Sex Difference in Thyroidal Response to Administration of Progesterone in the Rat (37447)

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A number of experimental studies have shown that thyroidal radioiodine uptake is highest in estrus and lowest in diestrus (1–4). Also thyroid serum iodide concentration ratio (T/S) is higher in estrus than in diestrus (4–6). Soliman and Badawi (2) and Boccabella and Alger (7) concluded that thyroid activity is stimulated during estrus period by an increased secretion of TSH. Although our previous study suggested a possible increase of TSH secretion produced by estrogen (8), a direct evidence for this view has recently been presented by Fisher and D'Angelo (9) who found that administration of small doses of estradiol to ovariectomized animals elevated pituitary and plasma TSH and induced thyroid hyperplasia.

Since estrogen and progesterone are secreted by the ovaries, it is possible that progesterone plays an additional role for the control of thyroid activity. However, effect of progesterone on thyroid activity has not been elucidated satisfactorily.

Materials and Methods. One hundred and twelve male rats and 64 female rats, weighing approximately 200 g, were used in this experiment. Animals were fed a low iodine diet[1] and water *ad libitum,* beginning 7 days before the experiment. Oophorectomized and castrated animals were used for the experiment 15 days after the operation. Hypothalamic lesions (7–8 mm anterior from the ear hole and 0.5 mm above the base of the skull) were made using a direct current of 7 mA for 15 sec. These positions of brain lesions were selected depending on stereotaxic coordination by Krieg (10). Immediately after making lesions, 12 animals (6 female and 6 male) were killed, and the position of the lesions was ascertained under the dissecting microscope. The other animals served in the following experiment 14 days after making lesions. Five milligrams of progesterone[2] in 1 ml saline suspension was injected daily subcutaneously (sc) for 10 days. With the last dose of progesterone, 10–20 μCi of ^{131}I was injected and 12 hr later autopsy was performed. At autopsy, 5 ml of blood was obtained by cardiac puncture using heparinized syringes. Plasma $PB^{131}I$ was measured as reported previously (11). Thyroid weight was expressed as milligrams per 100 g body weight. Vaginal smears were taken twice daily (9–10 AM and 4–5 PM) starting 7 days after arrival in the laboratory and the animals were followed throughout at least 3 complete cycles before being used. Any animals not showing regular predictable 4–5 day cycle were discarded.

Results. Expt 1. Effect of progesterone on thyroidal activity in intact female and male rats. In the first part of this experiment, effect of progesterone on thyroid activity was studied in 10 intact female rats. Administration of 5 mg progesterone caused diestrus within 2–5 days, and diestrus continued during progesterone administration. For comparison, 2 groups (9 diestrus and 8 estrus animals) were selected from the control animals with cyclic changes demonstrated by vaginal smears. Regardless of the stage of vaginal smear or progesterone administration (Fig. 1 left), thyroid weight was about 12 mg/100 g body weight. Thyroidal radioiodine

[1] Iodine content of this diet was approximately 90 to 120 μg/kg.

[2] Progesterone was obtained from Mochida Pharmaceutical Co., Tokyo, Japan.

