Plasma Lipid Secretion and Clearance in Hyperlipidemic JCR:LA-Corpulent Rats

James C. Russell, Dorothy G. Koeslag, Roger M. Amy, and Peter J. Dolphin

The JCR:LA-corpulent rat is an obese, hyperlipidemic, hyperinsulinemic strain that is atherosclerosis-prone and develops myocardial lesions. The hyperlipidemia is due to elevated plasma levels of a large relatively triglyceride-rich very low density lipoprotein (VLDL). Both corpulent and lean male and female rats were studied. Postheparin lipid clearance and apparent hepatic secretion rate after Triton WR1339 inhibition of lipoprotein lipase were determined. The concentrations of cholesterol and cholesteryl esters were not significantly altered by either treatment. Triglycerides showed rapid postheparin clearance in corpulent rats. The apparent hepatic secretion rate was markedly higher in corpulent male rats than in lean male rats, and the rate in corpulent females was again higher, reflecting the higher serum triglyceride concentrations in corpulent female rats. The relative secretion rate of C:48 triglyceride molecular species was lower than that of C:50 to C:56 species, while the postheparin clearance of C:48 triglyceride molecular species was impaired compared to the C:50 species and those with higher carbon numbers. This effect was more marked in the male than in the female corpulent rats. The results indicate that VLDL hyperlipidemia in the corpulent rat is due to hepatic hypersecretion of VLDL and not to a defect in lipoprotein lipase. Further, the atherogenesis that is characteristic of the corpulent male rat may be related to the differential metabolism of fatty acids. (Arteriosclerosis 9:989–976, November/December 1989)

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From the Departments of Surgery and Pathology, University of Alberta, Edmonton, Alberta, and the Department of Biochemistry, Dalhousie University, Halifax, Nova Scotia, Canada.

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Address for correspondence: Dr. J.C. Russell, Department of Surgery, 12-103 Clinical Sciences Building, University of Alberta, Edmonton, Alberta, Canada T6G 2G3.
in contrast, inhibits lipoprotein lipase activity leading to an accumulation of VLDL at a rate reflecting net secretion from the liver.12 We report here on studies using these techniques to test the above two possible origins of the VLDL hyperlipidemia in the JCR:LA-cp rat.

Methods

Animals

The JCR:LA-cp rats were bred in our colony at the University of Alberta, a colony established with nucleus breeding stock generously donated by Carl T. Hansen, Veterinary Resources Branch, National Institutes of Health, Bethesda, MD. The colony is derived from the fifth backcross to the LA/N strain, whereas other colonies (including that at the National Institutes of Health) have been taken to 12 backcrosses. The colony has been maintained as an outbred closed colony since establishment. The rats were bred cp/cp and +/+ of both sexes as previously described.6,7,13 They were maintained in polycarbonate cages on wood chip bedding (Aspen chips, Northeastern Products, Warrensburg, NY) at 20°C and 40% to 50% relative humidity on a 12:12 hour light cycle. All rats were fed ad lib a standard rat chow, Wayne Lab Blox (Continental Grain, Chicago, IL) with tap water available at all times. All rats were studied at 3 months of age.

Experimental Procedures

Rats were fasted overnight and anesthetized with pentobarbital (40 mg/kg body weight). The dosage was increased for corpulent rats to achieve and maintain an adequate depth of anesthesia. The jugular vein was cannulated with Silastic tubing (0.51 mm i.d., Dow Corning, Midland, MI). The tip of the cannula was positioned 1.0 cm superior to the right atrium, and the cannula was filled with normal saline. Triton WR1339 (Tyloxpal, Sigma Chemical, St. Louis, MO) was dissolved in normal saline at 0.11 g/ml. After initial blood sampling, 0.2 ml of this solution per 100 g body weight was injected into the jugular cannula and flushed with normal saline to a total volume of 1.0 ml. Sodium heparin solutions (Hepalean, Harris Laboratories, Toronto, Ontario) were also prepared in normal saline at 1000 U/ml. This was administered in the same manner as the Triton solution at 0.1 ml/100 g body weight. Blood samples were taken before injection of the heparin or Triton solution; at 5, 10, 15, and 30 minutes for the heparin experiments; at 30, 60, 90, and 120 minutes for the Triton experiments; and at 15, 30, 60, 90, and 120 minutes for control experiments. The latter experiments were identical to the others except that only normal saline was injected. The blood samples (1.0 ml) were taken into a syringe containing 1 mg each of ethylenediaminetetraacetic acid (EDTA) and phenylboronic acid (Sigma Chemical) in 0.05 ml of saline to inhibit plasmalecithin cholesterol acytytransferase14 and hepatic lipase. Immediately after removal of each blood sample, 1.0 ml of saline was injected into the venous cannula. Blood was centrifuged, and the plasma was separated immediately and frozen at -70°C until assayed. The plasma lipids were analyzed by using the total lipid profile technique of Kuksis et al.15 This technique involves preliminary digestion of the plasma sample with phospholipase C (Sigma Chemical) followed by derivatization with N,N-dimethylacetaamide (Pierce Chemical, Rockford, IL). Gas chromatographic analysis yields the concentration of free cholesterol, individual cholesteryl esters, diacylglycerols, and ceramides of the phospholipids and triglycerides with individual results by fatty acid carbon numbers. Thus the triglyceride molecular species may be specified according to their number of acyl carbon atoms16 as follows:

