Hepatic triglyceride secretion in relation to lipogenesis and free fatty acid mobilization in fasted and glucose-refed rats

NOME BAKER, ARLENE S. GARFINKEL, and MICHAEL C. SCHOTZ

Radioisotope Research, Veterans Administration Center, Los Angeles, California 90073, and Department of Biological Chemistry, University of California at Los Angeles School of Medicine, Los Angeles, California 90024

ABSTRACT Plasma triglyceride concentrations were significantly lowered by a single feeding of glucose to rats that had been fasted for 22 hr. Three feedings of glucose produced a similar effect. In the glucose-refed animals mobilization of free fatty acids from adipose tissue was impaired more rapidly than hepatic lipogenesis was restored from its low fasting level. These effects of glucose were shown by both a 50% fall in plasma free fatty acid concentration and an 84% decrease in free fatty acid release by isolated epididymal fat pads within 30 min after a single refeeding of glucose. Hepatic lipogenesis from either acetate-1-^{14}C or glucose-U-^{14}C was not restored even after glucose had been fed three times at hourly intervals. Triton-induced hypertriglyceridemia was used to measure the hepatic triglyceride secretory rate; it was found that glucose refeeding decreased this rate in all but one of several experiments. This decreased secretion rate was sufficient to account for the nearly complete disappearance of triglyceride in very low density lipoproteins ($d < 1.019$) that occurred within 1 hr after a single glucose intubation.

KEY WORDS rat · fasting · glucose refeeding · triglycerides · free fatty acids · mobilization · hepatic lipogenesis · Triton-induced hypertriglyceridemia · ether anesthesia · very low density lipoprotein

A DELICATE BALANCE between rates of net hepatic TG secretion and of extrahepatic TG uptake normally maintains circulating TG at a constant concentration in fasted animals. However, this balance can be disrupted quickly. For example, when hepatic TG secretion is drastically impaired, as in CCl_4 poisoning (1), plasma TG concentration falls rapidly (1–3). On the other hand, the mere feeding of glucose (4–6) or sucrose (7) may cause a decrease in plasma TG concentration both in healthy, fasted human subjects (4, 5) and in fasted rats (6, 7).

The mechanism by which a treatment as mild as glucose feeding produces its marked hypotriglyceridemic effect is unknown. Havel (8) has suggested that after glucose ingestion the increased uptake of plasma TG by tissues could account for the phenomenon, which he had observed in man. His explanation, however, did not place any emphasis upon the nutritional state of the subject prior to glucose feeding. Data have been published that suggest that carbohydrate feeding may diminish levels of circulating TG only if the subjects or the experimental animals have been fasted prior to administration of sugar. In nonfasted human subjects or animals, carbohydrate feeding either does not affect or increases plasma TG (7, 9–14).[1]

We formulated the following hypothesis to explain how glucose might lower plasma TG concentration acutely in fasted, but not in fed, animals. First, consider that the rate of hepatic TG secretion into the circulation depends at all times upon the rate of hepatic TG formation either from plasma FFA or from newly synthesized fatty acids

Abbreviations: TG, triglyceride; FFA, free fatty acids; TGFA, triglyceride fatty acids; VLDL, very low density lipoproteins.

[1] After completion of this study, we noted the following exception to this relationship between nutritional state and the effect of carbohydrate feeding. Nikkila and Ojala reported recently that three feedings of glucose, at hourly intervals, to previously fasted rats did not lower plasma triglyceride concentration (14). This finding differs from results obtained in our laboratory in earlier studies (6) and confirmed by data presented here.

derived from glucose and amino acids by lipogenic pathways. Since lipogenesis is grossly inhibited in fasted rats (15–17), hepatic TG secretion would then be totally dependent upon the rate of conversion of circulating FFA to hepatic TG (18). In nonfasted carbohydrate-fed rats this would not be true since hepatic lipogenesis from carbohydrate would be operative. Feeding a large load of glucose to a fasted animal would remove one source of hepatic TGFA synthesis, to a large extent, since glucose feeding inhibits the flux of FFA from adipose tissue into plasma (19, 20). This assumes that when plasma FFA flux is inhibited, the rate of hepatic TGFA formation from circulating FFA is correspondingly retarded (21). It also assumes that FFA mobilization in fasted rats is inhibited by glucose feeding during and, perhaps, after post-alimentary hyperglycemia, but that conversion of glucose to hepatic TGFA would not occur at an appreciable rate until several hours after the refeeding of carbohydrate (17, 22). As a result, the feeding of a large glucose load may be expected to diminish hepatic TG secretion in fasted, but not in fed, animals. Decreased hepatic TG secretion would bring about lower plasma TG levels unless the rate of TG uptake by extrahepatic tissues were inhibited by glucose refeeding. Since glucose refeeding tends, if anything, to increase the rate of TG uptake by tissues (6, 23) lowering of the hepatic TG secretory rate by glucose refeeding would almost certainly lead to hypotriglyceridemia.