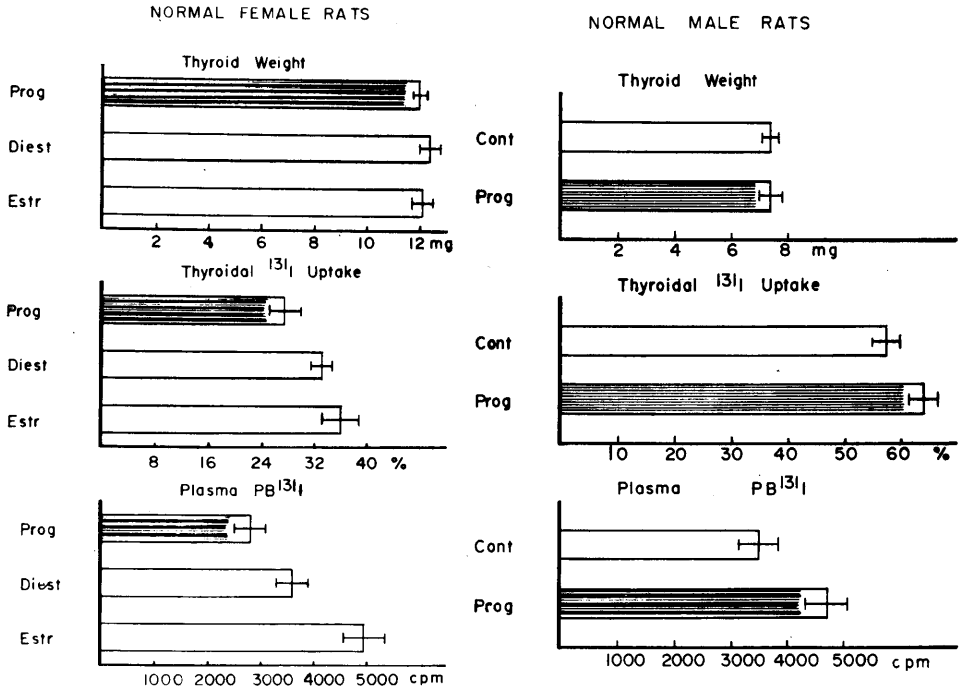

FIG. 1. Progesterone (5 mg) was injected sc daily for 10 days. Radioiodine was injected 12 hr before autopsy. Prog = progesterone group, Diest = group with diestrus for the past 20 hr, Estr = group with estrus, Cont = control group. Bars and lines indicate mean ± SE for 7–10 determinations.

uptake was 35.5 ± 2.7% (mean ± SE) in the estrus group, while it was slightly less in 9 diestrus animals. Thyroidal radioiodine uptake in the progesterone group was 27.5 ± 2.5% and was significantly less than that of diestrus group ($p < 0.05$). Approximately the same situation was found in plasma $PB^{131}I$. Plasma $PB^{131}I$ was highest in the estrus group (Prog-Est $p < 0.001$, East-Diest $p < 0.01$), intermediate in diestrus group (Prog-Diest $p < 0.05$), and least in progesterone group with continuous diestrus.

In the second part of this experiment, 15 male rats were divided into 2 groups (7 control animals, 8 animals treated with progesterone). Thyroid weight was not affected by the administration of 5 mg progesterone for 7 days (Fig. 1 right). In contrast to female rats, thyroidal radioiodine uptake increased significantly in male rats ($p < 0.05$). Also an increase of plasma $PB^{131}I$ was apparent in the progesterone group ($p < 0.01$). This situation was further studied by administering graded doses of progesterone for 7 days (Fig. 2). Thirty male rats were divided into 5 equal groups. As shown in Fig. 2, thyroid weight remained unchanged when 1–5 mg progesterone was given for 7 days. When 10 mg progesterone was administered, thyroid weight was slightly higher, but the difference was not statistically significant. Thyroidal radioiodine uptake increased progressively with increasing doses of progesterone. This increase was significant at the 5.0 and 10 mg dose levels ($p < 0.05$). Plasma $PB^{131}I$ increased at all dose levels of progesterone administered (Cont-P 1.0 $p < 0.05$). The increase was less at the 10 mg dose level, however. Pituitary weight increased progressively with increasing doses of progesterone. The increase was significant at 2.5 to 10 mg dose levels of progesterone ($p < 0.05$).

Expt 2. Effect of progesterone on thyroid activity in oophorectomized female and castrated male rats. In the first part of this experiment, the effect of 5 mg progesterone on

