Plasma leptin levels and triglyceride secretion rates in VMH-lesioned obese rats: a role of adiposity

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Suga, Asako, Tsutomu Hirano, Shuji Inoue, Masatoshi Tsuji, Toshimasa Osaka, Yoshio Namba, Masakazu Miura, and Mitsuru Adachi. Plasma leptin levels and triglyceride secretion rates in VMH-lesioned obeser rats: a role of adiposity. Am. J. Physiol. 276 (Endocrinol. Metab. 39): E650–E657, 1999.—To explore the role of adiposity on hypertriglyceridemia associated with obesity, we examined the relation between triglyceride secretion rate (TGSR) and plasma leptin, insulin, or insulin resistance in ventromedial hypothalamic (VMH)-lesioned rats in the dynamic and static phases (2 and 14 wk after lesions, respectively). VMH-lesioned rats gained body weight (BW) at fivefold higher rates in the dynamic phase compared with sham-operated control (sham) rats, and BW gain reached a plateau in the static phase. Parametrical fat pad mass was increased 2.5-fold in VMH-lesioned rats compared with sham rats in both phases. Leptin levels were sixfold higher in VMH-lesioned rats of the dynamic phase and even higher in the static phase. Insulin levels were twofold higher in VMH-lesioned rats than in sham rats in both phases. In the dynamic phase, VMH-lesioned rats had 2-fold higher plasma triglyceride (TG) levels and 2.6-fold higher TGSRs, whereas steady-state plasma glucose (SSPG) values, an indicator of insulin resistance, were lower. SSPG values became significantly higher in VMH-lesioned rats in the static phase, but TGSR was not further accelerated. TGSR was significantly associated with leptin, independent of insulin. Leptin was highly correlated with BW, fat mass, and nonesterified fatty acids (NEFA). These results suggest that adiposity itself plays a critical role in TGSR probably through increased NEFA flux from enlarged adipose tissues. Insulin resistance is not associated with the overproduction of TG in this animal model for obesity.

hyperinsulinemia; insulin resistance; ventromedial hypothalamic lesions

It is well known that hypertriglyceridemia is frequently accompanied by obesity in human beings, which is a risk factor for coronary heart disease (9). The mechanisms for hypertriglyceridemia associated with obesity are multifactorial. It has been suggested that insulin resistance and/or hyperinsulinemia plays a key role in stimulating very low density lipoprotein (VLDL)-triglyceride (TG) secretion by the liver (2, 15, 23). However, the role of hyperinsulinemia in the pathogenesis of VLDL-TG overproduction remains controversial (24, 33). Short-term administration of insulin suppresses VLDL-TG secretion in vivo (11, 26), and the addition of insulin to the medium also suppresses VLDL-TG secretion from cultured hepatocytes (14, 32). Chronic hyperinsulinemia induced by multiple injections of insulin stimulates the TG secretion rate (TGSR) in rats fed sucrose or fructose-rich diets (22, 34). The feeding of sucrose or fructose, however, is known to cause insulin resistance (21, 36, 40), and this, although not hyperinsulinemia, might induce a rise in TGSR. Some authors have emphasized the role of insulin resistance in VLDL secretion by the liver (1, 25, 35). According to their hypothesis, insulin itself suppresses hepatic VLDL secretion, but an inability of insulin action leads to a diminution of its inhibitory power on this secretion, which results in VLDL hypersecretion (24, 25).

Bilateral lesions of the ventromedial nuclei in the hypothalamus (VMH) can produce obesity in rats, and VMH-lesioned rats are frequently used as a representative animal model of obesity (4, 29). Inoue et al. (19) reported that VMH-lesioned obese rats have marked hypertriglyceridemia due to increased TGSR and the limited capacity of TG uptake by adipose tissues. The higher TGSR was closely associated with increased plasma insulin levels (19). However, it remains obscure whether the hyperinsulinemia directly stimulates hepatic TG production or, alternatively, whether insulin resistance accompanied by obesity is responsible. It is difficult to distinguish the influence of hyperinsulinemia on TG metabolism from that of insulin resistance in genetically transmitted animal models of obesity, because hyperinsulinemia and insulin resistance usually develop simultaneously (4). Unlike congenitally obese animals, VMH-lesioned obese rats have an initial rapid period of weight gain (dynamic phase) followed by a steady-state plateau of body weight (static phase) (4, 29). Previous experiments have shown that plasma insulin concentrations are higher soon after the creation of VMH lesions before development of massive obesity (4). If the lesioned rats have hyperinsulinemia without accompanying insulin resistance, we would be able to identify the role of hyperinsulinemia in the hepatic TG secretion, apart from that of insulin resistance.

