

Capacity of Old Versus Young Female Rats to Secrete LH, FSH and Prolactin

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ABSTRACT

Serum LH, FSH and prolactin levels were measured by radioimmunoassays before and after ovariectomy and during and after estradiol benzoate (EB) treatment in 4-5 month old young mature female rats, in 22-24 month old constant estrous and pseudopregnant rats, and in 26-30 month old anestrus rats. Serum LH in intact old constant estrous rats was significantly higher than in young rats on the day of estrus, about the same in intact old pseudopregnant rats as in young rats in diestrus, and was undetectable in the old anestrus rats. By 7 weeks after ovariectomy, serum LH rose about 26 fold in young rats, only about 3 fold in the old constant estrous rats, about 14 fold in the old pseudopregnant rats, and remained unmeasurable in the old anestrus rats. After daily EB injection for 8 days, the relative fall in serum LH in old constant estrous and pseudopregnant rats was significantly smaller than in the young rats, and 2 weeks after estrogen treatment was terminated the rise in serum LH was significantly less in the old constant estrous and pseudopregnant than in young rats. Serum LH in the old anestrus rats remained undetectable.

Intact old constant estrous and pseudopregnant rats showed about the same serum FSH values as young rats on the day of estrus, but exhibited a significantly smaller FSH rise after ovariectomy and a smaller FSH fall after 8 days of EB administration than the young rats. Intact old anestrus rats had as low serum FSH levels as young rats in diestrus, showed only a small rise in serum FSH after ovariectomy and no change after estrogen injections. After estrogen treatment was withdrawn, the rise in serum FSH in the old constant estrous and pseudopregnant rats was significantly less than in the young rats, and showed no increase in the old anestrus rats. The intact old constant estrous rats had 2 to 3 times more serum prolactin than young rats, and the intact old pseudopregnant rats had about as much serum prolactin as young rats on the day of estrus. Serum prolactin in intact old anestrus rats was twice as high as in old constant estrous rats and 4 to 8 times greater than in old pseudopregnant or young rats. After ovariectomy, serum prolactin decreased significantly in the old constant estrous and young rats, but not in the old pseudopregnant or anestrus rats. EB administration increased serum prolactin in all categories of rats, and fell after estrogen treatment was terminated. These observations suggest that the hypothalamo-pituitary system of old female rats has less capacity to secrete FSH and LH and more capacity to secrete prolactin than young cycling female rats, and are believed to largely explain why old female rats cease to cycle.

INTRODUCTION

Aging female rats and mice show a gradual decline in number of ova, ovulations and litter size (Mandl and Zuckerman, 1951; Ingram et al., 1958; Mandl and Shelton, 1959), and finally cease to cycle and reproduce (Ingram,

1959; Thung et al., 1956). Examination of daily vaginal smears reveal that beginning at about 8-12 months of age, or even earlier, rats gradually change from regular to irregular cycles and then to constant estrus; this is followed by pseudopregnancies of irregular length and finally to an anestrus state in the oldest rats (Aschheim, 1961; Huang and Meites, 1975). Some rats may continue to cycle irregularly even up to 2 years of age, and a few may revert temporarily from the constant estrous or pseudopregnant state to irregular cycles. We have never observed that old anestrus rats return to an earlier pattern. The constant estrous rats have well-developed and sometimes cystic follicles, no corpora lutea and do not ovulate; the

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pseudopregnant rats have ovaries with numerous corpora lutea and exhibit diestrous vaginal smears for 10–30 days interspersed by 1 or 2 days of estrus; the anestrus rats show atrophic ovaries with some primary follicles and an infantile uterus (Huang and Meites, 1975).

Limited information is as yet available on hypothalamo-pituitary function in aging female rats. We have reported that in 20–24 month old constant estrous Sprague-Dawley rats, there is a lower pituitary content of LH and more FSH and prolactin than in 3–4 month old rats on the day of estrus (Clemens and Meites, 1971). In 23–30 month old female Long-Evans rats, not separated according to their vaginal smear patterns, serum LH values were about the same and prolactin levels were about 6 times greater than in 4–5 month old cycling female rats of the same strain (Shaar et al., 1975). It was the purpose of the present investigation to measure serum LH, FSH and prolactin in old constant estrous, pseudopregnant, anestrus and young cycling rats; to determine the effects of ovariectomy and estrogen administration on serum levels of these 3 hormones; and to attempt to relate the serum hormone levels to the reproductive patterns exhibited by these rats.