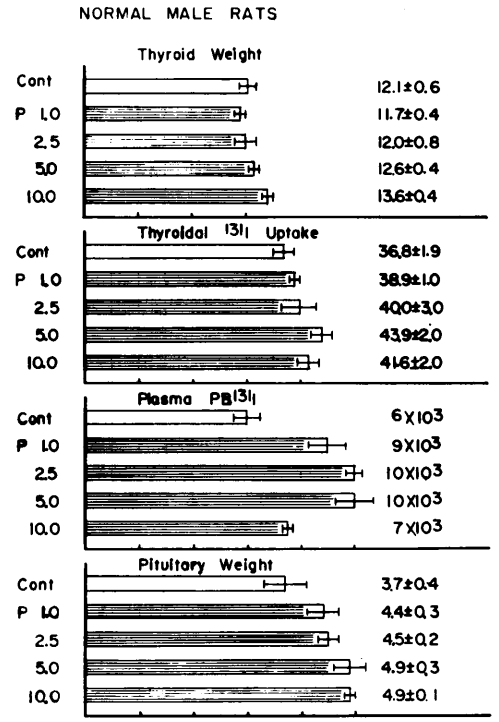

FIG. 2. Effect of graded doses of progesterone on thyroid parameters was indicated. P 1.0 = 1 mg progesterone was injected sc daily for 10 days, Cont = control animals. Radioiodine was injected similarly as in Fig. 1. Bars and lines indicate mean ± SE for 6 determinations. Right column indicates actual values of determination (mean ± SE). Thyroid and pituitary was expressed as mg/100 g body weight. Thyroidal ^{131}I uptake and plasma $PB^{131}I$ were expressed as percentage of administered dose or as cpm/ml plasma.

thyroid activity was studied in 18 oophrectomized female rats. After oophrectomy, all the animals showed diestrus. Progesterone administration failed to affect thyroid weight (Fig. 3 left). In contrast to intact female rats, progesterone administration did not depress thyroidal radioiodine uptake in oophrectomized female rats (Fig. 3 left). Also progesterone failed to affect plasma $PB^{131}I$ in oophrectomized female rats.

For comparison, effect of progesterone on thyroid activity was studied in castrated male rats. Twenty-two castrated animals were divided into 2 equal groups. As found in Expt 1, administration of 5 mg progesterone did not affect thyroid weight (Fig. 3 right). Even after castration, a slight but significant increase of thyroidal radioiodine uptake was found in progesterone-treated animals ($p < 0.05$). Also plasma $PB^{131}I$ was higher in the progesterone-treated group than in the control ($p < 0.001$).

Expt 3. Effect of progesterone on thyroid activity in female and male rats with hypothalamic lesions. To localize the lesioned area, 12 rats were killed immediately after making brain lesions. As Krieg reported in the diagram (10), electrical coagulation at 7.5 mm anterior from the ear hole produced a lesion of 1 mm in diameter at the level of the optic chiasma when the brain was examined under a dissecting microscope. The variations of lesioned areas were less than 0.5 mm.

In the first part of this experiment, the effect of progesterone on thyroid activity was studied in female rats with such hypothalamic lesions. Nineteen animals with the lesion were divided into 2 groups. Two weeks after making the lesion, all the animals showed continuous estrus. Progesterone administration produced diestrus within 4 days in lesioned animals. Thyroid weight was not affected by progesterone administration (Fig. 4 left). As found in intact female rats, thyroidal radioiodine uptake was significantly less in progesterone-treated animals than in control animals with continuous estrus produced by lesion ($p < 0.001$). Plasma $PB^{131}I$ was also depressed markedly after administration of progesterone ($p < 0.001$).

In the second part of this experiment, the effect of progesterone on thyroid activity was studied in male rats with hypothalamic lesions (7 or 8 mm anterior from the ear hole, and 0.5 mm above the skull). Twenty-one male rats with hypothalamic lesions were divided into 3 groups. Progesterone administration had no effect on thyroid weight (Fig. 4 right). As observed in intact male rats, progesterone produced a significant increase of thyroidal radioiodine uptake in 2 groups with hypothalamic lesions ($p < 0.001$). An increase of plasma $PB^{131}I$ was also found in 2 groups with hypothalamic lesions after administration of progesterone ($p < 0.01$) (Fig. 4 right).

