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Effects of the Synthetic Androgen Fluoxymesterone on Triglyceride Secretion Rates in the Rat (38826)

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(Introduced by Edwin L. Bierman)

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In addition to anabolic and masculinizing effects, androgens influence a number of other important biological processes. The principle androgen in man, testosterone, and its derivatives stimulate erythropoiesis and hence provide a useful adjunct to the treatment of refractory anemia. As a result, testosterone and a number of androgenic compounds have been used to treat patients with the severe anemia that accompanies chronic renal failure (1–3). When large doses of fluoxymesterone, a C-17 methylated derivative of testosterone and dromostanolone, a similar anabolic steroid, have been employed for this purpose in uremic patients undergoing chronic hemodialysis, however, an increase in plasma triglyceride concentration occurs (4, 5).

Since it has been generally believed that androgens lower rather than elevate the triglyceride-rich, very low-density lipoprotein class (VLDL) (6), this hyperlipidemic effect contrasts with previous concepts of their influence on lipid transport. In order to determine whether fluoxymesterone has unique lipid-elevating properties which distinguish it from other testosterone derivatives, its effect on basal plasma triglyceride levels, and triglyceride secretion rates were quantitated in the rat.

Methods. Experimental protocol. Young adult male Sprague–Dawley rats (150 g) were placed in cages and fed Lab Chow (Purina) ad lib. Room temperature was controlled and lights were automatically turned on at 7:00 AM and off at 8:00 PM. After a 1-wk period of stabilization, food was withdrawn from all cages at 2:00 AM, and between 9:00 and 11:00 AM, each animal was weighed, lightly anesthetized with ether, and blood obtained from the tail vein for basal triglyceride measurements. The group was then divided into treatment and control groups each containing 10 rats. The treated group received daily intraperitoneal injections of fluoxymesterone (2.3 mg/kg). Controls were injected similarly with an equal volume of saline.

After 2 wk of the injection protocol, triglyceride secretion rates (TGSR) were determined employing the nonionic detergent Triton WR-1339. For this study, intraperitoneal pentobarbital was used to establish general anesthesia. Body temperature was maintained with heat lamps. After blood was obtained at zero time for triglyceride and insulin measurement, 120 mg of Triton was injected through a tail vein, and blood samples again obtained at 50 and 100 min after Triton administration from a different tail vein. This dose of Triton was based upon experiments which indicated that triglyceride levels in normal rats increase linearly with increasing doses of Triton up to 60 mg, after which further increases in Triton concentration led to no further increase in triglyceride levels (13). Plasma volumes of 15 normal rats were estimated by standard dye-dilution techniques after the intravenous injection of Evans blue. Since no difference in hematocrit was observed in control and fluoxymesterone-treated rats, this curve was employed for the determination of plasma volume in both groups.

Chemical Procedures. All blood samples were collected in tubes containing EDTA. Hematocrits were determined using a microhematocrit method. Plasma triglyceride (TG) was measured by an automated enzymatic method (7), and immunoreactive insulin (IRI) determined in six rats from each group by an ^{125}I radioimmunoassay by double antibody (8). Triglyceride secretion responses (TGSR) after Triton WR-1339 were calculated as previously described (9).

Results. Prior to fluoxymesterone adminis-

TABLE I. BODY WEIGHTS, BASAL PLASMA TRIGLYCERIDE AND INSULIN LEVELS, AND TRIGLYCERIDE SECRETION RATES IN 10 CONTROL AND 10 FLUOXYMESTERONE-TREATED RATS (MEAN ± SD).

	Fluoxymesterone	Control
Body weights (g)		
Before treatment	185 ± 5	184 ± 5
After treatment	266 ± 5	270 ± 7
Triglyceride (mg/100 ml)		
Before treatment	139 ± 28	136 ± 40
After treatment	117 ± 19*	144 ± 28
Basal insulin (μU/ml)		
Before treatment (n = 6)	34 ± 10	35 ± 9
After treatment n = 6)	43 ± 8	50 ± 16
Triglyceride secretion rate (mg/min)		
After treatment	.252 ± .05	.263 ± .06

* $P < 0.05$.

tration, body weights and TG and IRI were similar in treatment and control groups (Table I). During the 2-wk period of injection, growth rates were similar, and no differences in mean body weight of the two groups was observed. After androgen treatment, TG was significantly decreased in the treated group ($P < 0.05$). TGSR, however, were similar in both experimental groups (Table I).

