Studies on Hypothalamic Regulation of FSH Secretion in the Androgen-Sterilized Female Rat.* (27497)

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Many investigators have observed that destruction of anterior hypothalamic regions in the rat produces persistent-estrus, and they attribute the cause of this syndrome to interruption of the ovulatory discharge of gonadotropin from the pituitary(1,2,3). Recent studies have attempted a more critical analysis of the imbalances in gonadotropin secretion which produce this syndrome. These studies demonstrated that estrogen-sensitive neurons exist in the hypothalamus and presumably it is through these neurons that estrogen acts to regulate FSH secretion(4). Flerkó has proposed that because of destruction of these hypothalamic regions FSH is continuously secreted and it (FSH) in turn maintains continuous estrogen production by the polyfollicular ovary. D'Angelo and Kravatz (5) and Flerkó(6) have reported that the adenohypophysis of the persistent-estrous rat (with a hypothalamic lesion) loses its capacity to augment secretion of FSH under the demand of unilateral ovariectomy. The former investigators(5) also noted that although pituitary FSH content was maintained in this preparation, the serum titers decreased. We, on the other hand, have suggested that it is not necessary to postulate an imbalance in FSH secretion to explain the phenomenon of persistent-estrus. Rather, the particular malfunction in gonadotropin secretion which produces this syndrome could be explained by a deficiency in release of LH, with FSH being secreted in tonic concentration. However, it is difficult to study the differential regulation of FSH or LH in animals with hypothalamic lesions since the lesion which destroys one regulatory mechanism may simultaneously eliminate the other. This report concerns an investigation of the hypothalamic regulation of FSH secretion under the demand of unilateral ovariectomy in the androgen-sterilized rat. This preparation exhibits the same anovulatory persistent-estrous syndrome as does the rat with a hypothalamic lesion, but in the androgen sterilized animal the hypothalamus is anatomically intact.

Materials and methods. Three groups of adult Sprague-Dawley female rats were used. *Group I.* Fifteen normal adult virgin female rats which had exhibited at least 3 weeks of normal vaginal cycles were selected for study. *Group II.* Thirty-eight female rats were pretreated with 1.0 mg of testosterone propionate at 5 days of age to produce permanent sterility(7). Four to 5 months later sterility was verified by the persistence, for 30 days, of a cornified vaginal mucosa. *Group III.* Bilateral electrolytic lesions (1-2 mA) were placed in the anterior hypothalamus of 8 androgen-sterilized rats. Daily vaginal smears were then taken for one month to confirm the persistence of a cornified vaginal mucosa. The left ovary was removed from all rats and autopsy was performed 19-20 days later. Due to variation in body weight among the various groups, all ovarian weights were expressed as mg/100 g body weight, and the percentage hypertrophy of the right as compared to the left ovary constituted the response. In addition, for control data, the normal variation between right and left ovary was determined in the intact normal and androgen-sterilized rat.

Results. The right ovary of the normal intact rat is 5.1% larger than the left and a similar 6.5% difference exists between right and left ovaries in the intact sterile rat (Table I). Although this natural variation is not significant, unilateral ovariectomy of the normal cyclic rat resulted in a significant 56% hypertrophy of the remaining gonad. Similarly, removal of the left gonad of the androgen-sterilized rat resulted in a comparable 53% hypertrophy of the right ovary 19-20 days following surgery. Furthermore, this hypertrophy could be attributed to an apparent increase in number of large vesicular follicles but luteinization did not occur.

In contrast to the previous groups, sterile

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TABLE I. Ovarian Compensatory Hypertrophy in Normal Rats and Androgen-Sterilized Rats With and Without Hypothalamic Lesions.

Treatment	No. rats	Body wt (g) at autopsy	Ovarian wt (mg/100 g body wt) Left	Ovarian wt (mg/100 g body wt) Right	% ovarian hypertrophy‡
Normal intact	15	262 ± 5*	12.5 (32.7 ± 1.3)†	13.0 (34.0 ± 1.1)	5.1 ± 4.0
Normal unilateral ovaryx	9	274 ±13	16.0 (38.1 ± 2.2)	23.0 (62.3 ± 2.4)	56.4 ± 8.8
Sterile intact	14	301 ±11	5.05 (14.9 ± .9)	5.30 (15.6 ± 1.0)	6.5 ± 6.8
Sterile unilateral ovaryx	16	276 ± 7	5.60 (14.4 ± .7)	8.45 (23.1 ± 2.9)	53.2 ± 6.1
Sterile + lesion unilateral ovaryx	8	289 ± 7	7.61 (22.0 ± .8)	8.86 (25.4 ± 1.2)	16.8 ± 6.1

* Mean ± stand. error. † Avg actual organ wt ± stand. error. ‡ Based on left ovarian wt (100%).

rats with anterior hypothalamic lesions exhibited only a 16.8% hypertrophy of the right ovary following unilateral ovariectomy. This hypertrophy was significantly less than that observed in the unlesioned sterile rat ($P < 0.001$) but not significantly different from the control variation in the intact sterile rat. The area of destruction was confirmed histologically and generally did not extend more than 1 mm lateral from the ventricular wall. The suprachiasmatic nuclei were partially destroyed in 5 animals and the paraventricular nuclei in 3 rats. However, neither of these nuclei was involved in the area of destruction that was common to 6 of 8 animals (Fig. 1).