C:48, triglycerides with C-16:16:16 or C-14:16:18 fatty acyl chains;
C:50, triglycerides with C-16:16:18 or C-14:16:20 fatty acyl chains;
C:52, triglycerides with C-16:18:18 or C-16:16:20 fatty acyl chains;
C:54, triglycerides with C-16:18:20 or C-16:16:22 or C-18:18:18 fatty acyl chains;
C:56+>, triglycerides with C-18:18:20 or C-16:18:22 fatty acyl chains or greater fatty acyl carbon number.

The results reported for cholesteryl esters, phospholipids, and triglycerides represent the sum of the concentrations of the particular molecular species. We also report separately on the individual triglyceride molecular species in appropriate instances.

Calculations

The lipid concentrations as a function of time for individual rats were used to calculate the initial rates of net clearance or secretion. The data were fitted to a quadratic equation:

\[ [\text{lipid}] = a + bxt + cxt^2 \quad (1) \]

using a least squares method,17 where a is a constant (initial concentration), b and c are constants, and t is time (in minutes). The resulting constant, b, gives the initial slope of the time concentration curve and thus represents the initial rate of change of concentration for the lipid in question. Corrections were applied for the effect of the sample removed and volume replacement with saline. If the postheparin clearance is a first-order kinetic process, the following relationship should hold:

\[ b = d[\text{lipid}] / dt = k \cdot [\text{lipid}] \quad (2) \]

Thus the rate constant, k, which is independent of the concentration is given by Equation (3). The rate constant
LIPID KINETICS IN CORPULENT RATS

Table 1. Body Weights and Plasma Volumes of 3-Month-old JCR:LA-Corpulent Rats

<table>
<thead>
<tr>
<th>Genotype</th>
<th>N</th>
<th>Body weight (g)</th>
<th>Plasma volume (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cp/cp</td>
<td>5</td>
<td>511±7.4</td>
<td>11.4±2.5</td>
</tr>
<tr>
<td>+/+</td>
<td>5</td>
<td>315±5.6</td>
<td>10.4±2.0</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cp/cp</td>
<td>5</td>
<td>387±8.6</td>
<td>9.88±1.40</td>
</tr>
<tr>
<td>+/+</td>
<td>6</td>
<td>192±4.7</td>
<td>7.45±0.93*</td>
</tr>
</tbody>
</table>

The values are the means±SD. *p<0.01, +/+ vs. cp/cp.

Results

Table 1 shows mean body weights and plasma volumes. In spite of the large difference in body weights, cp/cp and +/+ male rats had similar plasma volumes and thus significantly different volumes per 100 g of body weight. The female rats showed an even greater difference in body weight between +/+ and cp/cp rats. However, the plasma volumes were much closer, and only the +/+ females were significantly different (lower volume) from the other genotypes.

The initial whole plasma lipid concentrations of rats of the four genotypes are shown in Table 2. These values are not significantly different from those previously reported for serum concentrations. The corpulent rats are characterized by elevations (approximately 100%) of both unesterified and esterified cholesterol. The phospholipid concentrations are more markedly elevated. The triglycerides, in contrast, show dramatically higher concentrations in the corpulent rats, with this being significantly greater in the females than in the males. Administration of heparin caused only nonsignificant decreases in cholesterol and cholesteryl esters, moderate decreases in phospholipids, and rapid clearance of triglycerides. Figure 1 shows the mean plasma lipid concentrations of cp/cp male rats after heparin administration, together with polynomial regression lines based on the mean data. Figure 2 shows the equivalent mean data after administration of Triton WR1339 to cp/cp male rats. There were minimal changes in the concentrations of cholesterol and cholesteryl esters. Phospholipids increased at an initial and substantial rate of 2.09 mg/100 ml/min in cp/cp males, while triglycerides increased very rapidly (9.52 mg/100 ml/min). Similar results (not shown) were obtained from cp/cp female rats. In view of the already very low plasma lipid concentrations in +/+ rats (triglycerides are less than 20 mg/dl in male rats), heparin was not administered to lean rats of either sex.