The flux of excess nonesterified fatty acids (NEFA) from adipose tissue into the circulation is an important abnormality in obesity (10). It is reasonable to assume that NEFAs released from adipose tissue are dependent on the amount of fat tissue and that the NEFA flux to the liver stimulates VLDL-TG production in a dose-
independent manner. However, there is only a poor understanding of the direct association between adiposity and hepatic TG production, because hyperinsulinemia or insulin resistance is concomitantly developed with the progression of obesity (7). A recently discovered obese gene product, leptin (41), is secreted by adipose cells and functions in the regulation of food intake and energy expenditure (8). A number of clinical and experimental data have revealed a marked correlation between the circulating leptin level and an absolute or a relative fat mass in the body (8, 13, 16, 31). Thus plasma leptin concentration can quantitatively indicate the degree of adiposity in the whole body.

In the present study, we measured plasma leptin and insulin concentrations and determined TGSR and insulin resistance in VMH-lesioned obese rats in different phases of obesity and attempted to define the role of adiposity per se in hepatic TG production, independent of hyperinsulinemia or insulin resistance.

**MATERIALS AND METHODS**

Rats. Female Sprague-Dawley rats of 220-250 g in body weight (Japan SCL, Hamamatsu, J apan) were kept in individual cages on a rotating 12:12-h light-dark cycle with free access to both standard rat chow (Oriental Food, Tokyo, Japan) and water. The animals were anesthetized by inhalation of isoflurane (Forane, Dainabot, Osaka, J apan), and electrolytic bilateral VMH lesions were produced by the method previously described (4, 19, 29). Control animals received sham VMH lesions (no current passed through the electrode). We designated the early phase of obesity (2 wk after creating VMH lesions) as the dynamic phase and the late phase of obesity (14 wk after VMH lesions) as the static phase (4, 19, 29). On the day of experiments, food was withdrawn at 9:00 AM and experiments were carried out after a 5-h fast (9:00 AM to 2:00 PM). The parametrial fat pad was removed and weighed immediately after the following.

**RESULTS**

Profiles of sham-operated and VMH-lesioned rats. Table 1 shows general and metabolic characteristics of sham-operated and VMH-lesioned rats in the dynamic phase and in the static phase. The food intake of rats with bilateral VMH lesions increased significantly compared with that of sham-operated rats 2 wk after the operations; however, the hyperphagia in VMH-lesioned rats became less obvious in the static phase. In the dynamic phase, the VMH-lesioned rats gained body weight at 5-fold higher rates and had a 2.5-fold increased parametrial fat pad weight compared with sham-operated rats. In the static phase, body weight gain in VMH-lesioned rats reached a plateau, but the final body weight and the parametrial fat pad weight were 1.3- and 2.6-fold greater than those in sham-operated rats, respectively. In sham-operated animals, body weight and fat pad weight were increased 1.3- and 2-fold 14 wk after the operation compared with those at 2 wk, respectively. VMH-lesioned rats had a 2-fold increase in TG concentration per minute multiplied by the plasma volume of rat and expressed in milligrams per minute per 100 g body wt to adjust significant differences in body weight among groups. The validity of the Triton method for estimating TgSR has been described elsewhere (18, 39). A majority of plasma TG (90%) was recovered in the VLDL fraction (density >1.006 g/ml) in both pre- and post-Triton plasma. Therefore, the TgSR determined by the Triton WR 1339 method virtually implies the rate of hepatic VLDL-TG secretion (18). Because food was withdrawn 5 h before the experiment, intestinal contribution to TgSR would not be significant, if any (30).

Steady-state plasma glucose method for evaluation of insulin resistance. Insulin resistance in the whole body was assessed by the steady-state plasma glucose (SSPG) method originally developed by Reaven’s laboratory (37, 40) and modified by Harano et al. (17). Rats were anesthetized with pentobarbital and then given a constant infusion of glucose (8 mg·kg⁻¹·min⁻¹), insulin (2.5 mU·kg⁻¹·min⁻¹, Humulin R, Eli Lilly-Shionogi, Osaka, J apan), and somatostatin (0.5 µg/min, Sigma) for 170 min through a cannula inserted into the right jugular vein. Blood samples were collected before the infusion was started and 150, 160, and 170 min after the infusion from a cannula inserted into the femoral vein. Under these conditions, endogenous insulin release was inhibited by somatostatin and SSPG was maintained during the last 20 min of the infusion. The mean of 150-, 160-, and 170-min samples was used to determine the SSPG values. Because the SSPG response is a direct reflection of the efficiency of insulin-mediated glucose disposal, higher SSPG values imply proportionally greater insulin resistance.

