

Effect of Estradiol on Uterine Weight, Thyroid Function, Food Intake, and Pituitary Weight of Genetically Obese (Fatty-Zucker) and Lean Rats (39486)

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The fatty rat inherits obesity as an autosomal Mendelian recessive trait (1). In previous publications (1-6), we have described small pituitaries (2), decreased thyroid function (3, 4), and impaired reproductive function in these animals (5). The abnormalities in reproductive function included: (1) a delayed vaginal opening; (2) a longer period between vaginal estrus cycles; and (3) small uteri (5, 6). The finding of small uteri suggested either that there were low levels of estrogen or that the uterus was less responsive to the circulating estrogen levels. The present experiments were designed to test the latter possibility. Three of the other abnormalities noted in the fatty rat might also result, at least in part, from a deficiency of estrogen. Food intake is reduced by treatment with estrogens and rises after bilateral oophorectomy (7). Second, thyroid function, as measured by the weight of the thyroid gland and the uptake of radioactive iodine, is increased by treatment with estrogens (8, 9). Low levels of estrogen might, therefore, decrease thyroid function. Finally, the weight of the pituitary is increased by high levels of estrogen and reduced by oophorectomy. The response of these systems as well as of uterine weight was used to test the response to estradiol.

Methods and materials. The experiments performed used genetically obese and lean female rats obtained from Dr. Lois Zucker (Stow, Massachusetts) or through breeding these animals in our laboratories. At the time of the experiment, the lean animals weighed 226 to 235 g and the fatty rats weighed 330 to 440 g, and they ranged in

age from 4 to 7 months. The rats were maintained singly in metabolism cages or in suspended wire bottom cages in groups of four rats. Laboratory chow was fed except for the last 3 weeks when a low iodine diet, purchased from Nutritional Biochemicals Company, was given (10).

Twenty-six fatty and twenty lean rats were divided into groups of four rats each except for two groups of fatties which had only three rats (those receiving 0.01 $\mu\text{g}/100$ g or 100 $\mu\text{g}/100$ g of body wt). One subgroup of lean and obese rats was maintained as intact controls and the remainder were castrated. The protocol was similar to one published earlier (11). On the fifth day after castration, the various groups received injections of peanut oil or estradiol-17 β for a 3-day period, after which they were sacrificed. The estradiol-17 β was dissolved and diluted in peanut oil and given intramuscularly in doses ranging from 0.01 to 100 $\mu\text{g}/100$ g of body wt. Radioactive iodine uptake was determined by injecting 50 μCi of ¹²⁵I intraperitoneally 24 hr prior to sacrifice. Beginning 12 hr after the last dose of estradiol-17 β , pairs of rats, including one lean and one fatty, were killed until all animals had been sacrificed. The ovary (at castration or autopsy), the pituitary, and the thyroid were carefully removed and weighed, and the radioactivity in the thyroid was counted in a well-type scintillation counter. The Student's *t* test was used to compare group differences and significance was claimed if $P < 0.05$.

Results. In a preliminary experiment, groups of 10 fatty and 10 lean rats were castrated and half of the animals were treated with estradiol benzoate, 1 $\mu\text{g}/\text{day}$, for 1 week. The increase in uterine weight was smaller in the obese (fatty) rats than in the lean animals. To obviate the problem of

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a single dose of estradiol-17 β given to rats of different body weights, the present experiment was designed using a log-dose treatment schedule in which estradiol-17 β was given intramuscularly in doses ranging between 0.01 and 100 $\mu\text{g}/\text{body wt}$ (Figs. 1-3). There was a clear dose-response relationship between estradiol-17 β and the weight of the uterus (Fig. 1). Indeed, the genetically obese rats showed a somewhat greater rise in uterine weight than did lean rats when given weight-related doses of estradiol-17 β . At 0.1 $\mu\text{g}/100\text{ g}$, the uterus of the castrated fatty rats was significantly heavier than the uterus of the castrated lean animals treated with the same dose. With increasing doses of estradiol-17 β , the weight of the pituitary increased in both groups (Fig. 2).

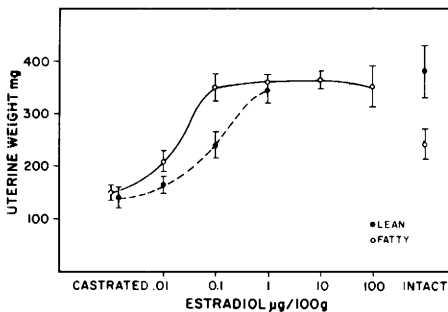


FIG. 1. Effect of estradiol on uterine weight of castrated rats. Rats were castrated 5 days before treatment and treated for 3 days. Uterine weight (mean \pm SEM) is plotted against the dose of estradiol. Weights for castrated rats are shown at the left end and the uterine weight for intact is shown at the right. The genetically obese rats appear to be slightly more sensitive to estradiol.

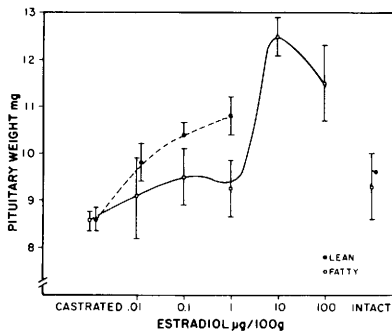


FIG. 2. Effect of estradiol on the weight of the pituitary. The weight (mean \pm SEM) of the pituitary did not differ between lean and fatty rats. After castration, the pituitary was smaller, but increased in weight during treatment with estradiol.

