The Rapid Response of Ovarian and Uterine Veins of Mice to Sex Hormones

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Subcutaneous injections in sesame oil of testosterone and estradiol-17β into ovariectomized and ovariectomized-hysterectomized young adult mice were followed in six hours or less by significant increases in the diameters of the ovarian and uterine veins as compared to the same vessels in sesame oil-injected controls. The circumflex iliac, femoral, and superior mesenteric veins and inferior vena cava failed to respond. The results demonstrate the specificity and speed of response of ovarian and uterine veins of mice and the control of the response by sex hormones.

In ovariectomized and ovariectomized-hysterectomized adult mice in which pellets of testosterone or estradiol-17β had been implanted, the ovarian and uterine veins were found to have increased significantly in diameter when the mice were autopsied 21 days after pellet administration. The superior mesenteric, circumflex iliac, and femoral veins and the inferior vena cava did not respond [1]. In the intact mouse a similar specific enlargement of the ovarian and uterine veins occurs in response to endogenous ovarian hormones. Both the response and the subsequent regression of the veins take place within the span of the 4½–5 day estrous cycle [2]. A question arose as to just how rapidly the specific venous enlargement can occur. The experiments to be described were devised in part to answer this question.

MATERIALS AND METHODS

Each control and experimental group consisted of ten young adult (6–8-week-old) female mice of the B6D2F1 strain. Body weights were 21–25 gm. The mice were supplied with food and water ad libitum.

All surgery was carried out under ether anesthesia. Some mice were bilaterally ovariectomized by a fine cautery via a dorsal incision. The ovaries of the remaining mice were first removed by this method; then the animals were hysterectomized by cautery through a midventral incision. In all cases great care was taken to minimize damage to the ovarian, uterine, and other major blood vessels.

Seven days after surgery the control mice were injected with 0.15 ml sesame oil, while the experimental mice received 0.13 mg testosterone or estradiol-17β dissolved in 0.15 ml sesame oil. All injections were subcutaneous and middorsal. (Earlier, intraperitoneal injections were abandoned when signs of peritoneal inflammation were subsequently discovered.) The mice were killed by ether inhalation at intervals of 1, 419

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1½, 3, 6, and 24 hours after injection. Selected major veins were exposed without pulling on or touching them and without blood loss. The venous diameters were measured at standardized locations in the arbitrary units (59.5 units = 2 mm) of an ocular micrometer in a dissecting microscope [3,4].

The ten measurements for a given vein in a given group were averaged. Control and experimental averages were compared. The degree of significance of the difference between an average for an experimental group and the average for its control group was determined by application of the Student $t$-Independent Test.

**RESULTS**

Sesame oil alone never caused significant ($p < 0.01$) changes in venous diameter. Neither testosterone nor estradiol-17β in oil significantly affected the diameters of circumflex iliac, femoral, or superior mesenteric veins or inferior vena cava. The average measurements of the ovarian and uterine veins are presented in Table 1.

Ovarian veins regularly showed significant response by six hours after injection in