**Intravenous glucose tolerance test.** The test involved in an injection of a 0.5 g/ml glucose solution via the catheter at a 1.0 g/kg body wt dose. Blood samples were collected before glucose injection and 5, 10, 30, and 60 min afterward. The blood was immediately centrifuged at 4°C, and plasma was stored at −20°C until it was assayed.

Measurements. Plasma TG concentration was determined by the enzyme method with a commercially available kit (Triglyceride-G test, Wako Pure Pharmaceutical, Osaka, J apan). Plasma glucose levels were determined by glucose oxidase method (Glucose B-test, Wako Pure Pharmaceutical). Plasma NEFA concentration was determined by the enzyme method with a commercially available kit (NEFA-C test, Wako Pure Pharmaceutical). Immunoreactive insulin concentrations were determined by a radioimmunossay kit (no. RI-13K, Linco Research, St. Charles, MO) standardized against rat insulin. Plasma leptin concentrations were determined by a radioimmunoassay kit (no. RL-83K, Linco Research) for specifically determining rat leptin.

**Statistics.** Data are expressed as mean ± standard deviation (SD). Statistical significance was assessed by one-way ANOVA, and P < 0.05 was accepted as an significant difference. The correlation coefficients between two parameters were determined by Pearson’s simple linear regression analysis. In an attempt to evaluate the partial influence of parameters on the TgSR, independent of plasma insulin level, multiple regression analysis was performed with the TgSR as the dependent variable, and insulin was entered as the independent variable. An F value greater than four was accepted as indicating independent significance.
Table 1. General and metabolic characteristics of sham-operated and VMH-lesioned rats in different phases of obesity

<table>
<thead>
<tr>
<th></th>
<th>Dynamic Phase</th>
<th>Static Phase</th>
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<tr>
<td></td>
<td>Sham</td>
<td>VMH</td>
</tr>
<tr>
<td>n</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td>Initial BW, g</td>
<td>250 ± 30</td>
<td>264 ± 10</td>
</tr>
<tr>
<td>Final BW, g</td>
<td>272 ± 36</td>
<td>355 ± 19*</td>
</tr>
<tr>
<td>BW gain, g/day</td>
<td>0.9 ± 0.7</td>
<td>4.1 ± 2.7*</td>
</tr>
<tr>
<td>Parametrial fat pad, g</td>
<td>2.6 ± 16</td>
<td>6.7 ± 2.1*</td>
</tr>
<tr>
<td>Food intake, g/day</td>
<td>13.7 ± 0.8</td>
<td>29.3 ± 9.3*</td>
</tr>
<tr>
<td>Triglyceride, mmol/l</td>
<td>0.77 ± 0.28</td>
<td>1.35 ± 0.64*</td>
</tr>
<tr>
<td>NEFA, μmol/l</td>
<td>1.035 ± 440</td>
<td>1.594 ± 741*</td>
</tr>
<tr>
<td>Insulin, ng/ml</td>
<td>1.4 ± 0.9</td>
<td>3.1 ± 1.4*</td>
</tr>
<tr>
<td>Leptin, ng/ml</td>
<td>3.3 ± 3.9</td>
<td>19.2 ± 8.2*</td>
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Data are means ± SD. Dynamic phase 2 wk after creation of ventromedial hypothalamus (VMH) lesions; static phase of obesity, 14 wk after lesions; sham, sham-operated control rats; BW, body weight; NEFA, nonesterified fatty acid. n is as shown except for parametrial fat pad sham in dynamic and static phases (n = 7 and 8, respectively) and VMH-lesioned rats in dynamic and static phases (n = 5 and 10, respectively). Significantly (P < 0.05) different by 1-way ANOVA: * vs. sham-control (2 wk); † vs. sham control (14 wk); ‡ vs. VMH-lesioned rats of dynamic phase.

Higher plasma TG concentration in the dynamic phase and a 2.5-fold higher plasma TG concentration in the static phase than those in respective controls. Plasma NEFA levels were significantly increased in VMH-lesioned rats in both phases compared with those in the respective control rats. Plasma insulin levels were twofold higher in VMH-lesioned rats of the dynamic phase compared with controls. These levels tended to be further increased in VMH-lesioned rats of the static phase, but this figure did not reach statistical significance. Plasma insulin levels were comparable between the control rats of 2 wk and those of 14 wk after the sham operation. Plasma leptin concentrations were sixfold higher in VMH-lesioned rats in the dynamic phase, and the levels were further elevated in the static phase. In sham-operated rats, plasma leptin levels were doubled 14 wk after the operation compared with those at 2 wk.