The initial rates of change in lipid concentrations after injection of Triton WR1339 or heparin calculated individually for each rat are shown in Table 3. These results are for the constant b of Equation (1). Thus, they have units of mg/100 ml/min and are negative in the heparin experiments and positive in the Triton experiments. The calculated values of b for the control groups are small and, with one exception, not significantly different from zero. The data in Table 3 show that the changes in the concentrations of cholesterol and cholesteryl esters were generally small and not significant. This was true after both Triton and heparin injections and for all groups of rats. Phospholipids showed moderate changes, especially in the corpulent rats, with decreases after Triton treatment that were not statistically significant. Decreases in phospholipid concentrations after heparin administration were larger but not significant compared to the control animals. The triglyceride concentrations showed large and significant changes. The postheparin rates of clearance were large and not significantly different between the male and female corpulent rats. The rate of increase in plasma triglyceride concentration after Triton administration was very high in the corpulent rats, and the rate of increase was greater in the females (p<0.05). The +/+ rats of both sexes showed much lower rates of increase than the cp/cp rats (p>0.001).

Table 2. Initial Whole Plasma Lipid Concentrations in JCR:LA-Corpulent Rats

<table>
<thead>
<tr>
<th>Genotype</th>
<th>N</th>
<th>Cholesterol</th>
<th>Cholesteryl esters</th>
<th>Phospholipids</th>
<th>Triglycerides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cp/cp</td>
<td>6</td>
<td>33.6±8.1</td>
<td>144±30.5</td>
<td>233±59</td>
<td>344±180</td>
</tr>
<tr>
<td>+/+</td>
<td>5</td>
<td>14.4±5.3</td>
<td>62.5±8.1</td>
<td>69.1±11.8</td>
<td>19.6±5.2</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cp/cp</td>
<td>7</td>
<td>23.6±4.3</td>
<td>101±14.8</td>
<td>226±17.1</td>
<td>523±159</td>
</tr>
<tr>
<td>+/+</td>
<td>6</td>
<td>19.0±2.3</td>
<td>73.7±4.6</td>
<td>95.1±12.1</td>
<td>32.5±12.2</td>
</tr>
</tbody>
</table>

The lipid concentrations are for 3-month-old rats in mg/dl (means±SD).
Figure 1. Whole plasma lipid concentrations (means±SD) in cp/cp male rats (n=6) after administration of heparin. The lines for the calculation of the initial rate of clearance as described in the text are shown and the results were: A. Cholesterol, b=-0.63. B. Cholesteryl esters, b=-2.31. C. Phospholipids, b=-6.32. D. Triglycerides, b=-27.3. All units are mg/dl/min and are based on the mean concentrations shown in the figures. Thus, they are not identical to the results from individual animals shown in the tables.

Figure 2. Whole plasma lipid concentrations (means±SD) in cp/cp male rats (n=5) after administration of Triton WR1339. See Figure 1 legend for details. The initial secretion rates were: A. Cholesterol, b=0.07. B. Cholesteryl esters, b=0.18. C. Phospholipids, b=2.09. D. Triglycerides, b=9.52. The units are mg/dl/min and are based on the mean concentrations shown in the figure.
The calculated rate constants for postheparin clearance of phospholipids and triglycerides, k in Equation (3) derived from the raw data in Tables 2 and 3 for cp/cp rats, are shown in Table 4. The rate constants for cholesterol and cholesteryl esters were smaller (3.6 to 12.6 min⁻¹×10⁻³) and not significantly greater than zero. Those for both phospholipids and triglycerides were significant for all groups. The rate constants showed no significant differences between male and female animals.