| Surgery, hours | Injection | Ovarian | Uterine |
|---------------|-----------|---------|---------|
|               |           | L       | R       | L       | R       |
| O,1           | C         | 8.9     | 9.6     | 9.9     | 9.8     |
| O,1½          | C         | 9.0     | 9.5     | 9.7     | 10.2    |
| O,3           | C         | 10.3    | 10.8    | 10.9    | 10.8    |
| O,6           | C         | 9.6     | 10.3    | 10.1    | 10.4    |
| O,24          | C         | 8.2     | 8.4     | 9.7     | 9.4     |
| O,1           | E         | 8.5     | 8.2     | 10.0    | 9.7     |
| O,1½          | E         | 9.9     | 10.0    | 12.2    | 13.0    |
| O,3           | E         | 11.0    | 10.6    | 14.1    | 13.4    |
| O,6           | E         | 11.7    | 11.0    | 14.7    | 14.5    |
| O,24          | E         | 12.9    | 13.3    | 14.8    | 14.9    |
| O,1           | T         | 8.8     | 9.5     | 10.1    | 10.6    |
| O,1½          | T         | 9.9     | 9.1     | 11.5    | 11.7    |
| O,3           | T         | 10.3    | 10.3    | 13.3    | 14.3    |
| O,6           | T         | 10.8    | 10.5    | 14.3    | 14.5    |
| O,24          | T         | 12.0    | 12.1    | 13.4    | 14.4    |
| OH,1          | C         | 9.1     | 9.2     | 9.8     | 10.2    |
| OH,1½         | C         | 8.4     | 8.9     | 9.9     | 10.4    |
| OH,3          | C         | 9.8     | 11.3    | 10.7    | 11.4    |
| OH,6          | C         | 8.5     | 9.8     | 10.5    | 10.0    |
| OH,24         | C         | 8.0     | 9.3     | 10.6    | 10.1    |
| OH,1          | E         | 9.3     | 9.9     | 11.4    | 10.6    |
| OH,1½         | E         | 9.3     | 10.3    | 11.4    | 12.3    |
| OH,3          | E         | 11.9    | 12.2    | 14.5    | 13.9    |
| OH,6          | E         | 13.6    | 12.9    | 14.7    | 14.8    |
| OH,24         | E         | 12.0    | 12.1    | 13.4    | 14.4    |
| OH,1          | T         | 9.1     | 9.6     | 10.5    | 11.2    |
| OH,1½         | T         | 10.3    | 10.6    | 11.1    | 11.5    |
| OH,3          | T         | 10.6    | 11.0    | 14.1    | 14.1    |
| OH,6          | T         | 10.4    | 10.9    | 13.5    | 14.3    |
| OH,24         | T         | 10.7    | 12.2    | 14.3    | 14.6    |

$^{a}p < 0.05; ^{b}p < 0.01; ^{c}p < 0.001.$
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ovariectomized-hysterectomized mice and 24 hours after injection in ovariectomized mice. Uterine veins, on the other hand, had almost always responded regularly and significantly to testosterone and estradiol-17β by 1½ hours after injection (Fig. 1).

At autopsy no gross change was observed in urinary bladders. The uteri were enlarged at 24 hours after subcutaneous injection but not at the earlier intervals.

DISCUSSION

The present study is consistent with earlier observations [5,6] on the surprising speed with which mouse tissues are able to remove sex steroids from the sesame oil in which they are dissolved. Rapid response to an administered hormone, as in the present experiment, is made possible by equally rapid absorption of the hormone.

As in our earlier experiments [1–4,7,8], only ovarian and uterine veins responded to sex steroids. Present results also provide experimental confirmation of the earlier observation made in intact mice during the estrous cycle, pregnancy, and the postpartum period [8] that ovarian and uterine veins respond swiftly to changing levels of endogenous sex hormones. Progressive enlargement of ovarian and uterine veins is a well-known feature of pregnancy in many species [9]. It is not clear why the uterine are somewhat more responsive than the ovarian veins. The specificity and speed of the venous response emphasizes the need for a study of the histological and cytological changes and mechanisms involved. Such an investigation is now under way. Spaziani [10] has reviewed the endocrine control of blood volume in the reproductive system in response to gonadal hormones; it appears that the diameter of ovarian and uterine vessels has received relatively little attention.

Finally, the results confirm our earlier finding that, providing an adequate amount of testosterone or estradiol-17β is administered, the ovarian and uterine veins will undergo significant enlargement even in the absence of ovaries and uterus. Venous hypertrophy, which is effected rapidly, is not general but is specific to meet the special needs of the reproductive tract. Control of ovarian and uterine vessel size is revealed

FIG. 1. Venous diameters (means and standard errors) of right uterine veins in OH control and experimental animals.

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Control
--- Estradiol-17β
--- Testosterone

| Hours | Venous Diameter (units) |
|-------|-------------------------|
| 0     | 9                       |
| 1     | 10                      |
| 2     | 11                      |
| 3     | 12                      |
| 4     | 13                      |
| 5     | 14                      |
| 6     | 15                      |
| 24    | 15                      |

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- Control
- Estradiol-17β
- Testosterone
as depending not on uterine growth, fetal development, or postpartum uterine regression per se but rather on the concomitant ebb and flow of sex hormones.

In previous experiments, bladder distention secondary to urinary tract obstruction was noted at 21 days after the implantation of pellets of estradiol-17β in ovariectomized mice [1,5]. Absence of such a response here is ascribed to the shorter period of treatment.

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