Correlation of plasma leptin concentrations with adiposity. Plasma leptin levels were highly correlated with body weight, parametrial fat pad weight, and percent fat pad (the fat pad weight divided by body weight) in all rats (Fig. 1). The fat pad weight was significantly correlated with body weight (n = 30, r = 0.830, P < 0.0001).

TGSR and insulin resistance. TGSRs in VMH-lesioned rats were increased by 2.5-fold in the dynamic phase and 1.5-fold in the static phase compared with the respective sham-operated controls (Fig. 2). In sham-operated rats, the TGSR was increased twofold at 14 wk compared with that at 2 wk. Although the TGSR increase was marked, SSPG values were not increased in VMH-lesioned rats 2 wk after the creation of VMH lesions and, in fact, were lower than those in sham-operated controls. SSPG values, however, were substantially elevated in rats with VMH lesions of the static phase. Despite the marked increase in SSPG values, the TGSRs in the static phase showed only a nonsignificant rise compared with those in VMH-lesioned rats of the dynamic phase. Unlike VMH-lesioned rats, SSPG values were not altered in control rats 2 or 14 wk after the sham operation. In all animals, there was an excellent positive correlation between plasma TG concentrations and TGSRs (r = 0.708, P < 0.0002, n = 22), indicating that an increase in TG production causes hypertriglyceridemia.

Intravenous glucose tolerance test. Basal plasma glucose levels were identical in all groups of rats. These levels peaked 5 min after glucose injection and then declined (Fig. 3). The levels after glucose load were significantly higher in VMH-lesioned rats of the static phase compared with their sham-operated counterparts, whereas such glucose intolerance was not observed in VMH-lesioned rats of the dynamic phase. VMH-lesioned rats in both phases showed a marked increase in insulin response to glucose load compared with controls.
with control rats. In VMH-lesioned rats, the magnitude of the hyperinsulinemia was comparable between animals in the two phases. Plasma NEFA levels before glucose injection were significantly higher in VMH-lesioned rats in both the dynamic and static phases compared with respective control rats. The levels in these rats in the dynamic phase declined immediately after the glucose injection, and then the difference in NEFA levels at the baseline between VMH-lesioned and control rats disappeared. In the dynamic phase animals, plasma NEFA levels gradually rose from 10 min after the administration of the glucose, whereas in sham-operated rats, they continued to decline for up to 60 min after the load. When the plasma NEFA response was indicated as a percent change from the basal level, the percent suppression of NEFA at 10 min postglucose load was significantly larger in VMH-lesioned rats of the dynamic phase compared with that in control rats. Plasma NEFA levels were higher in VMH-lesioned rats of the static phase before and 30 and 60 min after the glucose injection than those in their sham-operated counterparts. The levels were almost normally suppressed in the early phase of the intravenous glucose tolerance test (IVGTT) (up to 10 min), but the suppression became weaker in the late phase (after 30 min).

Correlations of TGSR with plasma insulin or adiposity. As depicted in Fig. 4, TGSR was significantly related to both plasma insulin and leptin concentrations.
Correlations between adiposity, NEFA, and insulin. Correlations between basal plasma levels of NEFA, insulin, leptin, parametrial fat pad mass, and percent fat pad (parametrial fat pad mass/body weight) are demonstrated in Table 3. Plasma NEFA levels were significantly correlated with the fat pad mass, the percentage of that mass, and plasma leptin and insulin levels. Plasma insulin was also significantly correlated with these parameters related to adiposity.

**DISCUSSION**

In the present study, we demonstrated that insulin resistance was not developed in VMH-lesioned rats of the dynamic phase despite marked hyperinsulinemia. The lack of insulin resistance in this phase was confirmed by a low SSPG value, a normal glucose response, and an augmented NEFA suppression in the IVGTT. Thus we may conclude that hyperinsulinemia seen in the early phase of obesity is not a consequence of insulin resistance and that the elevated TGSR is entirely dissociated with insulin resistance in this phase. Similarly to other obese animals, insulin resistance was then developed in VMH-lesioned rats 14 wk after the creation of VMH lesions when body weight gain reached a plateau and obesity became the static state. In this phase, development of insulin resistance was confirmed by a high SSPG value, an impaired glucose tolerance, and a diminished NEFA suppression in the IVGTT. However, the developed insulin resistance did not accelerate TGSR further in VMH-lesioned rats. We previously reported that treatment with pioglitazone, an enhancer of insulin action, cannot suppress elevated TGSR in fructose-fed Wistar fatty rats, although it markedly ameliorated severe insulin resistance in these obese models (21). Taken together, these studies suggest that insulin resistance might not be an obligate factor to produce a hepatic overproduction of TG in rats with obesity.