Table 5 shows the net secretion of phospholipids and triglycerides in milligrams per minute. The net rate of secretion of cholesterol and cholesteryl esters was low, and the small changes that occurred over the short time period of the experiment lead to nonsignificant or even negative results. However, the net secretion of triglycerides was much greater in the cp/cp rats and significantly greater in cp/cp females than cp/cp males. The initial concentrations and net secretion rates of the triglyceride molecular species were different before and after heparin administration as shown by the results in Tables 6 and 8. The fractional (or percentage) composition of the triglycerides by molecular species was calculated before and after treatment with heparin and Triton. The ratio of the final to the initial fractional composition for each triglyceride molecular species gives an index of compositional change. The results in Table 8 show that the cp/cp rats showed a marked variation between molecular species (p<0.001, both sexes) with a significant relative increase in C:48 triglycerides, after release of lipoprotein lipase in both males and females. However, the variance was larger enough that this apparent trend was not significant (p>0.05).

The relative concentrations of individual triglyceride molecular species were different before and after heparin administration as shown by the results in Tables 6 and 8. The fractional (or percentage) composition of the triglycerides by molecular species was calculated before and after treatment with heparin and Triton. The ratio of the final to the initial fractional composition for each triglyceride molecular species gives an index of compositional change. The results in Table 8 show that the cp/cp rats showed a marked variation between molecular species (p<0.001, both sexes) with a significant relative increase in C:48 triglyceride molecular species after heparin (p<0.001, both sexes). The effect was more marked in the male cp/cp rats than in the females (p<0.05). There was a concomitant decrease in C:50 and greater molecular species but similar secretion rates for C:48 and C:50 molecular species.
Table 6. Initial Concentrations and Rates of Secretion of Triglyceride Molecular Species in cp/cp JCR:LA-Corpulent Rats

<table>
<thead>
<tr>
<th>Molecular species</th>
<th>Concentration (mg/dl)</th>
<th>Secretion rate (mg/min)</th>
<th>Concentration (mg/dl)</th>
<th>Secretion rate (mg/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C:48</td>
<td>19.1±1.5</td>
<td>0.033±0.024</td>
<td>28.5±6.1</td>
<td>0.028±0.028</td>
</tr>
<tr>
<td>C:50</td>
<td>47.8±12.4</td>
<td>0.152±0.073</td>
<td>81.6±26.4</td>
<td>0.163±0.057</td>
</tr>
<tr>
<td>C:52</td>
<td>95.7±20.5</td>
<td>0.245±0.165</td>
<td>213±64</td>
<td>0.529±0.190*</td>
</tr>
<tr>
<td>C:54</td>
<td>41.7±7.8</td>
<td>0.156±0.061</td>
<td>98.0±34.6</td>
<td>0.251±0.056*</td>
</tr>
<tr>
<td>C:56+&gt;</td>
<td>48.8±13.9</td>
<td>0.150±0.088</td>
<td>101±35</td>
<td>0.297±0.080*</td>
</tr>
</tbody>
</table>

The values for the concentrations are given in mg/dl and those for the secretion rates are in mg/min (both means±SD).

The triglyceride molecular species are designated according to their number of acyl carbon atoms as follows:
- C:48, triglycerides with C-16:16:16 or C-14:16:18 fatty acyl chains;
- C:50, triglycerides with C-16:16:16 or C-14:16:20 fatty acyl chains;
- C:52, triglycerides with C-16:16:18 or C-14:16:19 fatty acyl chains;
- C:54, triglycerides with C-16:16:20 or C-16:16:22 and fatty acyl chains;
- C:56+>, triglycerides with C-18:18:20 or C-16:18:22 fatty acyl chains and triglycerides of higher carbon number which were not resolved.

The results from the lipid secretion and clearance rates were also highly significant (p<0.001).

Table 7. Calculated Rate Constants for Postheparin Clearance of Triglyceride Molecular Species from Plasma of JCR:LA-Corpulent Rats

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Molecular species</th>
<th>Concentration (mg/dl)</th>
<th>Postheparin clearance rate constant (min⁻¹x10⁻³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male cp/cp</td>
<td>C:48</td>
<td>8.60±0.96</td>
<td>0.521±0.08</td>
</tr>
<tr>
<td>Male cp/cp</td>
<td>C:50</td>
<td>3.75±1.07</td>
<td>0.755±0.26</td>
</tr>
<tr>
<td>Male cp/cp</td>
<td>C:52</td>
<td>5.28±2.00</td>
<td>1.881±0.826</td>
</tr>
<tr>
<td>Male cp/cp</td>
<td>C:54</td>
<td>3.26±1.39</td>
<td>11.10±4.37†</td>
</tr>
<tr>
<td>Male cp/cp</td>
<td>C:56+&gt;</td>
<td>5.50±8.61</td>
<td>15.11±7.10†</td>
</tr>
<tr>
<td>Female cp/cp</td>
<td>C:48</td>
<td>36.7±17.8</td>
<td>62.7±24.0</td>
</tr>
<tr>
<td>Female cp/cp</td>
<td>C:50</td>
<td>94.1±31.7</td>
<td>63.9±14.6</td>
</tr>
<tr>
<td>Female cp/cp</td>
<td>C:52</td>
<td>91.3±21.0†</td>
<td>58.7±14.2</td>
</tr>
<tr>
<td>Female cp/cp</td>
<td>C:54</td>
<td>97.7±19.9†</td>
<td>62.0±14.5</td>
</tr>
<tr>
<td>Female cp/cp</td>
<td>C:56+&gt;</td>
<td>120±26†</td>
<td></td>
</tr>
</tbody>
</table>

