Mechanism of Hypertriglyceridemia in Dahl Rats

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Plasma triglyceride concentrations were shown to be higher in hypertensive (153±2 mm Hg) male Dahl salt-sensitive rats than in control Sprague-Dawley rats (122±2 mm Hg). These differences in triglyceride concentrations were seen when blood was drawn at 9 AM from unfasted animals (229±27 versus 111±8 mg/dL), at 1 PM after a 4-hour fast (186±13 versus 88±4 mg/dL), or at 9 AM after a 13-hour fast (151±6 versus 90±6 mg/dL), all p<0.001. Total triglyceride secretion was also compared in groups of rats by determining the increment in plasma triglyceride concentration for 2 hours after blocking triglyceride removal from plasma by injecting Triton. Studies performed at 1 PM and 9 AM, after the 4- and 13-hour fast, demonstrated that total triglyceride secretion was greater (p<0.05) in Dahl rats only when studied at 1 PM. Direct estimates of hepatic triglyceride secretion at 1 PM also demonstrated a significant (p<0.02) increase in secretion rate by perfused livers from Dahl rats, due in part to their increased liver size. In addition, removal of prelabeled very low density lipoprotein–triglyceride in the intact rat was significantly (p<0.05) decreased in Dahl rats. Lipoprotein lipase activity measured in skeletal muscle, heart, and adipose tissue was also significantly decreased at 9 AM and 1 PM (after 0 and 4 hours of fasting) in tissue from Dahl rats. These data confirm that Dahl rats have higher plasma triglyceride concentrations than Sprague-Dawley rats. Since both total and hepatic triglyceride secretion were somewhat greater in Dahl rats, in association with a decrease in both removal of very low density lipoprotein from plasma and decreased muscle and adipose tissue lipoprotein lipase activity, it seems likely that hypertriglyceridemia in Dahl rats results from a combination of increased triglyceride secretion and decreased triglyceride removal. (Hypertension 1993;21:373–379)

KEY WORDS • hypertriglyceridemia • rats, inbred strains • lipoprotein lipase • triglycerides • lipoproteins, VLDL

It has recently been demonstrated that plasma triglyceride (TG) concentration is increased in Dahl salt-sensitive (Dahl S) rats. 1 Since hypertriglyceridemia has also been noted in patients with hypertension, 2,3 as well as in two other models of rodent hypertension, 4,5 it seemed possible that an increased understanding of the cause of hypertriglyceridemia in a rodent model of hypertension would provide useful information relevant to the change in lipoprotein metabolism seen in patients with high blood pressure. As a first step in this process, we initiated a series of studies to define the mechanism of hypertriglyceridemia in Dahl S rats. Increased plasma very low density lipoprotein–TG (VLDL-TG) concentration in Dahl S rats may be due to increased hepatic VLDL-TG secretion, decreased VLDL-TG removal, or both, with the latter process dependent on the activity of lipoprotein lipase (LPL). 6 We determined TG secretion in both the intact rat and isolated perfused liver, VLDL-TG removal in the intact rat, LPL activity in adipose tissue and cardiac and skeletal muscle, and hepatic lipase activity. Our results confirm the initial observation 1 that plasma TG concentrations are higher in Dahl S rats and provide evidence that these higher concentrations result from both an increase in hepatic TG secretion and a decrease in TG clearance from plasma.

Methods

Male Sprague-Dawley (S-D) rats were obtained from Bantin and Kingman, Fremont, Calif., at approximately 5 weeks of age, and male Dahl S rats of the same age were obtained from Harlan Sprague Dawley, Indianapolis, Ind.). Both groups were fed Purina laboratory chow (No. 5012) for 2 to 3 weeks after arrival to acclimate them to a common diet before measurements were taken. All experimental procedures were designed according to the Guiding Principles in the Care and Use of Animals approved by the Council of the American Physiological Society. Surgery was performed for liver perfusion studies, and animals were anesthetized with thiamylal sodium (70 mg/kg i.p.).

