

## Sex-Related Difference in Antral and Serum Gastrin Levels in the Rat (39307)

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(Introduced by M. I. Grossman)<sup>1</sup>

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Sex-related differences in gastric acid secretion (1, 2) and ulcer prevalence (3, 4) in the rat have been reported. To date, however, no evidence has been found to indicate that the pituitary-gonadal hormones act upon the gastrointestinal mucosa directly. It is conceivable, therefore, that these hormones exert their effect by secondary endocrine interactions. One possibility is that sex-related hormones modify the serum levels of gastrin, a known stimulant of both gastric acid secretion (5, 6) and gastrointestinal cell proliferation (7, 8, 9) which, in turn, induces the corresponding changes in gastrointestinal structure and function. Since it is not known whether tissue and serum gastrin levels are regulated by the pituitary-gonadal hormones, we decided to measure both antral and serum gastrin levels in the following groups of animals: normal male and female rats, ovariectomized rats with and without estrogen treatment, and mother rats in their third week of lactation. In addition, food consumption measurements were made in normal males and females in an attempt to investigate possible mechanisms of the interrelationships between the sexual status of normal rats and gastrin levels.

**Methods. Animals.** Eighty-day old Sprague-Dawley (Simonson) male and female rats were used in all studies. The males and females weighed approximately 380 and 260 g, respectively. All animals were housed in the animal colony maintained on a 12-12 lighting schedule (lights on from 7:00 AM to 7:00 PM) and given *ad libitum* access to Purina rat chow and water. Food consumption was measured daily for normal males and females. Male rats were injected

daily with 0.05 ml of sesame oil over a 14-day period. Female rats were divided into three groups: Two groups were ovariectomized under ether anesthesia and the third group served as unoperated controls. One of the ovariectomized groups was injected daily with 2  $\mu$ g of estradiol benzoate in 0.05 ml of sesame oil for 14 days. The other ovariectomized group and the controls received daily injections of 0.05 ml of sesame oil over the same time period. Vaginal smears were not obtained.

A fourth group of female rats was 2 days postpartum at the start of the study. This group of rats was allowed to suckle their young (litter size 8 to 12) for 2 weeks while receiving daily control injections of sesame oil.

**Tissue preparation and gastrin analysis.** At the end of the study period, the rats were anesthetized with ether, a midline incision was made, and blood was withdrawn from the inferior vena cava. A small section of antrum located along the lesser curvature in close proximity to the pyloric junction was excised and weighed and the gastrin was extracted by a previously described method (10). These procedures were performed at the same time of day (between 9 AM and 11 AM) to avoid possible diurnal variation. The antral and serum gastrin concentrations were determined by the radioimmunoassay using the procedure, antisera, and label described elsewhere (11).

**Statistical analysis.** Student's *t* test for unpaired values was employed in all statistical comparisons, and a *P* value of less than 0.05 was considered significant.

**Results. Antral and serum gastrin concentration.** The serum gastrin levels of the various groups of rats are shown in Fig. 1. Males had a significantly higher serum gastrin concentration than did female rats. However, serum gastrin levels of female rats

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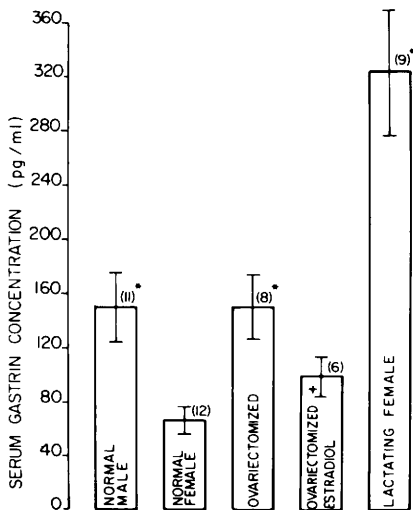


FIG. 1. Serum gastrin levels (mean  $\pm$  SE) in rats following a 2-week experimental period. The groups include oil injected intact male, female, and lactating rats, and oil or estrogen treated ovariectomized animals. \* indicates a significant difference ( $P < 0.05$ ) in comparison to oil injected intact females. The number of animals per group is indicated in parentheses.

were significantly increased to male levels following ovariectomy. Estrogen treatment of ovariectomized rats decreased the serum gastrin concentration toward the levels found for normal female rats. The serum gastrin levels of the estrogen treated group were not significantly different from either untreated ovariectomized or normal female values. Lactating females had the highest serum hormone levels, being significantly greater than even the male gastrin concentrations ( $P < 0.01$ ).

The differences in antral gastrin concentration among the groups was less dramatic but paralleled the differences seen in serum hormone levels (Fig. 2). Male rats had a significantly higher antral gastrin concentration than did females. However, ovariectomy increased antral gastrin levels only slightly to levels between and not statistically different from that of normal males or females. Estrogen treatment of ovariectomized rats appeared to prevent this slight increase in antral gastrin concentration. The antral gastrin concentration of lactating rats was significantly higher than the tissue hormone levels of any other group tested.

*Food intake of normal males and females.* As indicated in Fig. 3, male rats consumed a

significantly greater amount of ground Purina chow than did females over a 5-day period of analysis during oil injection.