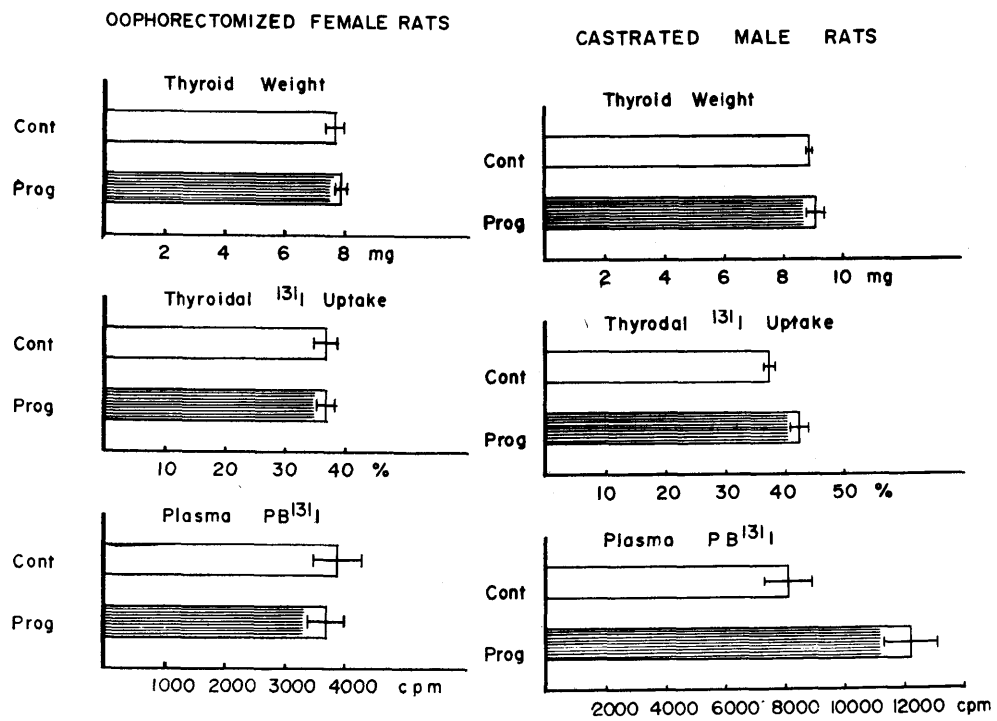

FIG. 3. Oophorectomy or castration was performed 15 days before the experiment. Abbreviations and experimental procedures were the same as in Figs. 1 and 2. Bars and lines indicate mean ± SE for 9–11 determinations.

Expt 4. Effect of progesterone on thyroid activity in thyroxine-treated male rats. Twenty-four male rats were divided into 2 groups. Control animals were injected with 5 μg *l*-thyroxine ip daily for 10 days, while the progesterone group received 5 μg *l*-thyroxine ip and 5 mg progesterone sc daily for a similar period. Thyroid weights were 8.0 ± 0.3 mg and 8.2 ± 0.4 mg/100 g body weight, respectively, in the control and progesterone-treated groups. Thyroidal radioiodine uptake was depressed by thyroxine administration (5.6 ± 0.6%) in contrast to 57% in Fig. 1 and 36.8% in Fig. 2, and this low thyroidal radioiodine uptake was not affected by progesterone administration (6.4 ± 0.6%). Similarly, plasma $PB^{131}I$ was not affected by progesterone administration in thyroxine-treated animals (1188 ± 28 and 1198 ± 19 cpm/ml in the control and progesterone groups, respectively).

Discussion. In general agreement with the previous studies (1–4), we found that thyroidal radioiodine uptake was higher in estrus female rats than in diestrus rats. In addition, our present study clearly indicated that plasma $PB^{131}I$ was higher in estrus rats than in diestrus rats, indicating that thyroid hormone release was increased during estrus. As shown by other investigators (12, 13), administration of 5 mg progesterone daily for 10 days produced diestrus and suppressed thyroidal radioiodine uptake and plasma $PB^{131}I$. When progesterone was administered to female rats with continuous estrus due to hypothalamic lesions, thyroidal radioiodine uptake and plasma $PB^{131}I$ were also suppressed. Since large doses of progesterone depressed pituitary release of gonadotropins (13–15) and thereby ovarian activity, our findings can be comparable to the decrease of thyroid activity in oophorectomized rats (16). In support of this concept, progesterone had no effect on thyroid activity in oophorectomized female rats.