In the present study, these assumptions, as well as the hypothesis that glucose lowers the rate of hepatic TG secretion in fasted rats, have been investigated by the use of acetate-^{14}C and glucose-^{14}C to measure (*a*) lipogenesis in liver slices, (*b*) plasma FFA concentrations plus FFA release from isolated epididymal fat pads (to indicate the FFA-mobilizing capacity of adipose tissue), and (*c*) Triton-induced hypertriglyceridemia [as a measure of TG secretory rates (1)].

METHODS

Male Sprague-Dawley rats, 150–180 g (Charles River Farms Breeding Laboratories) were used. 22 hr prior to the study all rats were deprived of food but allowed free access to water. Except for light ether anesthesia induced for 3–5 min in half the animals in one experiment, all rats were unanesthetized during the experimental period. During the series of experiments the fasted rats were either studied without further treatment or intubated with 2 ml of water or 2 ml of 50% glucose (w/v). A measure of the rate of TG secretion in these rats was obtained by injecting some of the animals intravenously with 0.5 ml of Triton WR 1339 (200 mg/ml in 0.85% NaCl). This agent blocks removal of TG from the circulation. At various times after feeding and (or) Triton injection the rats were decapitated and serum or plasma TG concentration was determined using tripalmitin as a standard (24). In some experiments plasma FFA was also determined. The time schedules for feeding, Triton injection, and decapitation are listed in the tables and figures.

To learn whether Triton (oxyethylated *t*-acyl-phenol formaldehyde polymer) had entered the circulation we employed a colorimetric test (25) to determine its presence in the serum. According to this test several animals had extremely low levels of serum Triton; they were eliminated from the experiment.

Rates of hepatic TG secretion in Triton-treated rats were calculated on the basis of a plasma volume of 4.0% of body weight which was measured in a separate study[2] of fasted and glucose-refed rats under identical conditions: [(mg TG/ml at t_2, post-Triton) − (mg TG/ml at t_1, pre-Triton)] × 4.0 ml ÷ (t_2 − t_1) = mg TG secreted/min per 100 g body weight. Statistical evaluation was based upon Student's "*t*" test for the special case in which the variances of the mean values are not assumed to be the same. We have assumed that prior glucose feeding does not prevent Triton from blocking completely the removal of TG from the circulation.

Hepatic lipogenesis[3] was measured by incubation of liver slices (500 mg), obtained from the left lateral lobe, in 5 ml of Krebs-Henseleit bicarbonate buffer (26) containing 0.2 μc of sodium acetate-2-^{14}C (5.51 mc/mmole) or 0.3 μc of glucose-U-^{14}C (42 mc/mmole). The glucose concentration was adjusted to 20 μM; the tissues were shaken in an atmosphere of 5% CO_2–95% O_2 for 90 min at 37°C. The flask contents were then acidified, the tissue was washed, and the liver was saponified in alkali. After alkaline hydrolysis the fatty acids were isolated and a portion was assayed in a liquid scintillation counter (27). As a control for measurement of lipogenesis, livers from a group of animals fed ad libitum with access to 20% glucose in drinking water for 24 hr were also included.

VLDL-TG was isolated from pooled samples of plasma representing four or five rats by the method described by Lombardi and Ugazio (3). TG was separated by thin-layer chromatography (28) on silicic acid and the TG concentration was measured (24).

FFA release from isolated fat pads was estimated by incubating the epididymal fat pads in Krebs-Henseleit bicarbonate buffer containing 5% bovine serum albumin in an atmosphere of 5% CO_2–95% O_2 at 37°C for 1 hr. FFA concentration of the medium before and after incubation was determined (29).

[2] N. Baker and H. Rostami. Manuscript in preparation.

[3] "Lipogenesis" is used in this paper to mean synthesis of new fatty acids. We have assumed that incorporation of ^{14}C into total fatty acids is an index of the rate of lipogenesis. Therefore, the terms "incorporation of isotope into fatty acids" and "lipogenesis" are used interchangeably.