*Discussion.* The present results indicate that there are reliable sex differences in antral and serum gastrin concentration. Furthermore, the data suggest that the low serum gastrin levels found in intact normal females in comparison to males may be due to an inhibitory action of ovarian estrogen. Ovariectomy was found to eliminate the sex difference in serum gastrin, whereas estrogen treatment of spayed females tended to lower serum gastrin concentration. Al-

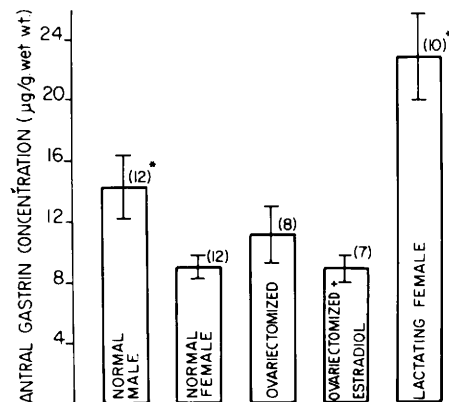


FIG. 2. Antral gastrin levels (mean  $\pm$  SE) in the same rats illustrated in Fig. 1, although in a few animals serum gastrin levels were not determined. (See numbers of animals per group in parentheses.) \* indicates a significant difference ( $P < 0.05$ ) in comparison to normal females.

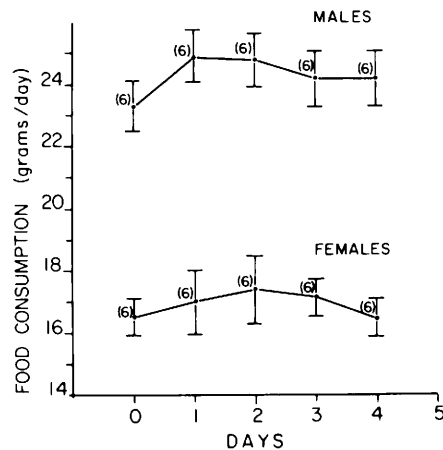


FIG. 3. Mean daily food consumption ( $\pm$  SE) in oil injected intact male and female rats over a 5-day period.

though a sex difference in antral levels of gastrin was observed, no clear-cut difference in tissue hormone concentration was seen in response to ovariectomy or estrogen treatment. The most striking alterations in gastrin levels were seen during lactation, where both antral and serum levels far exceeded those of even male rats.

Gastrin is known to be a potent stimulant of gastric acid secretion in the rat (5, 6). The sex-dependent differences in gastrin levels observed in our studies may be related to the sex-dependent differences in gastric acid secretion reported in the literature. It has been reported that gastric secretion is greater in male than in female rats (2). This sex difference is decreased by ovariectomy (12, 13), as is the difference in gastrin levels between males and females. Lactation has been shown to have a marked stimulatory effect on gastric acid secretion. It has been reported that during the third week of lactation both basal and stimulated acid secretion are increased to levels two- to threefold greater than that found prior to pregnancy (1).

These differences in gastric acid secretion among the various sexual states correlate well with the differences in serum gastrin levels in similar groups of rats investigated in our study. This suggests that the sex dependence of gastric acid secretion may be causally related to the sex-dependent changes of serum gastrin levels in the rat.

The mechanism by which the ovarian or pituitary hormones influence gastrin levels is unknown. They could act directly on the antrum by changing the synthesis or secretion of the hormone, or they could induce sex-dependent changes in metabolism or behavior which, in turn, could secondarily influence gastrin levels. Several lines of evidence suggest that sex-dependent alterations in feeding behavior may be associated with the differences in gastrin levels among the groups: (i) Antral and serum gastrin concentration are dependent on oral food intake in the rat, markedly decreasing during starvation (10) or when rats are fed exclusively by vein (14). (ii) Male rats are known to consume a significantly greater amount of chow than females (13, 16), a finding which has been confirmed by our study (Fig. 3). Recent evidence indicates

that this may be due to the inhibitory influence of estrogen on feeding behavior (15-18). The most convincing evidence in this regard is that ovariectomy causes a marked increase in food intake in female rats, surpassing even male values (18), and that this increase is abolished by estrogen replacement (17). (iii) Lactating females are hyperphagic, consuming daily several times the amount of food eaten by normal males (19). There is presently no information on whether prolactin and oxytocin, which are both markedly elevated during lactation, have any effect on mammalian gastrin synthesis or secretion.

Our findings of clear-cut and parallel sex differences in gastrin levels and food intake indicate that sex-dependent alterations of food consumption may be the determinant factor in causing the disparity between gastrin levels of males and females. The possibility, however, cannot be dismissed that these parallel changes in food intake and gastrin levels are not causally related and that both properties are directly under the influence of the pituitary-gonadal endocrine balance.

*Summary.* Antral and serum gastrin concentrations were found to be significantly lower in female than in male rats. Following ovariectomy, serum gastrin concentration significantly increased to male levels; tissue gastrin also increased, but not significantly. Daily injections of estradiol benzoate (2  $\mu\text{g}/\text{day}$ ) abolished the rise in gastrin levels after ovariectomy. Antral and serum gastrin concentrations were significantly higher in lactating rats than in any other group tested. The possible relationships among sex-dependent changes in food intake, gastrin concentration, and gastric secretion are discussed.

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