MATERIALS AND METHODS

Multiparous female Long-Evans rats, 10–12 months old, were obtained from Blue Spruce Farms, Altamont, NY. They were housed in steel cages in an air-conditioned and temperature-controlled ($24^{\circ} \pm 2^{\circ}$ C) room. Light was provided daily from 0600 to 2000 h by fluorescent lamps. The animals were fed a diet of Wayne Lab Blox pellets (Allied Mills, Chicago, IL), and were given tap water *ad libitum*. When the animals reached 22–24 months of age, daily vaginal smears were taken. Animals that showed vaginal cornification continuously for 20 days or more were considered to be in constant estrus (8 rats), those that exhibited diestrous periods of 10–30 days interspersed with 1 to 2 days of estrus were judged to be pseudopregnant (6 rats), and rats that showed no cyclic activity and only vaginal leucocytes were considered to be anestrus (6 rats). Four to five month old regular cycling female rats were used as controls (12 rats).

Two ml of blood were collected between 1200 and 1300 h before bilateral ovariectomy and thereafter at the same time once every week for 7 weeks. Estradiol benzoate (EB) (Nutritional Biochemical Co., Cleveland, OH) was dissolved in corn oil and injected sc at a dose of 0.5 μ g/100 g body weight between 1000 and 1100 h daily beginning on Day 1 of the eighth week and continuing for 8 days. Two ml of blood were collected 2–3 h after EB injection on Days 2, 5, 8, and at 1 and 2 weeks after steroid treatment was terminated. Blood samples were taken under light ether anesthesia by orbital sinus puncture. Serum was

separated and frozen at -20° C until assayed. Body, ovarian and pituitary weights were recorded. Only healthy rats were used in this study.

Serum LH was measured by a double antibody radioimmunoassay (RIA) (Niswender et al., 1964) using the ovine LH provided by Dr. L. Reichert, Emory University, Atlanta, GA, and ovine LH antibody provided by Dr. G. Niswender, Colorado State University, Fort Collins, Colorado. Values were expressed as ng/ml of NIAMDD Rat LH-RP-1. Because of the problems inherent in obtaining sufficient volumes of blood serum for multiple hormone determinations from aging rats, we used "micro" RIAs for FSH and prolactin developed in our laboratory by Marshall, Bruni, Campbell, Kledzik, details of which will be published elsewhere. These modifications increased the sensitivity of both assays approximately 3-fold, and were shown to give results identical with the standard RIAs. Values for FSH and prolactin were expressed in terms of NIAMDD Rat FSH-RP-1 and NIAMDD Rat Prolactin-RP-1.

Analysis of variance coupled with Student-Newman Keuls multiple range test, was used to evaluate the effects of age, treatment and age-treatment interactions (Sokal and Rohlf, 1969). Differences between age and treatment means were considered significant only when the P value was less than 0.05.

RESULTS

Serum LH

Figure 1 shows that in intact young rats serum LH was significantly higher on the day of estrus than on diestrous Day 2 (34.8 ± 4.0 ng/ml vs. 20.7 ± 3.2 ng/ml). By 7 weeks after ovariectomy, serum LH increased to 736.1 ± 14.4 ng/ml. After daily injection of estrogen for 8 days, serum LH fell to 84.2 ± 4.2 ng/ml.

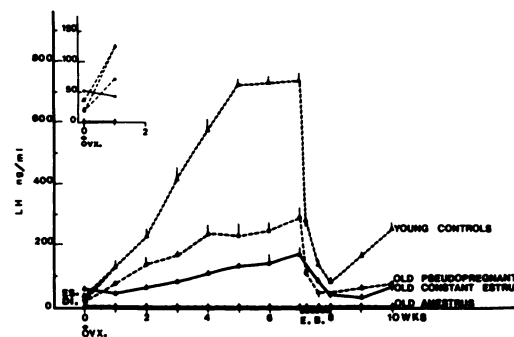


FIG. 1. Serum LH in intact rats, during 7 weeks after ovariectomy, during estradiol benzoate (EB) treatment for 8 days, and during 2 weeks post-EB treatment. Groups consisted of old constant estrous (N = 8), old pseudopregnant (N = 6), old anestrus (N = 6) and young control rats (N = 12). In young intact rats serum LH levels were measured during estrus and diestrus (N = 6). ES = Estrus, DI = Diestrus, OVX = Ovariectomized, WKS = Weeks.

