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### Research Article

The effect of 17beta-estradiol or progesterone administration on adipose tissue lipoprotein lipase activity was studied in male and ovariectomized female rats. Lipoprotein lipase activity was measured in acetone-ether-extracted preparations of adipose tissue with doubly labeled (14C-fatty acid, 3H-glycerol) chylomicron triglyceride as substrate. Administration of 17beta-estradiol to male rats lowered adipose tissue lipoprotein lipase activity from 8.22 plus or minus 1.8 U/g (1 U = 1 mumol triglyceride hydrolyzed per h) to 4.96 plus or minus 0.5 U/g in the treated group. Ovariectomy increased adipose tissue lipoprotein lipase activity from 10.4 plus or minus 1.8 U/g in controls to 22.7 plus or minus 4.3 U/g. 17beta-Estradiol administration to ovariectomized rats caused a marked fall in adipose tissue lipoprotein lipase activity: 17beta-estradiol (2.5 mug/day) lowered the enzyme activity to 9.00 plus or minus 1.2 U/g, whereas 25 mug/day further decreased lipoprotein lipase activity to 3.2 plus or minus 0.6 U/g. Blood triglyceride levels increased from 0.8 plus or minus 0.05 mumol/ml in ovariectomized rats to 1.4 plus or minus 0.09 mumol/ml in 25 mug/day 17beta-estradiol-treated rats. Progesterone administration did not affect adipose tissue lipoprotein lipase activity in either male or ovariectomized rats. Heart and lung lipoprotein lipase activity was unaffected by hormone treatment. We suggest that the rise in blood triglyceride concentrations, which accompanies high plasma estrogen levels, could be due to [...]

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# The Effect of Estrogen on the Lipoprotein Lipase Activity of Rat Adipose Tissue

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**ABSTRACT** The effect of  $17\beta$ -estradiol or progesterone administration on adipose tissue lipoprotein lipase activity was studied in male and ovariectomized female rats. Lipoprotein lipase activity was measured in acetone-ether-extracted preparations of adipose tissue with doubly labeled ( $^{14}\text{C}$ -fatty acid,  $^3\text{H}$ -glyceryl) chylomicron triglyceride as substrate. Administration of  $17\beta$ -estradiol to male rats lowered adipose tissue lipoprotein lipase activity from  $8.22 \pm 1.8$  U/g (1 U = 1  $\mu\text{mol}$  triglyceride hydrolyzed per h) to  $4.96 \pm 0.5$  U/g in the treated group. Ovariectomy increased adipose tissue lipoprotein lipase activity from  $10.4 \pm 1.8$  U/g in controls to  $22.7 \pm 4.3$  U/g.  $17\beta$ -Estradiol administration to ovariectomized rats caused a marked fall in adipose tissue lipoprotein lipase activity:  $17\beta$ -estradiol (2.5  $\mu\text{g}/\text{day}$ ) lowered the enzyme activity to  $9.00 \pm 1.2$  U/g, whereas 25  $\mu\text{g}/\text{day}$  further decreased lipoprotein lipase activity to  $3.2 \pm 0.6$  U/g. Blood triglyceride levels increased from  $0.8 \pm 0.05$   $\mu\text{mol}/\text{ml}$  in ovariectomized rats to  $1.4 \pm 0.09$   $\mu\text{mol}/\text{ml}$  in 25  $\mu\text{g}/\text{day}$   $17\beta$ -estradiol-treated rats. Progesterone administration did not affect adipose tissue lipoprotein lipase activity in either male or ovariectomized rats. Heart and lung lipoprotein lipase activity was unaffected by hormone treatment. We suggest that the rise in blood triglyceride concentrations, which accompanies high plasma estrogen levels, could be due to the marked inhibition of adipose tissue lipoprotein lipase activity.

## INTRODUCTION

There is now considerable evidence that plasma triglycerides are hydrolyzed to free fatty acids during their removal from blood. This process is catalyzed and regulated by lipoprotein lipase, an enzyme active in or near the capillary wall (1).