If progesterone depressed thyroid activity

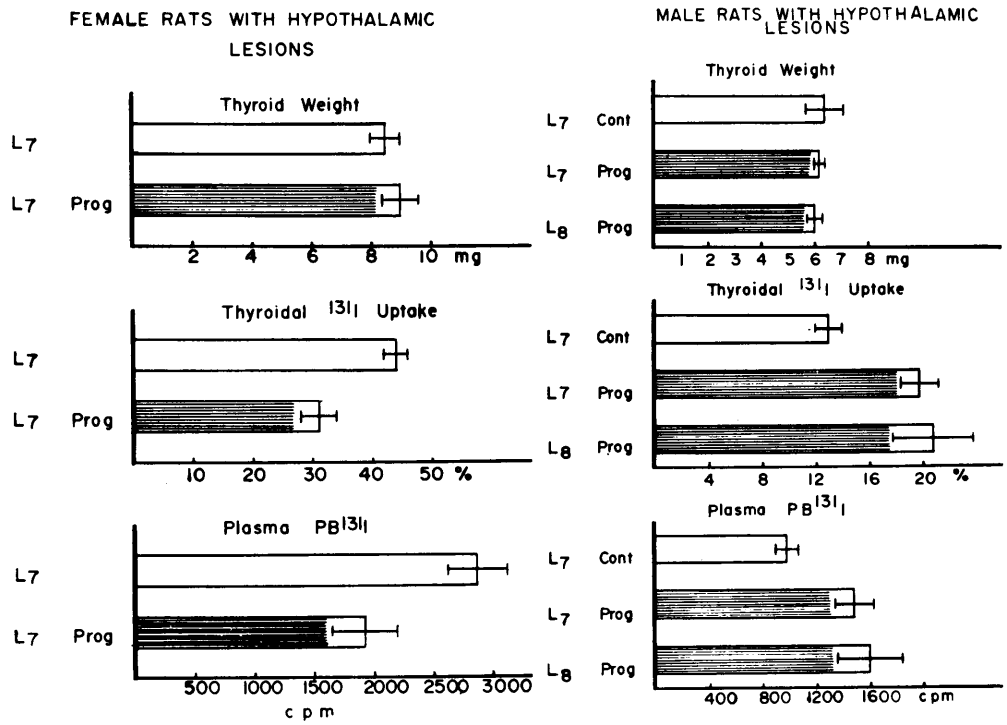

FIG. 4. Hypothalamic lesion was made 14 days before experiment. L_7 = hypothalamic lesion was made 7 mm anterior from the ear hole. Abbreviations and experimental procedures were the same as in Figs. 1 and 2. Bars and lines indicate mean ± SE for 7–10 determinations.

by inhibiting ovarian secretion of estrogen, little or no effect on the thyroid could be expected in male rats. Surprisingly, however, progesterone increased thyroidal radioiodine uptake and plasma $PB^{131}I$ in intact and hypothalamic lesioned male rats. Furthermore, an increase of these parameters was roughly proportional to the doses of progesterone administered. In sharp contrast to female rats, progesterone was also effective in castrated male rats. This strongly suggested that progesterone manifested its stimulatory effect on the thyroid without intervention of testes or testicular hormone in male rats. Since progesterone was ineffective in thyroxine-treated animals, it seems that progesterone stimulated the thyroid by augmenting pituitary release of TSH through some unknown mechanism.

Brown-Grant (17) has reported that a single injection of 2 mg progesterone delayed the expected rise of *T/S* ratio for iodide in female rats. However, Money *et al.* (18) have shown that 5 mg progesterone increased thyroidal radioiodine uptake in male rats. Together with our findings, these data were compatible with the hypothesis that there was a sex difference in thyroidal response to progesterone in the rat. Recent studies by Kato, Takahashi and Omori (19) and Breuer (20) have indicated that disappearance of progesterone from the blood was faster in male than in female rats, because of more rapid transformation of progesterone to metabolites in the liver. Thus it seems that the liver is the possible site responsible for sex difference of thyroidal response to progesterone in the rat.

Summary. In intact female rats, thyroidal radioiodine uptake and plasma $PB^{131}I$ were greater in estrus, intermediate in diestrus and least in continuous diestrus produced by progesterone. Progesterone also depressed thyroidal radioiodine uptake and plasma $PB^{131}I$ in hypothalamic lesioned female rats, but was without effect in oophorectomized rats. In contrast, progesterone increased thyroidal ra-

dioiodine uptake and plasma PB^{131}I in intact, castrated and hypothalamic lesioned male rats. The increase was roughly proportional to the doses of progesterone administered. It was concluded that there is a sex difference in thyroidal response to progesterone in the rat.

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