The values in units of min⁻¹x10⁻³ (means±SD) and were calculated as the rate of clearance of each molecular species for each rat divided by the mean initial concentration of the species.

*p<0.05, †p<0.01, males vs. females.

Table 8. Relative Concentration Changes of Triglyceride Molecular Species after Heparin and Triton Administration in cp/cp Rats

<table>
<thead>
<tr>
<th>Molecular species</th>
<th>Male cp/cp</th>
<th>Postheparin concentration (mg/dl)</th>
<th>Relative concentration change</th>
<th>Female cp/cp</th>
<th>Postheparin concentration (mg/dl)</th>
<th>Relative concentration change</th>
</tr>
</thead>
<tbody>
<tr>
<td>C:48</td>
<td>8.60±0.96</td>
<td>4.00±1.18</td>
<td>0.730±0.139</td>
<td>36.7±17.8</td>
<td>2.495±1.074</td>
<td>0.687±0.192</td>
</tr>
<tr>
<td>C:50</td>
<td>3.75±1.07</td>
<td>0.803±0.052</td>
<td>1.256±0.027</td>
<td>94.1±31.7</td>
<td>0.949±0.169</td>
<td>1.164±0.244</td>
</tr>
<tr>
<td>C:52</td>
<td>5.28±2.00</td>
<td>0.593±0.084</td>
<td>1.140±0.066</td>
<td>63.9±14.6</td>
<td>0.772±0.099</td>
<td>1.045±0.038</td>
</tr>
<tr>
<td>C:54</td>
<td>3.26±1.39</td>
<td>0.739±0.142</td>
<td>0.931±0.044</td>
<td>58.7±14.2</td>
<td>0.245±0.165</td>
<td>0.163±0.057</td>
</tr>
<tr>
<td>C:56+&gt;</td>
<td>5.50±8.61</td>
<td>0.791±0.289</td>
<td>0.748±0.080</td>
<td>62.0±14.5</td>
<td>0.033±0.024</td>
<td>0.297±0.080</td>
</tr>
</tbody>
</table>

All values are means±SD. The fractional composition of the triglyceride molecular species was calculated for zero time (data as in Table 6) and for 30 minutes after heparin (as above column 1) and 120 minutes after Triton administration. The relative concentration change is the ratio of the final to the initial fractional concentration. It is a dimensionless index of proportional change in the contribution of the triglyceride molecular species to the total triglyceride concentration. Values greater than 1.0 indicate an increasing fractional concentration, and values less than 1.0, a decreasing fractional concentration.

*p<0.02, †p<0.01, ‡p<0.001, male vs. female.

Discussion

The results from the lipid secretion and clearance rates are normally presented as amounts per 100/g of body weight of the animal. However, the great differences in body weight of the lean and corpulent rats were not associated with major differences in lean body mass or plasma volume. Thus, we feel it would be misleading to express the results in terms of body mass, and we have reduced our concentration changes to rate constants or mass secreted per unit of time, thereby avoiding the confounding effects of the fat body mass. On this basis, direct comparison can be made between the cp/cp and +/+ rats in these experiments, since they were tightly controlled for age.

The results for postheparin plasma lipids indicate a marked clearance of VLDL. Figure 1 shows that the clearance of triglycerides from the plasma was complete.
in 15 minutes. This, together with the quantitative data in Tables 3 and 4, makes it clear that the lipoprotein lipase of the cp/cp rat is readily released from the endothelium by a low dose of heparin and that the released enzyme is effective in mediating triglyceride hydrolysis. The male and female rats are similar in this regard. The data in Table 7 suggest a preferential activity toward the triglycerides with longer-chain fatty acids.