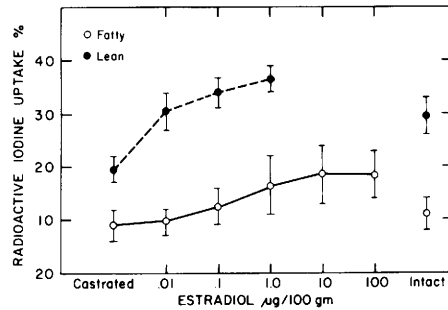


FIG. 3. Effect of estradiol on the uptake of radioactive iodine. The mean (\pm SEM) for 24-hr uptake of radioactive iodine is plotted against the dose of estradiol. The genetically obese rats had lower thyroidal uptake of radioiodine throughout, but estradiol enhanced the uptake in both obese and lean animals.

Estradiol-17 β also increased the uptake of radioactive iodine by the thyroid in lean and fatty rats (Fig. 3). At each dose of estradiol-17 β , however, the lean rats had a significantly higher uptake of radioactive ^{125}I than the fatty rats. The mean weight of the adrenal glands was heavier in the obese animals (6), but this difference was not significant and there were no significant effects on the weight of this gland by treatment with estradiol-17 β . Food intake in the control periods and after castration usually ranged from 13 to 15 g/day in the lean animals. After treatment with the highest dose of estradiol-17 β , there was a significant drop in food intake in the lean animals but no effect from the lower doses. The fatty rats ate more food (16-20 g/day) than the lean animals, and even the highest dose of estradiol-17 β did not decrease food intake. The highest dose of estradiol-17 β significantly reduced the body weight of the fatty rat by 30%, but the lower doses did not.

Discussion. The present experiments confirm that the uteri of the fatty rats are significantly smaller than the uteri from lean animals (2, 5, 6). Similar atrophic changes in the uterus have also been observed in most other genetically obese rodents (1). The rise in uterine weight in response to exogenous estradiol-17 β is normal in the fatty rat and the other obese rodents (1). This suggests that the reduced uterine weight in the fatty rat may result from a low concentration of circulating estradiol-17 β . Attempts to measure this hormone by the radioimmu-

noassay system for estradiol-17 β available in our laboratory were unsuccessful in distinguishing between normal and low circulating levels of this estrogen. However, indirect evidence supports the contention that the fatty rat is hypoestrogenized. First of all, we found that over the dose range from 0.01 to 100 μg of estradiol-17 β /100 g of body wt, the increase in uterine weight of the fatty rats occurred at the same time or at a slightly lower dose of estradiol than that found in the lean controls. We could thus find no indication of a reduced sensitivity of the uterus of fatty rats to exogenous estrogens. However, the uterine weight of the intact fatty rats was significantly lower than that of the lean animals and was comparable to the weight of the uterus of rats treated with a daily dose of between 0.01 and 0.1 μg of estradiol-17 β . This suggests that ovarian production of estrogenic hormones in the fatty rat may be lower than in the lean rat.

Changes in the weight of the pituitary and in thyroidal uptake of radioactive iodine were also observed during treatment with estradiol. The pituitary of the fatty rat is usually smaller than in lean animals (1, 4-6). This was also observed in the preliminary study noted above, but was not demonstrated in the large dose-response study (see Fig. 2). Had larger numbers of rats been used, however, we would have anticipated a difference in pituitary weight between intact fatty and lean rats. After castration, the weight of the pituitary in the lean and fatty rats was identical. During treatment with estradiol, the weight of the pituitary increased in both groups, but at different doses. It is thus possible that the small pituitary usually observed in the fatty rat may result in part from low circulating concentrations of estradiol. It is also possible that some of the differences in uptake of radioactive iodine between lean and fatty rats (4, 6) may also result from differences in the levels of circulating estradiol-17 β . The rise in thyroidal uptake of radioactive iodine after treatment with estradiol-17 β is similar to data reported in the literature (8-10). Regulation of food intake in the fatty rat differs in several respects from its control in lean animals (11). Fatty rats adapt to changes in

the caloric density of their diet but rats with obesity and hypothalamic injury do not. In the cold, the food intake of fatty rats falls, but the lean rats compensate for heat loss by eating more (12). The present experiments show a third difference in food intake between fatty and lean rats. Treatment of lean rats with estradiol-17 β , 1 μg /day, reduced food intake. This dose, however, did not alter the food intake of the fatty rats.

Summary. Genetically obese (fatty) and lean rats were treated with several doses of estradiol-17 β . The uterus of the untreated fatty rats was significantly smaller than the uterus of the lean rats. The uterine weight of castrated lean or fatty rats increased in weight after treatment with 0.1 or 1.0 μg /day of estradiol-17 β , but doses of 10 or 100 μg /day produced no further effect. Although castration lowered the uptake of radioactive iodine by the thyroid of lean rats, it was still significantly higher than in the thyroid of fatty rats. Thyroidal uptake of radioiodine also increased with estrogen treatment in both groups but the lean animals were more sensitive. We concluded that the small uterus in the fatty rat may be due to decreased estrogenization and that this may also partly account for the small pituitary and low thyroidal uptake of radioiodine.

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