Intact old constant estrous rats had significantly higher serum LH (52.4 ± 6.3 ng/ml) than young rats on the day of estrus, and intact old pseudopregnant rats had about the same serum LH (20.8 ± 2.7 ng/ml) as young rats in diestrus. After ovariectomy serum LH increased significantly in both old constant estrous and pseudopregnant rats to 169.3 ± 18.4 ng/ml and 291.3 ± 32.4 ng/ml, respectively, but these increases were significantly less than in the young rats. After estrogen injections the fall in serum LH in both groups of old rats was significantly less than in the young rats, declining to 40.5 ± 7.6 ng/ml in the old constant estrous rats and to 49.2 ± 2.9 ng/ml in the old pseudopregnant rats. Two weeks after termination of EB treatment, serum LH increased from 84.2 ± 4.2 to 225.1 ± 14.5 ng/ml in the young controls, but only from 40.5 ± 7.6 ng/ml to 66.1 ± 9.0 ng/ml in the old constant estrous rats and from 49.2 ± 2.9 ng/ml to 69.5 ± 16.0 ng/ml in the old pseudopregnant rats. In the old anestrus rats, serum LH was not detectable (less than 3 ng/ml) under any condition of treatment, and remained undetectable after ovariectomy or estrogen treatment.

Serum FSH

Figure 2 shows that in intact young rats serum FSH was significantly higher on the day of estrus than during diestrus (124.0 ± 11.5 ng/ml vs. 26.5 ± 3.9 ng/ml). By seven weeks after ovariectomy, serum FSH increased to 485.9 ± 18.8 ng/ml in the young rats, and 8 days after daily injection of EB serum FSH fell to 140.3 ± 12.3 ng/ml. Intact old constant estrous and pseudopregnant rats showed about the same serum FSH values (121.5 ± 8.1 ng/ml and 85.7 ± 25.7 ng/ml, respectively) as in intact young estrous rats, but both old groups ex-

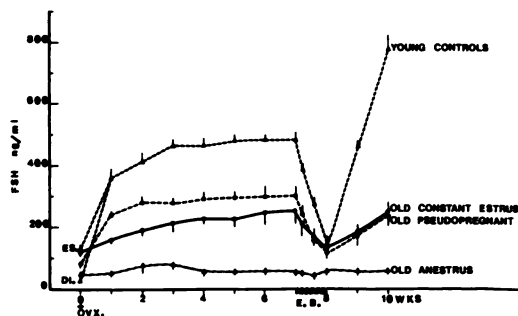


FIG. 2. Serum FSH in blood samples collected from same rats as in Fig. 1.

hibited a significantly smaller FSH rise after ovariectomy and a significantly smaller FSH decline after EB treatment than young rats. Seven weeks after ovariectomy, serum FSH in the old constant estrous rats rose from 121.5 ± 8.1 ng/ml to 250.8 ± 41.5 ng/ml, and 8 days after EB treatment fell to 137.0 ± 9.8 ng/ml. In the old pseudopregnant rats, serum FSH rose from 85.7 ± 25.7 ng/ml to 300.5 ± 30.4 ng/ml after ovariectomy, and declined to 116.8 ± 13.3 ng/ml after estrogen treatment. After estrogen treatment was terminated, serum FSH rose more quickly and to higher levels in the young rats than in both groups of old rats, increasing from 140.3 ± 12.3 ng/ml to 776.0 ± 39.4 ng/ml in the young rats and from 137.0 ± 9.8 ng/ml to 243.8 ± 34.0 ng/ml in the old constant estrous rats and from 116.8 ± 13.3 ng/ml to 244.3 ± 32.0 ng/ml in the old pseudopregnant rats. The old anestrus rats showed only a small rise in serum FSH after ovariectomy, from 47.6 ± 9.9 ng/ml to 70.0 ± 2.9 ng/ml, and no change occurred as a result of estrogen treatment or after termination of estrogen treatment.

Serum Prolactin

Figure 3 shows that serum prolactin trends in the old rats generally were opposite to those of the gonadotropins. Serum prolactin was significantly higher in the constant estrous and anestrus old rats than in the young rats, but the old pseudopregnant rats had values as high as in young rats on the day of estrus. Serum prolactin concentration in the intact young rats was significantly higher during estrus than on diestrus (175.5 ± 27.8 ng/ml vs. 108.7 ± 18.8

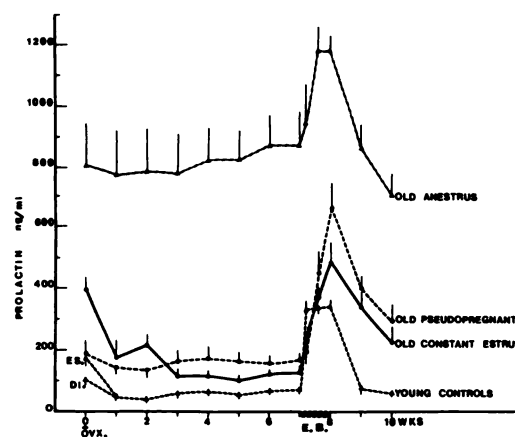


FIG. 3. Serum prolactin in blood samples collected from same rats as in Fig. 1.