Administration of Triton WR1339 caused a buildup of VLDL as reported by other investigators. Abrams and Cooper12 predicted their studies on a "demonstrated linear increase in serum triglycerides for 90 minutes after administration of Triton WR1339." The results in Figure 2 demonstrate that this is not the case in the cp/cp rat. However, our curve-fitting procedure allows calculation of the initial rate of change, and thus the steady-state assumption is not necessary. The initial rates of change of concentration in the cp/cp rats were much higher than in the lean rats, indicating a much higher net hepatic secretion of triglyceride. The data in Table 5 show that the significant net hepatic secretion is confined to triglycerides. The female cp/cp rats also had markedly higher net secretion rates, which is consistent with their greater plasma triglyceride levels. While the Triton technique is a relatively simple method that yields information on net concentration changes, the results are unequivocal, and it is evident that the hyperlipidemia is due to a hypersecretion of VLDL.

An analysis of the secretion rate by triglyceride molecular species in Table 6 shows that the higher rate of secretion in cp/cp females is confined to the longer-chain fatty acids. The cp/cp male rat preferentially clears the higher molecular weight triglycerides from the plasma, leading to enhanced concentrations of C:48 molecular species in VLDL remnants. Ridgeway and Dolphin18 have recently reported that both normal and hypothyroid Long Evans rats show preferential hydrolysis of short-chain fatty acids by lipoprotein lipase. This leads to sequestration of long-chain fatty acids in the intermediate density lipoprotein and LDL fractions. Nilsson et al.19 have suggested that such effects may be due to inhibition of hydrolysis of the prefered sn-1 or sn-3 acyl groups by the presence of a long-chain fatty acid at the sn-2 position. The observations reported here refer only to net clearance from the plasma compartment and reflect the sum of both hydrolysis of VLDL and uptake of hydrolysis products and remnant particles. Since the compositions of the major lipoprotein density classes were not measured, the whole serum values may not reflect the triglyceride molecular species composition of particular classes.

The characteristics of lipoprotein lipase may also be altered after release from its normal physiological site of action on the capillary endothelium. These factors, together with the major metabolic differences between the JCR:LA-cp rat and other strains, make the present observations complementary to those of Ridgeway and Dolphin18 and Nilsson et al.19

The corpulent rats may be compared to the fatty (fa/fa) Zucker rat, the other strain of obese rats. The fatty female has markedly lower plasma triglyceride concentrations (87.4±3.6 mg/dl) than either male or female cp/cp rats.20

The total cholesterol concentrations in both fatty and lean Zucker rats are similar to those of cp/cp and +/+ rats of our strain. Petit et al.20 have reported VLDL secretion of fa/fa and Fa/fa (lean) female rats to be 0.013 and 0.0045 mg/min, respectively. These values, which were obtained from perfused livers, are less than 1% and 3% of the rates we report for cp/cp and +/+ female rats in vivo. While there are major differences in technique, the results are consistent with the different fasting plasma concentrations of triglycerides in the two strains.

Taken together, the results show that the VLDL hyperlipidemia of the cp/cp rat is due to hepatic hypersecretion of the VLDL. The higher concentrations in the cp/cp female appear to be due to a greater secretion rate and perhaps to an overwhelmed lipoprotein lipase capacity, leading to a lower calculated rate constant for clearance. Identification of hepatic hypersecretion of VLDL as the source of the hyperlipidemia leaves open the further question of the mechanism of induction of the hypersecretion. This might be related to the hyperinsulinemia and impaired glucose tolerance of the corpulent rat.9,10

Certainly, a number of experimental manipulations of the rats, including food restriction and intensive exercise, reduce both the plasma lipid and insulin concentrations.21 However, the plasma VLDL levels of corpulent females are markedly higher than those of males, while their insulin resistance is much less severe.9,10 There is evidence that both activity of and mRNA expression for glycerophosphate dehydrogenase are increased in the cp/cp rat (Shillabeer, hornford, Russell, Wong, and Lau, unpublished results). Thus, modulation of hepatic lipogenic enzymes may play a fundamental role in pathogenesis in the corpulent rat. In addition, there are clear differences in the metabolism of triglyceride molecular species in cp/cp rats that may have important pathophysiological consequences. The solution to these problems will be important to understanding the regulation of lipid secretion and concentrations. It may have implications for treatment of humans with insulin resistance, hypertriglyceridemia, and susceptibility to atherosclerosis.

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References


Index Terms: lipid clearance • lipid secretion rate • very low density lipoprotein • hyperlipidemia • JCR:LA-corpulent rat
Plasma lipid secretion and clearance in hyperlipidemic JCR:LA-corpulent rats.

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