Blood Pressure Measurement

Rats were removed from the animal room and transported to the laboratory at 10 AM. They were kept in a quiet area before blood pressure measurements were recorded as described previously. 4,7 The tail-cuff...
was taken as the measurement of systolic blood pressure. Ambient temperature was kept at 30°C. The equipment used included magnetic animal holders connected to a manual scanner (model 65-12, IITC, Woodland Hills, Calif.), a pulse amplifier (model 59, IITC), and a dual-channel recorder (model 1202, Linear Instruments, Reno, Nev.). The systolic blood pressure was measured while the rats were in the conscious state. Each rat was acclimated to the holder and tail cuff by two to three training sessions several days before the definitive measurements. On the day of the test, the mean of five consecutive readings was taken as the measurement of systolic blood pressure for each rat.

Triglyceride Secretion Rate
Triglyceride secretion rate (TGSR) was determined by measuring the increase in plasma TG concentration after suppression of TG removal from plasma with Triton WR 1339.8,9 These studies were performed under two conditions. In one series of studies, food was removed at 8:30 AM, and Triton was injected between 12:30 and 1:30 PM. In a second series of experiments, food was removed at 9 PM, and Triton was injected between 9 and 10 AM. In both instances, blood samples were obtained before injection of Triton for measurement of TG concentration with Sigma kit No. 339, modified from the enzymatic method of McGowan et al.10 Rats were wrapped in a terry cloth towel to partially calm them before a 0.5-mL blood sample was obtained from an incision at the tip of the tail. The tail was sealed with laboratory tape, followed by injection of Triton (300 mg/mL) into the tail vein at a dose of 800 mg/kg body wt. Animals were returned to their cages, and subsequent blood samples of 0.2 mL were obtained for TG determination 60 and 120 minutes after injection of Triton.

Hepatic Triglyceride Production
Livers were isolated from S-D and Dahl S rats and perfused by established techniques in our laboratory.11 These animals were fasted at 8:30 AM, and perfusions were started between 12:30 and 1:30 PM. The perfusing medium consisted of 36% red blood cells, suspended in Krebs-Ringer bicarbonate buffer containing 4 g bovine serum albumin (BSA)/100 mL. The red blood cells were human salvage cells obtained from the Stanford University Blood Bank and used within 14 days of collection. On the day of perfusion, red blood cells were washed repetitively (4–5 times) with physiological saline solution containing KCl at 4.5 meq/L, followed by a final wash with Krebs-Ringer bicarbonate solution. At the start of perfusion, livers were initially flushed with 30 mL perfusing medium containing glucose (8 mM), free fatty acid (0.60 μeq/mL), insulin (4 ng/mL), and amino acids at physiological levels, followed by recirculation with a perfusate volume of 58 mL. During the next 120 minutes, all livers received an infusion of oleic acid and insulin to sustain perfusate free fatty acid concentrations at 0.60 μeq/mL and insulin concentrations of 8 ng/mL, respectively. Hepatic TG secretion was calculated from the change in perfusate TG concentration between 30 and 120 minutes, corrected for sampling losses, and expressed as net milligrams TG produced per hour per gram liver and milligrams TG per hour per gram liver.

Very Low Density Lipoprotein–Triglyceride Removal
VLDL-TG removal rates were determined by measuring the rate of disappearance of prelabeled VLDL-TG from the plasma of intact animals. The labeled VLDL was prepared by injecting 300–400-g donor rats with 400 μCi 2-[3H]glycerol via the tail vein. The donor rats were exsanguinated under methoxyflurane anesthesia 40 minutes later. The blood was defibrinated, and the serum was separated by centrifugation. The serum then underwent ultracentrifugation through a 0.9N NaCl solution, pH 7.3, containing 0.01% EDTA. The recovered VLDL was subsequently dia lyzed against the same solution for two exchanges of at least 6 hours each, followed by one overnight exchange against 0.9N NaCl solution without EDTA. Aliquots of this purified VLDL were then injected into rats from each experimental group. After administration of the label, 0.4 mL blood was collected into 1.5-mL centrifuge tubes at 3, 6, 9, and 12 minutes. These collections, timed with a stopwatch, took approximately 30 seconds to collect from the end of the tail, and the time used for the sampling point was calculated from the beginning and ending times of the blood collection. After storage on ice, the serum was separated after 2 minutes of centrifugation in a microcentrifuge, and aliquots were taken for determination of lipid extractable radioactivity and TG concentration. Lipid extraction was performed by the method of Folch et al.,12 and radioactivity was measured by liquid scintillation counting (Beckman LD) using a standard aqueous scintillation mixture. The counts recovered from the lipid extraction procedures were >95% of those in the plasma, indicating that the material injected was present almost entirely in lipid form. The half-time (t1/2) of VLDL-TG removal was determined directly from these measurements by a least-squares linear regression analysis.