ng/ml). By 7 weeks after ovariectomy, serum prolactin of young rats fell to 66.5 ± 9.4 ng/ml, and after 8 days of estrogen treatment it rose to 338.5 ± 16.8 ng/ml. The intact old constant estrous rats had significantly higher serum prolactin (395.0 ± 34.1 ng/ml) than the intact young rats, and this decreased to 127.6 ± 28.8 ng/ml by 7 weeks after ovariectomy, and increased to 487.7 ± 56.1 ng/ml after 8 days of estrogen treatment. The intact old pseudopregnant rats had about the same serum prolactin values (188.4 ± 42.7 ng/ml) as young estrous rats, showed only a slight but nonsignificant decline to 165.0 ± 25.0 ng/ml by 7 weeks after ovariectomy, and exhibited a significant rise to 665.2 ± 55.4 ng/ml after 8 days of estrogen treatment. The intact old anestrus rats showed much greater serum prolactin levels (807.8 ± 135.5 ng/ml) than any of the other groups, and no fall in serum prolactin after ovariectomy. Estrogen administration increased serum prolactin to 1169.0 ± 51.7 ng/ml. One week after termination of estrogen treatment, serum prolactin values in the young and old anestrus rats had returned to ovariectomy levels, but in the old constant estrous and pseudopregnant rats serum prolactin remained elevated.

Body, Pituitary and Ovarian Weights

Table 1 shows there were no significant differences in body weight between 4–5 month old female rats and 22–24 month old constant estrous or pseudopregnant rats by 10 weeks after ovariectomy. Old anestrus rats weighed significantly less than any of the other groups of rats. The pituitaries of the old constant estrous and pseudopregnant rats were significantly heavier than those of the young rats, and the pituitaries of the old anestrus rats were

large and tumorous in every case, as observed in our previous study (Huang and Meites, 1975). The ovaries of the old constant estrous rats weighed significantly less and the ovaries of the old pseudopregnant rats weighed significantly more than those of the young rats. The atrophic ovaries of the old anestrus rats weighed significantly less than any of the other groups.

DISCUSSION

The present study indicates the presence of different patterns of secretion of LH, FSH and prolactin in old noncyclic female as compared to young cycling female rats. It is clear that the capacity to increase FSH and LH release in response to ovariectomy is significantly reduced in all categories of old female rats, whereas the ability to secrete prolactin is enhanced. These results are in agreement with our recent report on the ability of noncategorized old female rats to secrete LH and prolactin as compared to young female rats (Shaar et al., 1975), but extend our observations to show the relationship of FSH, LH and prolactin to each category of old rats. Ovariectomy of old constant estrous and pseudopregnant rats resulted in a much smaller rise in serum FSH and LH than in young rats, and the old anestrus rats showed only a small rise in serum FSH and no rise in serum LH. Estrogen administration after ovariectomy also produced a relatively smaller decrease in serum FSH and LH in the old constant estrous and pseudopregnant rats than in the young rats, and had no effect on FSH or LH in the old anestrus rats. Cessation of estrogen treatment also elicited only a relatively minor rise in serum FSH and LH in the old constant estrous and pseudopregnant rats as compared to

TABLE 1. Body and pituitary weights of young and old rats 10 weeks after ovariectomy, and initial weights of ovaries.

Group and no. of rats	Av body wt, g	Av pituitary wt, mg	Av ovarian wt, mg
Young controls (12)	353 ± 17	15.3 ± 0.8	70.5 ± 1.4
Old constant estrus (8)	354 ± 13	$19.6 \pm 2.9^*$	$59.7 \pm 4.5^*$
Old pseudopregnant (6)	374 ± 22	$29.0 \pm 9.8^*$	$100.8 \pm 3.8^*$
Old anestrus (6)	$305 \pm 17^*$	$227.5 \pm 46.6^{**}$	$26.6 \pm 3.8^*$

* $P < 0.05$; young vs. old.

** Pituitary tumors.

± Standard error of mean.

the young rats, and no rise at all in the old anestrus rats.