The role of hyperinsulinemia in hepatic VLDL-TG production is controversial (24, 33). In vivo works have demonstrated that chronic hyperinsulinemia enhances the hepatic secretion rate of VLDL-TG (22, 28, 38), whereas acute hyperinsulinemia in vivo (11, 25, 26) or short-term incubation of insulin with hepatocytes (14, 32) has shown that the hepatic secretion rate of VLDL is decreased. The present study confirmed the close correlation between plasma insulin and TGSR in VMH-lesioned rats reported earlier by Inoue et al. (19). Plasma levels of glucose and NEFA were not reduced in the face of increased plasma insulin levels in VMH-lesioned rats of dynamic phase.}

![Correlation of TGSR with insulin and leptin.](http://ajpendo.physiology.org/)

[Fig. 4. Correlations of TGSR with insulin and leptin.](http://ajpendo.physiology.org/)

Table 2. Multiple regression and analysis of TGSR and adiposity, independent of insulin

<table>
<thead>
<tr>
<th>Independent Variable</th>
<th>Partial F value</th>
<th>P value</th>
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<tbody>
<tr>
<td>Leptin</td>
<td>9.63</td>
<td>0.0058</td>
</tr>
<tr>
<td>Insulin</td>
<td>4.24</td>
<td>0.0534</td>
</tr>
<tr>
<td>Body weight</td>
<td>11.09</td>
<td>0.0035</td>
</tr>
<tr>
<td>Insulin</td>
<td>6.68</td>
<td>0.0181</td>
</tr>
<tr>
<td>Parametrial fat pad</td>
<td>0.84</td>
<td>NS</td>
</tr>
<tr>
<td>Insulin</td>
<td>11.1</td>
<td>0.0034</td>
</tr>
</tbody>
</table>

Independent correlation between triglyceride secretion rate (TGSR) and adiposity was evaluated by multiple regression analysis with TGSR as a dependent variable, and factors indicating adiposity (leptin, body weight, or parametrial fat pad mass) and insulin as independent variables. n = 22; NS, nonsignificant.

Table 3. Correlation coefficients between NEFA, insulin, leptin, and adiposity

<table>
<thead>
<tr>
<th></th>
<th>NEFA</th>
<th>Insulin</th>
<th>Leptin</th>
<th>Fat Pad</th>
<th>% Fat Pad</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEFA</td>
<td>1</td>
<td>0.420</td>
<td>0.443</td>
<td>0.389</td>
<td>0.444</td>
</tr>
<tr>
<td>Insulin</td>
<td>0.420</td>
<td>1</td>
<td>0.616</td>
<td>0.673</td>
<td>0.692</td>
</tr>
<tr>
<td>Leptin</td>
<td>0.443</td>
<td>0.616</td>
<td>1</td>
<td>0.776</td>
<td>0.692</td>
</tr>
<tr>
<td>Fat pad</td>
<td>0.389</td>
<td>0.673</td>
<td>0.776</td>
<td>1</td>
<td>0.956</td>
</tr>
<tr>
<td>% Fat pad</td>
<td>0.444</td>
<td>0.692</td>
<td>0.692</td>
<td>0.956</td>
<td>1</td>
</tr>
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</table>

All correlations are statistically significant (P < 0.005); n = 30.
lesioned obese rats. Therefore, insulin could promote hepatic VLDL-TG production under an abundance of substrate availability. The data of VMH-lesioned obese rats may provide strong evidence demonstrating that hyperinsulinemia stimulates hepatic TG production even without insulin resistance in vivo.