Lipoprotein Lipase Activity
Two sets of experiments were performed. In the first study, 21 rats (11 Dahl S and 10 S-D) were anesthetized with sodium thiamylal (68 mg/kg i.p.) between 8:30 and 9:30 AM, whereas in the second experiment, 20 rats (10 Dahl S and 10 S-D) were anesthetized between 12:30 and 1:30 PM. Blood was collected and centrifuged; serum was obtained, aliquoted, and frozen for later analysis of TG concentration. In both instances, rats had free access to food and water until 8:30 AM. The body weights of the 21 Dahl S rats (268 ±1 g) and the 20 S-D rats (267 ±2 g) were similar.

Soleus and vastus intermedius skeletal muscles were removed first, followed by removal of the liver, epididymal fat pad, and heart. All tissues were rapidly frozen between blocks of solid CO2, enclosed in plastic bags, and stored at −90°C. Fragments (50–100 mg) of each tissue were homogenized for measurement of total protein content according to Lowry et al.13 Fat cell number was quantified on cells isolated with collagenase as previously described,14 lipid content determined by Dole extraction,15 and fat cell size (micrograms TG per cell) calculated by dividing the adipose cell number into total depot lipid.

Total LPL activity was measured after detergent extraction, as described by Iverius and Brunzell.16 Tissue fragments (adipose tissue, 100–150 mg; soleus,
60–100 mg; vastus intermedius, 80–150 mg; and heart, 100–150 mg) were homogenized in a polytron (Brinkmann Instruments) in 1 mL extraction buffer (5% deoxycholate, 0.2 M Tris, 0.25 M sucrose, 1% BSA, 10 units/mL heparin, and 0.02% nonidet P 40; pH 8.3) and centrifuged for 15 minutes at 12,000 rpm. Aliquots of the supernatant for muscles and the infranatant below the fat cake for adipose tissue were then diluted 1:15 with detergent-free extraction buffer. Either 100 or 150 µL were then mixed with 150 µL radioactive glycerol-stabilized triolein of Nilsson-Ehle and Schotz17 substrate emulsion containing, as a source of apo CII, fasted human serum. The media was incubated for 1 hour at 37°C in a water bath. Nonspecific LPL activity for each sample was determined by incubating each sample with 150 µL substrate emulsion that did not contain fasted human serum. Interassay variations and linearity of the assay were controlled by running a standard curve of a pooled rat postheparin plasma (1:20 dilution). One unit of LPL activity is defined as 1 µmol FFA hydrolyzed per hour.17

Hepatic lipase activity was measured as described by Doolittle et al.18 A portion of frozen liver (~100 mg) was homogenized in a polytron in 1 mL solubilization buffer (5 mM sodium barbital, 0.15 M NaCl, 10 units/mL heparin; pH 7.4) and centrifuged once at 60,000 rpm for 60 minutes. Aliquots (150 µL) were then mixed with 150 µL radioactive glycerol-stabilized triolein of Nilsson-Ehle and Schotz17 substrate emulsion and incubated without serum for 1 hour at 37°C in a water bath.18 One unit of hepatic lipase activity is defined as 1 µmol FFA hydrolyzed per hour per kilogram.

Calculations and Statistical Analysis

The formulas used to determine TGSR and t1/2 with the two experimental methods used were as follows:

\[
TGSR = TG_2 - TG_0 \times (\text{plasma volume}) \div 2
\]

where TGSR is expressed in milligrams per 100 grams body weight per hour, TG in milligrams per milliliter, and plasma volume in milliliters per 100 grams body weight. TG concentration was measured as described earlier. Plasma volume was determined with iodine-125-labeled albumin as previously described.18

The t1/2 of VLDL-TG removal was directly determined by following the disappearance of prelabeled VLDL-TG from plasma. The natural logarithm of the counts per minute of each sample was determined and plotted against time. A best-fit line was determined by a least-squares linear regression analysis, and the slope was determined. The following calculations were then made: slope = FTR (fractional turnover rate); t1/2 = ln 2/FTR.

