left common iliac vein; RCI, right common iliac vein; IVC, inferior vena cava.

the identity of the vein itself.

Summary. The response of selected major veins in the ovariectomized mouse to the implantation beside the right uterine horn of a pellet of a crystalline steroid was determined by comparing venous diameters to corresponding diameters in control mice in which glass pellets had been implanted. The left and right ovarian and uterine veins and the inferior vena cava underwent significant enlargement, particularly after treatment with estriol, androsterone, and androstenedione. The left common iliac was unresponsive. Some compounds caused decreases in the diameter of the right common iliac vein.

1. Forbes, T. R., and Glassen, G., Amer. J. Obstet. Gynecol. **113**, 678 (1972).
2. Forbes, T. R., Endocrinology **29**, 70 (1941).
3. White, C., Biometrics **8**, 33 (1952).
4. Holden, R. B., Endocrinology **25**, 593 (1939).
5. Hooker, C. W., Proc. Soc. Exp. Biol. Med. **45**, 270 (1940).
6. Kalman, S. M., J. Pharmacol. Exp. Ther. **124**, 179 (1958).
7. Reynolds, S. R. M., Amer. J. Obstet. Gynecol. **36**, 437 (1938).
8. Williams, M. F., Amer. J. Anat. **83**, 247 (1948).
9. Zweens, J., Cardiologia **40**, 17 (1962).
10. Bindon, B. M., J. Endocrinol. **44**, 523 (1969).
11. Wexler, B. C., Amer. J. Obstet. Gynecol. **107**, 6 (1970).
12. Forbes, T. R., Endocrinology **32**, 282 (1943).

Received June 12, 1972. P.S.E.B.M., 1972, Vol. 141.