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Lipemia of pregnancy, which is essentially a rise in plasma triglyceride concentration, is related to changes in the level of lipoprotein lipase activity in adipose tissue and mammary gland in the rat (2, 3). A few days before parturition, during the peak of hyperlipemia adipose tissue lipoprotein lipase is almost completely inhibited. Disappearance of the lipemia just before parturition is directly related to a marked rise in mammary gland lipoprotein lipase activity. In addition to pregnancy, increased plasma triglyceride levels have been reported in women on mixed contraceptives (4, 5); the lipemia seems to be caused by the estrogen component only (5).

There are marked changes in blood estrogen concentration during the estrous cycle in the rat (6). A comparison of lipoprotein lipase activity in adipose tissue of male with that of female rats showed that in males the activity level was almost constant, whereas wide fluctuations were observed in females.<sup>1</sup> This observation raised the possibility that female sex hormones might affect the activity of adipose tissue lipoprotein lipase.

## METHODS

*Animals.* Adult male and female Sprague-Dawley rats delivered by cesarean section were used in this study. The rats were purchased from Charles River Breeding Laboratories, Inc., Wilmington, Mass. The animals were caged individually and had free access to food (Purina Laboratory Chow, Ralston Purina Co., St. Louis, Mo.) and water.

*Hormone preparations.*  $17\beta$ -Estradiol (Depo-estradiol cypionate) and progesterone (Depo-Provera [medroxyprogesterone acetate suspension U.S.P.]) were purchased from the Upjohn Co., Kalamazoo, Mich. Male rats were given the hormones by intraperitoneal injection once weekly for 8 wk:  $17\beta$ -estradiol 50  $\mu\text{g}$ , or progesterone 5 mg, in 0.1 ml saline. Hormone treatment of ovariectomized rats was started 2 wk after surgery. The rats were given  $17\beta$ -estradiol or progesterone in 0.1 ml corn oil by subcutaneous

<sup>1</sup>Hamosh, M., P. Hamosh, and R. O. Scow. Unpublished observations.

TABLE I  
Effect of 17 $\beta$ -Estradiol\* and Progesterone† on Adipose Tissue Lipoprotein Lipase Activity of Male Rats

Treatment§	No. of animals	Lipoprotein lipase activity¶ U/g
None	12	8.22±0.88
17 $\beta$ -Estradiol	12	4.96±0.52**
Progesterone	12	8.36±0.67

Results are mean±SE.

\* 17 $\beta$ -Estradiol was injected i.p. 50  $\mu$ g in 0.1 ml once weekly.

† Progesterone was injected i.p. 5.0 mg in 0.1 ml once weekly.

§ Hormones were administered for a period of 8 wk.

|| Weight gain during the 8-wk period of treatment was 335±10.7 g in control, 320±24 g in progesterone-treated, and 290±7.8 g in 17 $\beta$ -estradiol-treated rats.

¶ 1 unit of lipoprotein lipase = 1  $\mu$ mol triglyceride hydrolyzed per h. The activity rate for each tissue is the result of four separate determinations.

\*\* Values significantly different from control ( $P < 0.05$ ).

injection daily for 7 days. One group of animals received 2.5  $\mu$ g 17 $\beta$ -estradiol, a second group 25  $\mu$ g, a third group was given 5 mg progesterone; controls received 0.1 ml corn oil daily. The dosage of 17 $\beta$ -estradiol was chosen to be in the range administered by Chen and Meites (7) and lower than that given by Cairns and Constantinides (8).

*Lipoprotein lipase assay.* The animals were anesthetized with sodium pentobarbital (12.5 mg/rat) and exsanguinated through the heart. Ovariectomized rats were examined at autopsy to insure the complete removal of the ovaries. The uteri were dissected and weighed in order to check the effect of hormone treatment. Dried defatted powders of adipose tissue, heart, and lung were prepared and assayed

for lipoprotein lipase activity as described previously (3, 9). Lipoprotein lipase activity was measured by the amount of rat chylomicron triglyceride hydrolyzed to fatty acids and glycerol with 1 U of activity = 1  $\mu$ mol of triglyceride hydrolyzed per h (3, 9).