Results are expressed as mean±SEM. Student's t test for unpaired data was used to compare blood pressure, hepatic TG production, and VLDL-TG removal of S-D and Dahl S rats. Plasma TG concentrations, TGSR, hepatic lipase activity, and adipose and muscle LPL activity of S-D and Dahl S rats measured under different fasting conditions were compared by two-way analysis of variance. Student's t test was used to examine specific paired comparisons when significant differences were obtained for the main effects of rat strain and length of fast. Differences were considered statistically significant at p<0.05.

Results

Blood pressure of Dahl S and S-D rats during ad libitum feeding of normal laboratory chow are shown in Figure 1. The data indicate that mean systolic blood pressure of Dahl S rats was 25% higher (p<0.001) than in S-D rats.

Plasma TG concentrations were determined on blood samples taken from Dahl S and S-D rats after varying periods of fasting. These results are shown in Figure 2 and indicate that plasma TG values were significantly higher (p<0.001) in Dahl S rats, irrespective of either time of day or duration of time without food. However, it can also be seen from Figure 2 that the longer the period without food, the lower the TG concentrations in both groups.

Plasma TG concentrations before and after injection of Triton are listed in Table 1 as well as the incremental increase in TG concentration after Triton administration (Δ 0–120 minutes). These data indicate that TG concentrations were significantly higher in Dahl S rats, both before and after injection of Triton, and this was true irrespective of duration of fast. Although the accumulation of TG in plasma was greater in Dahl S rats when measured under both conditions, the TGSR was significantly increased in Dahl S rats only when measured 4–5 hours after food withdrawal.

Basal plasma TG concentrations were also higher in the Dahl S rats used for liver perfusion (176±16 versus 84±9 mg/dL, p<0.001). Although the body weights of the two groups of rats were similar, the liver of Dahl S rats weighed more (Table 2). As a result, the percentage of body weight as liver was greater in Dahl S as compared with S-D rats (4.55±0.10 versus 4.06±0.09%, p<0.01). The data in Table 2 also show that hepatic TG
production was significantly greater in Dahl S rats \((p<0.02)\) when expressed as milligrams per hour per liver. On the other hand, when the difference in liver size was taken into account, the increase in hepatic TG production per gram liver in Dahl S rats did not reach statistical significance.

The rate of TG removal from the plasma of S-D and Dahl S rats was quantitated by measuring the half-time of disappearance of triglyceride (TG). The upper portion of Figure 3 shows the relative disappearance of radioactive VLDL from animals injected after a 4-6-hour fast. The 1/2 values calculated from these disappearance curves are illustrated in the lower portion of Figure 3 and show a prolongation of \((p<0.04)\) disappearance time of VLDL-TG in Dahl S rats.

Plasma TG concentrations were higher in Dahl S rats when blood was removed at 9 AM without fasting \((229±27 \text{ mg/dL}, p<0.001)\), as well as at 1 PM after a 4-hour fast \((186±13 \text{ mg/dL}, p<0.001)\) immediately before obtaining tissue for measurement of LPL activity. Total adipose tissue LPL activity of the two groups of rats at these same times are seen in Figure 4. It is apparent that values of total LPL activity of adipose tissue from both groups were higher at 9 AM in nonfasted animals than at 1 PM after a 4-5-hour fast \((p<0.05)\). In addition, these results demonstrate that total LPL activity was significantly lower \((p<0.01)\) in Dahl S rats compared with S-D rats at both times measured. It should be noted that the decrease in LPL activity in Dahl S rats was not due to differences in adipose tissue mass. Specifically, fat cell number \((\text{cells per gram} \times 10^5)\) was similar in Dahl S \((15.23±1.18)\) and S-D rats \((13.62±1.36)\) when measured at 9 AM in nonfasted animals, as well as at 1 PM after a 4-5-hour fast \((18.69±2.33 \text{ versus } 20.27±2.86)\). Similarly, fat cell size \((\text{micrometers lipids per cell})\) was not significantly different in Dahl S as compared with S-D rats when determined at either 9 AM \((0.184±0.015 \text{ versus } 0.194±0.020)\) or 1 PM \((0.193±0.027 \text{ versus } 0.154±0.013)\).