Although compensatory hypertrophy was greatly reduced in the lesioned rat the weight of its right ovary was equivalent to the sterile ovary after a 53% hypertrophy. Since the control (left) ovary of the lesioned rat was significantly larger ($P < 0.001$) than that of the intact sterile rat (Table I), it is possible that the anterior hypothalamic lesion permitted release of excess FSH prior to the stimulus of unilateral ovariectomy. The bioassay results of D'Angelo and Kravatz(5), however, do not support a concept of increased FSH release, and no explanation for the increased ovarian weight is possible at this time.

Discussion. Flerkó has proposed that hypothalamic regulation of FSH and LH secretion is a function of anatomically separate neurons which exist in the region of the paraventricular and suprachiasmatic nuclei respectively. He further interprets the persistent-estrous syndrome which occurs following placement of a hypothalamic lesion as due to destruction of both neural elements(8). This investigator, however, considers the primary cause of persistent-estrus to be an unabated release of FSH which maintains continuous estrogen secretion(4,6). While the present study supports the concept of discrete FSH and LH regulatory centers within the hypothalamus

MIDLINE PROJECTION OF LESIONS INHIBITING COMPENSATORY OVARIAN HYPERTROPHY

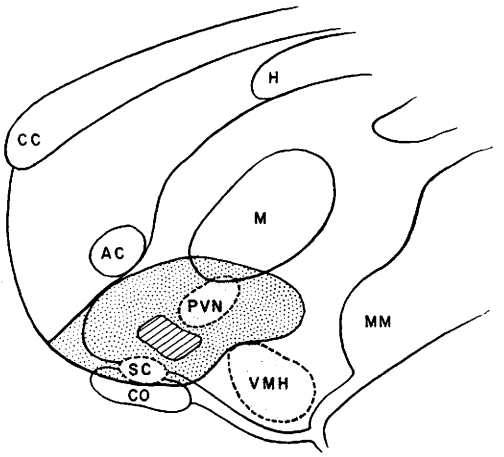

FIG.1. Stippling: inclusive area destroyed by all lesions; striping: area of destruction common to 6 of 8 lesions; shading: hypothalamic nuclei projected on midline. Abbreviations: AC, anterior commissure; CC, corpus callosum; CO, optic chiasm; H, hippocampus; M, massa intermedia; MM, mammillary body; PVN, paraventricular nucleus; SC, suprachiasmatic nucleus; VMH, ventral medial nucleus.

the results also suggest that the imbalance in gonadotropin secretion that produces persistent-estrus may be principally a malfunction in hypothalamic control of LH secretion. Previous studies have demonstrated that prepubertal treatment of rats with androgen deleteriously affects the hypothalamic ovulatory controlling mechanism and that the specific site of androgen action is the preoptic-suprachiasmatic region of the hypothalamus (9). Such treatment, on the other hand, apparently does not alter at least one phase of the regulation of FSH secretion, for on the demand of unilateral ovariectomy an increased secretion of this gonadotropin occurs and the degree of hypertrophy which ensues is comparable to that of the control rat. Furthermore, this effect can be significantly decreased by placing a lesion in the anterior hypothalamus which presumably destroys the FSH component. Critchlow (personal communication) has also noted a decreased release of pituitary FSH following unilateral ovariectomy of the light-induced constant-estrous rat. However, the degree of hypothalamic refractoriness produced by constant light is not as pronounced as that produced by a lesion, for he observes a 56% hypertrophy of the control ovary as compared with a 36% hypertrophy of the experimental gonad. From present and previous data we therefore propose the following hypothesis to explain the syndrome of persistent-estrus in the androgen-sterilized rat. Prepubertal androgen treatment deleteriously alters the function of neurons in the preoptic-suprachiasmatic region of the hypothalamus which regulate the ovulatory discharge of LH from the pituitary (9). Since ovulation does not occur the large vesicular follicles of the ovary persist, and they are subsequently replaced by new vesicular follicles. Constant estrogen production by these follicles is maintained by the tonic release of LH from the pituitary. The feedback action of estrogen presumably modifies FSH secretion only to the extent that it is released in constant concentration to maintain follicular development. Thus a new equilibrium of tonic FSH and LH secretion is established. Alterations in this equilibrium, as for example, a decrease in the blood level of estrogen, result in a comparable increase in FSH secretion.

These data also indicate that a secondary level of FSH control may exist in the hypothalamus. Although the compensatory hypertrophy response is markedly reduced after destruction of the anterior hypothalamus, an increased release of FSH still occurs to produce a 16% ovarian hypertrophy. Lisk(10) has shown that the arcuate nuclei and the mammillary body areas of the hypothalamus are "estrogen-sensitive" and it may be at such sites that the secondary level of control exists.

Summary. The hypothalamic regulation of FSH secretion has been studied in the unilaterally ovariectomized androgen-sterilized female rat. Comparable degreees of ovarian hypertrophy were observed in sterile and normal cyclic rats. Destruction of the anterior hypothalamus of the sterile rat markedly curtailed the release of FSH from the adenohypophysis. These data suggest not only that discrete FSH and LH centers exist in the hypothalamus of the rat but also that the syndrome of persistent-estrus results more likely from an imbalance in LH rather than in FSH secretion.

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