## RESULTS

*Effect of 17 $\beta$ -estradiol and progesterone on lipoprotein lipase activity in adipose tissue of male rats (Table I).* There was a marked decrease in lipoprotein lipase activity in epididymal adipose tissue of male rats treated with 17 $\beta$ -estradiol for a period of 8 wk. Progesterone treatment had no effect on adipose tissue lipoprotein lipase activity. The weight gain in the three groups of rats was not markedly different. Lipoprotein lipase activity in heart and lung of male rats was unaffected by estrogen or progesterone treatment.

*Effect of 17 $\beta$ -estradiol and progesterone on lipoprotein lipase activity in adipose tissue of ovariectomized rats (Table II).* The level of lipoprotein lipase activity in adipose tissue rose after ovariectomy from 10.40±1.8 U/g in control female unoperated rats to 22.72±4.3 U/g 3 wk after the operation. Plasma triglyceride concentration was in the normal range in both control and ovariectomized rats. Administration of 2.5  $\mu$ g 17 $\beta$ -estradiol daily for a period of 7 days to ovariectomized rats decreased lipoprotein lipase activity in adipose tissue to levels similar to those in control unoperated animals. Increasing the dose of 17 $\beta$ -estradiol to 25  $\mu$ g daily caused a further decrease in the level of adipose tissue lipoprotein lipase activity and a concomitant rise in plasma triglyceride concentration. Animals in the five different groups had a similar weight gain during the

TABLE II  
Effect of 17 $\beta$ -Estradiol and Progesterone on Lipoprotein Lipase Activity in Adipose Tissue of Ovariectomized Rats

Animals	Treatment*	No. of animals‡	Lipoprotein lipase activity§ U/g	Plasma triglyceride $\mu$ mol/ml
Control	None	6	10.40±1.8	0.85±0.05
Ovariectomized	None	9	22.72±4.3	0.80±0.05
	17 $\beta$ -Estradiol, 25 $\mu$ g	5	9.00±1.17¶	—
	17 $\beta$ -Estradiol, 25 $\mu$ g	5	3.20±0.60  ¶	1.40±0.09  ¶
	Progesterone, 5 mg	8	22.28±1.71	—

Results are mean±SE.

\* 17 $\beta$ -Estradiol or progesterone were dispersed in corn oil and injected daily (0.1 ml subcutaneous) for a period of 7 days.

‡ Weight gain during the 7 days of treatment was 29±5 g in control, 32±4 g in ovariectomized, 24±3 and 21±2 g in 17 $\beta$ -estradiol-treated rats (2.5 and 25  $\mu$ g/day, respectively), and 21±3.2 g in progesterone-treated rats.

§ The activity rate for each tissue is the result of four separate determinations.

|| Values significantly different from control ( $P = 0.01$ ).

¶ Values significantly different from ovariectomized ( $P = 0.01$ ).

hormone treatment period. Lipoprotein lipase activity in heart and lung was not affected by 17 $\beta$ -estradiol administration.