Measurements of muscle LPL activity are shown in Figure 5. It can be seen that the values in all three muscles changed much less as a function of time of day measured, duration of fast, or both than did adipose tissue. The results in the left panel indicate that LPL activity of heart muscle was significantly lower in Dahl S rats compared with S-D rats when measured at both 9 AM and 1 PM (in the absence of food withdrawal) or 1 PM (after a 4-5-hour period of food withdrawal) or 1 PM (after a 4-5-hour period of food withdrawal) or 1 PM (after a 4-5-hour period of food withdrawal) or 1 PM (after a 4-5-hour period of food withdrawal).

### Table 1. Triglyceride Concentration and Triglyceride Secretion Rate of Sprague-Dawley and Dahl Salt-Sensitive Rats

<table>
<thead>
<tr>
<th>Group ((n))</th>
<th>Fast ((h))</th>
<th>Body weight ((g))</th>
<th>Plasma volume ((\text{ml/100 g}))</th>
<th>TG concentration ((\text{mg/dl}))</th>
<th>TGSR ((\text{mg/100 g per hour}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-D (11)</td>
<td>4-5</td>
<td>252±2</td>
<td>4.07±0.04</td>
<td>97±6</td>
<td>862±17</td>
</tr>
<tr>
<td>Dahl S (10)</td>
<td>4-5</td>
<td>259±3</td>
<td>4.14±0.06</td>
<td>214±25</td>
<td>1,195±54</td>
</tr>
<tr>
<td>(p)</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>S-D (9)</td>
<td>12-13</td>
<td>257±2</td>
<td>4.29±0.12</td>
<td>90.6±6</td>
<td>754±31</td>
</tr>
<tr>
<td>Dahl S (8)</td>
<td>12-13</td>
<td>258±3</td>
<td>4.13±0.10</td>
<td>151.6±5</td>
<td>906±25</td>
</tr>
<tr>
<td>(p)</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

TG, triglyceride; \(\Delta\), increment in plasma TG concentration after Triton WR 1339; TGSR, triglyceride secretion rate; S-D, Sprague-Dawley rats; Dahl S, Dahl salt-sensitive rats. Values are mean±SEM. Probability values for S-D versus Dahl S rats were obtained by Student's \(t\) test. Two-way analysis of variance (ANOVA) indicated no significant differences \((p<0.05)\) for the body weight and plasma volume data. For TG concentration at 0 and 120 minutes, the change in TG concentration between 0 and 120 minutes \((\Delta\)), and the TGSR, two-way ANOVA indicated significant differences between S-D and Dahl S \((p<0.03-0.001)\) and with length of fast \((p<0.02-0.001)\). There were no significant interaction effects.
Blood pressure as well as higher plasma TG concentrations than do control S-D rats. This was true when plasma TG concentrations were measured in the morning in nonfasted animals after an overnight fast of 13–15 hours or in the early afternoon after a 4-hour fast. Total LPL activity data are mean±SEM of desoxycholate-treated homogenates of epididymal adipose tissue from seven S-D and seven Dahl S rats at both 9 AM and 1 PM. **p<0.01 as determined by Student's t test. Two-way analysis of variance indicated a significant difference for type of rat (p<0.001) and length of fast (p<0.001), and no significant interaction was noted.

**Discussion**

The results presented provide additional support for the earlier observation that Dahl S rats have higher blood pressure as well as higher plasma TG concentrations than do control S-D rats. This was true when plasma TG concentrations were measured in the morning in nonfasted animals after an overnight fast of 13–15 hours or in the early afternoon after a 4-hour fast. Total LPL activity data are mean±SEM of desoxycholate-treated homogenates of epididymal adipose tissue from seven S-D and seven Dahl S rats at both 9 AM and 1 PM. **p<0.01 as determined by Student's t test. Two-way analysis of variance indicated a significant difference for type of rat (p<0.001) and length of fast (p<0.001), and no significant interaction was noted.