Serum prolactin was significantly higher in the old as compared to the young rats, and in the old pseudopregnant rats was as high as in young rats on the day of estrus. This agrees with our earlier reports of high pituitary and serum prolactin levels in old as compared to young rats (Clemens and Meites, 1971; Shaar et al., 1975). The extraordinary high levels of serum prolactin in the old anestrus rats have not been reported previously. These rats all had pituitary tumors, as observed by us previously in old anestrus rats (Huang and Meites, 1975), and apparently are similar to prolactin secreting pituitary tumors observed in other strains of old rats (Ito et al., 1972). The higher pituitary and serum levels of prolactin observed in the present and earlier studies by us in old rats is believed to account at least in part for the increased incidence of spontaneous mammary tumors in old female rats (Meites et al., 1972).

The failure of old female rats to cycle is believed to be associated with an altered capacity of the hypothalamo-pituitary system to secrete gonadotropins in response to physiological stimuli. Thus the constant estrous syndrome in old rats may be due, at least in part to a deficiency in the LH release mechanism as indicated by the significantly reduced capacity to release LH after ovariectomy when compared to young female rats. Earlier we reported that old constant estrous rats do not respond to cervical stimulation with induction of pseudopregnancy (Clemens et al., 1969) as do cycling rats on the day of estrus. The ovaries of old constant estrous rats also do not contain corpora lutea (Clemens and Meites, 1971; Huang and Meites, 1975) and probably are deficient in progesterone secretion. We recently found that administration of small doses of progesterone to such rats induces regular cycling (Huang et al., 1976). We also have reported that the pituitary of old constant estrous and pseudopregnant rats shows a significantly smaller release of LH in response to administration of synthetic LRH than young mature female rats (Watkins et al., 1975), suggesting a change in pituitary response in these old rats.

The old pseudopregnant rats appear to have a relatively greater capacity to increase release of LH and FSH after ovariectomy than old constant estrous rats, which may explain the occasional ovulations observed in these rats.

The sustained high serum prolactin levels in these old rats could account for the maintenance of the corpora lutea during each pseudopregnancy period. The anestrus state observed in the oldest female rats apparently results from the inability of the pituitary tumors to secrete sufficient gonadotropins. The ovaries of these anestrus rats were atrophic, contained only few small follicles, and apparently secreted little or no estrogen as indicated by the presence of an infantile uterus, in agreement with our earlier report (Huang and Meites, 1975). The increase in serum prolactin as a result of estrogen administration to these anestrus rats probably is due to the direct stimulatory action of estrogen on pituitary prolactin secretion (Meites et al., 1972).

We previously have expressed the opinion that major changes occur in the hypothalamo-pituitary system of aging female rats (Clemens et al., 1969; Clemens and Meites, 1971; Quadri et al., 1973), and have provided some evidence to substantiate this view. Thus we reported that old constant estrous rats can be induced to ovulate by electrochemical stimulation of the preoptic area or by injections of progesterone or epinephrine (Clemens et al., 1969; Wuttke and Meites, 1973). Regular cycles were induced in old constant estrous rats by daily injection of progesterone or ACTH (Huang et al., 1976) and mainly irregular cycles by daily injection of epinephrine (Clemens et al., 1969), L-dopa, iproniazid or ether stress (Quadri et al., 1973; Huang et al., 1976). We have suggested that old female rats may be deficient in hypothalamic catecholamines (Clemens et al., 1969; Clemens and Meites, 1971; Quadri et al., 1973), and preliminary evidence indicates that old rats have less norepinephrine and dopamine in the hypothalamus than young mature rats (Riegle et al., unpublished). Finch (1973) also reported that old male mice have lower hypothalamic norepinephrine and dopamine turnover than young mature mice. Hypothalamic catecholamines, particularly norepinephrine, have been strongly implicated in the release of gonadotropins (Sawyer, 1975), whereas dopamine has been shown to inhibit prolactin release (Meites et al., 1972). It also is possible that the hypothalamus of old rats exhibits increased serotonergic activity (Huang and Meites, unpublished). Serotonin has been demonstrated to inhibit gonadotropin (Kamberi et al., 1971) and to promote prolactin release (Meites et al., 1972).

Although aging female rats usually cease to cycle, their ovaries remain capable of a considerable degree of function. We have observed that transplantation of ovaries from old constant estrous, pseudopregnant or even anestrus rats to young ovariectomized females results in stimulation of these ovaries and in frequent resumption of cycling (Huang and Meites, unpublished). It appears that the ovaries of old rats remain capable of nearly normal function throughout their lifespan, and the primary cause for cessation of cycling lies in the hypothalamo-pituitary system.

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