Heart lipoprotein lipase was 41.3 $\pm$ 5.3 U/g in ovariectomized rats, 33.3 $\pm$ 3.0 U/g in 2.5  $\mu$ g and 43.9 $\pm$ 3.3 U/g in 25  $\mu$ g 17 $\beta$ -estradiol-treated animals, and 49.2 $\pm$ 1.4 U/g in progesterone-treated rats. Lipoprotein lipase in the lung was 13.0 $\pm$ 0.88 in control unoperated rats, 11.6 $\pm$ 1.6, 12.00 $\pm$ 2.54, 10.50 $\pm$ 0.60, and 12.2 $\pm$ 2.0 U/g in ovariectomized untreated, 2.5  $\mu$ g and 25  $\mu$ g 17 $\beta$ -estradiol- and progesterone-treated rats, respectively. Blood triglyceride levels were 0.85 $\pm$ 0.05  $\mu$ mol/ml in control unoperated rats, 0.80 $\pm$ 0.05  $\mu$ mol/ml in ovariectomized rats and 1.4 $\pm$ 0.09  $\mu$ mol/ml in ovariectomized rats treated with 25  $\mu$ g/day 17 $\beta$ -estradiol. There was a sevenfold increase in the wet weight of the uterus after treatment of ovariectomized rats with either 2.5 or 25  $\mu$ g 17 $\beta$ -estradiol daily for a period of 7 days; the uterus wet weight increased less than twofold after progesterone treatment.

## DISCUSSION

The effect of sex hormones on lipoprotein lipase activity has been limited to the study of the enzyme present in postheparin plasma (4, 5, 10, 11). These studies have been carried out mainly in the human (4, 5, 10, 11). Postheparin lipolytic activity is a mixture of enzymes containing lipoprotein lipase of extrahepatic origin and triglyceride lipase of hepatic origin (12). The two lipolytic activities, hepatic and extrahepatic, have different substrate specificity, triglyceride emulsions and lipoprotein-triglyceride, respectively, and respond differently to enzyme inhibition (12, 13). It has recently been shown that postheparin lipolytic activity of extrahepatic origin (12) is highest in postmenopausal women (13). In rats ovariectomy increases and estrogen administration decreases postheparin lipolytic activity (8). There is no information, however, on the effect of estrogen and progesterone on tissue levels of lipoprotein lipase in either man or other mammals. The present study shows that estrogen administration caused a marked decrease in the level of lipoprotein lipase activity in adipose tissue of male or ovariectomized rats (Tables I and II). There was a concomitant increase in plasma triglyceride concentration (Table II). Administration of progesterone did not affect the enzyme activity in adipose tissue of either male or ovariectomized rats.

Studies in vivo and in vitro in the rat have shown that lipoprotein lipase activity in adipose tissue is markedly decreased during fasting (14), lactation (2, 3), and in diabetes (14). The decrease in lipoprotein lipase activity after estrogen treatment was not caused by inadequate food intake since the rats in the different experimental groups (control, ovariectomized, and

hormone treated) had a similar weight gain (Tables I and II).

We have recently shown that the very low activity of lipoprotein lipase in adipose tissue of lactating rats is the result of inhibition of enzyme synthesis by prolactin (15). We do not know at present whether the low adipose tissue lipoprotein lipase activity in estrogen-treated rats is caused directly by this hormone or whether it is mediated through the secretion of prolactin.

Estrogen administration to ovariectomized rats has been shown to increase both anterior pituitary and serum prolactin concentrations (7). The high levels of adipose tissue lipoprotein lipase activity in some of the control females and in pregnant rats during the first 2 wk of gestation (3) could be due to the low levels of both estrogen (6) and prolactin (16) during metestrus and diestrus and during the first 2 wk of gestation. Estrogen or progesterone treatment did not affect lipoprotein lipase activity in heart and lung.

We do not know at present what is the quantitative contribution of hepatic and extrahepatic tissues to the clearing of blood triglyceride. However, the presence of very low levels of lipase of extrahepatic origin and normal levels of hepatic lipase in postheparin plasma of patients with hyperchylomicronemia (13) indicates that the extrahepatic tissues play a major role in the clearing of blood triglyceride. This assumption agrees well with the data of Bragdon and Gordon, who showed that in the rat, 32% of chylomicron-triglyceride fatty acids were present in adipose tissue 10 min after intravenous injection of <sup>14</sup>C-fatty acid-labeled chylomicrons (17). The decrease in adipose tissue lipoprotein lipase activity without the concomitant increase in enzyme activity in other tissues could lead to a rise in plasma triglyceride levels as a result of impaired clearing of blood triglyceride.

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