**Figure 3.** Plots show rate of disappearance of prelabeled very low density lipoprotein–triglyceride (VLDL-TG) from plasma and the calculated half time (t1/2) of removal in Sprague-Dawley and Dahl salt-sensitive (Dahl S) rats. Number of animals in each group is indicated in the bar graph. DPM, disintegrations per minute.

**Discussion**

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**Figure 4.** Bar graph shows total lipoprotein lipase (LPL) activity in adipose tissue obtained from Dahl salt-sensitive (Dahl S) and Sprague-Dawley (S-D) rats determined at 9 AM (0900) in nonfasting animals and at 1 PM (1300) after a 4-hour fast. Total LPL activity data are mean±SEM of desoxycholate-treated homogenates of epididymal adipose tissue from seven S-D and seven Dahl S rats at both 9 AM and 1 PM. **p<0.01 as determined by Student's t test. Two-way analysis of variance indicated a significant difference for type of rat (p<0.001) and length of fast (p<0.001), and no significant interaction was noted.
FIGURE 5. Bar graphs show total lipoprotein lipase (LPL) activity in heart and skeletal muscle (soleus and vastus intermedius) obtained from Dahl salt-sensitive (Dahl S) and Sprague-Dawley (S-D) rats determined at 9 AM (0900) in nonfasted animals and at 1 PM (1300) after a 4-hour fast. Heart and soleus muscle LPL data represent the mean±SEM of six rats at 9 AM and six at 1 PM. LPL data on vastus intermedius muscle represent 10 S-D and 10 Dahl S rats at 9 AM and nine S-D and 10 Dahl S rats at 1 PM. **p<0.01, *p<0.05 as determined by Student's t test. Two-way analysis of variance indicated a significant difference for type of rat for each muscle (p<0.02-0.001) and length of fast for vastus intermedius muscle only (p<0.001). No significant interactions were noted.

formed after a 4-hour fast but not after a 13-hour fast. Second, when measured at the same time (after a 4-hour fast) TG secretion was only approximately 16% higher, whereas TG removal was approximately 33% lower in Dahl S rats. Third, the decreases in adipose tissue and muscle LPL activity were observed in Dahl S rats, irrespective of the duration of fast, and significant differences were seen at a time when TG secretion rates were similar in Dahl S and S-D rats. In contrast, hepatic lipase activity was not decreased in Dahl S rats in the fed state or after a 4-hour fast. In light of these comparisons, it seems to us that a peripheral TG removal defect played the most central role in the hypertriglyceridemia seen in Dahl S rats. On the other hand, this formulation is not meant to deny that TG secretion was also increased in Dahl S rats, and this change undoubtedly contributed to the increase in plasma TG concentration.

Although the data presented provide a reasonable explanation for the development of hypertriglyceridemia in Dahl S rats, two fundamental questions remain to be addressed. Elevated plasma TG concentrations are also commonly seen in patients with hypertension, as well as in rats with either spontaneous or fructose-induced hypertension. It is certainly possible that similar changes in LPL activity also account for the hypertriglyceridemia in these other situations, but this need not be the case, and experiments to test this hypothesis need to be performed. Of greater importance is the need to understand why hypertension and hypertriglyceridemia are associated. We have previously suggested that both abnormalities are related to insulin resistance and compensatory hyperinsulinemia. In this context, it should be noted that Dahl S rats also appear to be hyperinsulinemic, and resistance to insulin-stimulated glucose uptake by their isolated adipocytes has also been demonstrated. Furthermore, Milan hypertensive rats have also been shown to be hyperinsulinemic and hypertriglyceridemic. Thus, the combination of insulin resistance, hyperinsulinemia, hypertriglyceridemia, and high blood pressure appears to occur quite commonly. Consequently, it is likely that information gained from the study of hypertriglyceridemic rodents with hypertension will provide mechanistic hypotheses that can be evaluated in patients with both hypertension and hypertriglyceridemia.

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References

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