Basal IRI levels did not differ significantly in treated and control animals. No correlation was demonstrable between TGSR and either basal IRI or the sum of the IRI measurements obtained at 0, 50, and 100 min after Triton injection.

Discussion. Past studies have shown that testosterone and its methylated derivatives decrease the total serum cholesterol as well as the high- and low-density lipoprotein fractions in man, the rat, and dog (6). While these compounds also appear to consistently decrease the plasma triglyceride level in man, their effects on plasma triglyceride in the rat is unknown. Results of this study indicate that the decrease in plasma triglyceride concentrations observed in the fluoxymesterone-treated rats is identical to that reported in man after testosterone treatment.

Since testosterone and its derivatives are believed to exert primarily hypolipidemic actions, the elevation of plasma triglyceride levels reported in renal-failure patients undergoing chronic hemodialysis after the administration of large doses of fluoxymesterone suggests that uremia may alter the metabolism of this compound, and cause a paradoxical increase in TG (4). It is also possible that the reported elevation of TG may have been influenced by the relatively massive doses given to these renal-failure patients.

The triglyceride-lowering effects of androgenic compounds such as fluoxymesterone could result from decreases in the rate of endogenous, very low-density lipoprotein (VLDL) production, or an acceleration in their rate of removal, a process believed to be mediated by the lipoprotein lipase enzyme system (LPL). The functional capacity of this important tissue enzyme has been routinely estimated indirectly by the measurement of lipolytic activity in plasma after the administration of heparin (PHLA). The recent demonstration that treatment with the synthetic androgen, oxandrolone, increased PHLA and lowered plasma triglyceride levels in hyperlipidemic patients (10) suggests that the triglyceride-lowering effects of androgens may result from accelerated removal.

Nevertheless, it is also possible that a decreased rate of VLDL formation could contribute to lower plasma triglyceride after androgen treatment. The decline observed in triglyceride levels with no reduction in the rate of hepatic triglyceride secretion in the fluoxymesterone-treated animals in this study, however, is consistent with the PHLA data in man which suggest that androgens lower plasma triglyceride by accelerated VLDL removal.

Although basal free fatty acid levels (FFA) were not determined in this study, androgens have been shown to increase basal lipolysis and elevate FFA in man and animals (11). Since the liver normally extracts a fixed proportion of fatty acids from plasma for esterification with alpha-glycerolphosphate, increased hepatic triglyceride synthesis might be expected when the availability of FFA is increased. However, androgen treatment also has been shown to increase hepatic oxidative

enzymes (12); consequently, the lack of any increase in triglyceride secretion rate in the setting of presumably increased FFA delivery to the liver may reflect this androgen-mediated diversion of FFA into oxidative pathways. While the mechanisms underlying the previously reported androgen-induced elevation of FFA remain unclear, the lack of any striking difference in basal IRI levels makes it unlikely that any disturbance in basal lipolysis results from a primary defect in the regulation of basal insulin secretion.

Summary. Fluoxymesterone, a C-17 methylated derivative of testosterone employed in the treatment of renal-failure patients with refractory anemia, was administered to Sprague–Dawley rats and the effects on plasma triglyceride (TG) and immunoreactive insulin (IRI) levels and the rate of hepatic triglyceride secretion (TGSR) into plasma determined (Triton). Animals treated with fluoxymesterone demonstrated significantly lower TG (<0.05) and no alteration in TGSR. These findings are consistent with other observations which suggest that the triglyceride-lowering effect of androgens results from an accelerated rate of removal of triglyceride-rich lipoproteins from plasma.

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