The weight-reduction action of leptin is thought to be mediated primarily by signal transduction through the leptin receptors in the hypothalamus (8). VMH-lesioned rats could not respond to substantially higher leptin levels (31), suggesting that a key target for the biological actions of leptin was destroyed by the production of VMH lesions (20). Although the physiological significance of the circulating leptin on extracerebral organs still remains unclear, it is generally accepted that the plasma leptin concentrations well reflect the amount of adipose tissue in the whole body (8, 13, 16, 31), irrespective of subcutaneous or visceral obesity (13). With the use of plasma leptin as an index of generalized adiposity, we examined whether the hepatic overproduction of VLDL-TG is directly attributable to an increase in adiposity. We found a substantial correlation between TGSR and plasma leptin level, an indicator of adiposity, and multiple regression analysis showed that this correlation was independent of insulin. Recent studies have found that insulin increases both secretion and production of leptin by adipocytes and its circulating levels (3). Therefore, there is a possibility that insulin directly elevates plasma leptin levels without affecting adiposity. Nevertheless, a significant association between TGSRs and the parametrial fat pad weight or body weight also supports the hypothesis that increased adiposity per se contributes significantly to hepatic TG production. There is another possibility that the peripheral actions of leptin may contribute to hypertriglyceridemia in VMH-lesioned rats. Recently, Lopez-Soriano et al. (27) have shown that intravenous leptin injection mildly elevates plasma TG concentration in mice. However, they fail to observe a significant change in hepatic lipogenesis by leptin administration. Therefore, further studies will be needed to elucidate whether or not leptin can directly stimulate hepatic TG secretion in rats.

How can adiposity contribute to the stimulation of hepatic TG production? We presume that excess NEFA flux into the liver from enlarged adipose tissues stimulates hepatic TG production. In IVGTT, plasma NEFA concentrations in baseline were increased in VMH-lesioned rats in the dynamic phase, whereas the percent decline in NEFAs was not suppressed but, rather, enhanced. These results demonstrate that the resistance to the antilipolytic action of insulin is not developed in the adipocytes in the dynamic phase, but the increased NEFA concentrations at the baseline may simply reflect an enlarged adipose tissue mass. Significant correlations between NEFA and parametrial fat pad weight or plasma leptin concentrations support this concept. Plasma NEFA levels were significantly higher in VMH-lesioned rats 60 min after glucose injection in the dynamic phase, suggesting that the NEFA is again released from the enlarged adipose tissues when insulin levels fall and that its antilipolytic power is diminished. On the other hand, the suppression of NEFA levels during the IVGTT was significantly sluggish in these obese animals in the late phase of obesity, suggesting that insulin resistance is developed on the adipocytes and that both increased adiposity and insulin resistance contribute to an increase in plasma NEFA concentration. NEFA may stimulate hepatic VLDL secretion by the substrate availability (24) and by the suppression of intracellular degradation of apoprotein B (12). Clinical studies conducted by Lewis et al. (26) have demonstrated that an acute hyperinsulinemia during euglycemic-hyperinsulinemic clamp suppresses plasma NEFA concentrations and hepatic secretion of VLDL-TG. The elevation of plasma NEFA levels by infusing an artificial TG emulsion (Intralipid) and heparin diminished the suppressive effect of insulin on the VLDL production. These results suggest that acute insulin-induced suppression of hepatic TG production is to a great extent mediated by the lowering effect of insulin on plasma NEFA concentrations. In vitro experiments also have shown that NEFA directly stimulates VLDL-TG secretion by cultured hepatocytes even in the presence of an excess amount of insulin (5, 6). These clinical and experimental observations suggest that NEFA plays a major role in stimulating hepatic TG production. This production was stimulated in VMH-lesioned rats with an increase in adiposity but was not further accelerated in extremely fatty rats (the fat pad mass >9 g), suggesting that the substrate availability (NEFA flux) is a saturable process, and the hepatic TG secretion is not further accelerated over a sufficient amount of NEFA.

In addition to the direct effect of insulin on hepatic TG production, there is also a possibility that hyperinsulinemia is linked to the increase in hepatic TG production by adiposity in these obese animals. Insulin is the major hormone promoting TG storage in adipocytes and increasing fat tissue mass. It is well recognized that hyperinsulinemia plays a central role in developing obesity in VMH-lesioned rats (4). We are able to confirm from this work a significant relationship between plasma insulin level and parameters related to adiposity. Therefore, adipose tissue may be another primary organ responsible for insulin that leads to the hepatic overproduction of VLDL-TG. That is, insulin increases adiposity through its TG storage and trophic actions on adipocytes, and then, enlarged fat tissue mass increases NEFA outflux, which finally results in increased VLDL-TG secretion by the liver.

In summary, our results suggest that adiposity itself is another major contributor to the increase in hepatic TG production, independent of hyperinsulinemia. Insulin resistance does not stimulate TG production in this animal model for obesity.

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References