RESULTS

Circulating TG Concentrations

In both experiments shown in Fig. 1, three feedings of glucose or water 1 hr apart to previously fasted rats lowered serum or plasma concentration significantly. Plasma TG levels did not change during the experiment in untreated fasted rats (Fig. 1, Expt. II). Feeding a glucose solution three times lowered serum or plasma TG concentrations significantly more than feeding water three times. In the combined experiments, glucose-fed rats had circulating TG levels averaging 42% of those found in fasted controls, whereas the water-fed rats had levels averaging 70% of the control level (Fig. 1).

A single feeding of glucose was found to lower serum or plasma TG levels significantly in each of four experiments 1 hr after the glucose load (Table 1). No significant change in circulating TG levels was found in water-fed rats compared with fasted controls under these experimental conditions. At 30 min plasma TG levels in glucose-refed animals were reduced slightly; however, the difference of the means was not statistically significant, compared to fasted controls. The relative plasma TG and FFA concentration of all four experiments is illustrated in Fig. 2. The fall in plasma TG to about 55% of the control level was complete by 1 hr after feeding and did not change during the next hr even though no additional glucose was fed (Fig. 2). The fall in plasma FFA seemed to be complete 30 min after feeding.

In normal fasted controls 89% of the total plasma TG was recovered in the d < 1.019 lipoprotein fraction. Feeding glucose had little or no effect on the TG concentration of d > 1.019 lipoprotein whereas the level of TG of the d < 1.019 fraction was strikingly decreased (Fig. 3). Thus the lowering of plasma TG levels after a single glucose feeding can be accounted for almost entirely by the fall in the d < 1.019 lipoprotein fraction.

TABLE 1 EFFECT OF A SINGLE FEEDING OF GLUCOSE OR WATER ON CIRCULATING TG CONCENTRATION

Expt.	Treatment	No. of Rats	Time after Feeding	Serum or Plasma TG Concentration
			min	*mg/ml*
I	Fasted controls	6	0	0.39 ± 0.07 (SD)
	Water-fed	6	60	0.38 ± 0.08
	Glucose-fed	6	60	0.22 ± 0.05*
II	Fasted controls	6	0	0.55 ± 0.075
	Water-fed	6	60	0.56 ± 0.066
	Glucose-fed	6	60	0.24 ± 0.028*
III	Fasted controls	5	0	0.56 ± 0.21
	Water-fed	5	30	0.50 ± 0.15
	Glucose-fed	3	30	0.46 ± 0.12
	" "	8	60	0.26 ± 0.11*
IV	Fasted controls	5	0	0.49 ± 0.21
	Water-fed	5	30	0.55 ± 0.12
	Glucose-fed	7	30	0.40 ± 0.16
	" "	5	60	0.30 ± 0.094*
	" "	5	120	0.29 ± 0.057*

* Significantly different from fasted controls; $P < 0.01$.

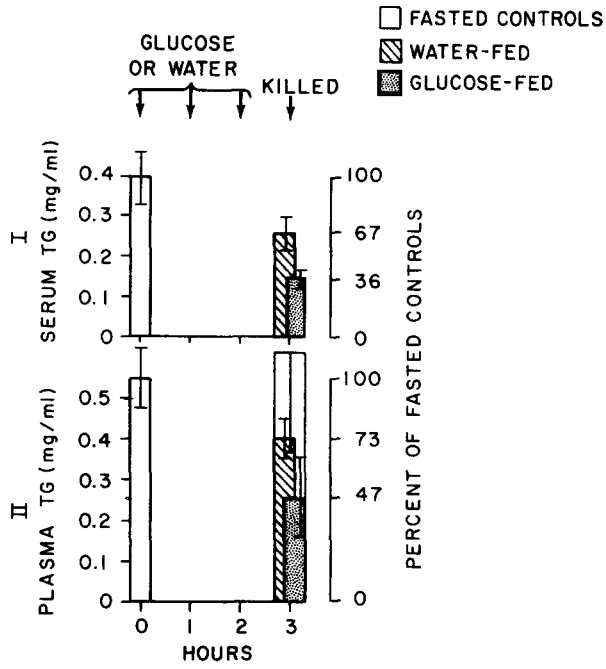

FIG. 1. Effect of three feedings of glucose or water on serum or plasma triglyceride concentration. Vertical line = ±SD (n = 6 for each group). All rats were fasted for 22–24 hr prior to intubation. Animals designated "fasted" were not intubated; others received either 2 ml of water or 2 ml of 50% glucose in water by gastric intubation at times indicated by arrows. The differences between treated aminals and the untreated control and between glucose-fed and water-fed rats are significant, $P<0.01$.

Lipogenesis from Acetate and Glucose

Fasting an animal for 22 hr caused a large decrease in incorporation of acetate-^{14}C into liver fatty acids. This level of incorporation in fasted animals was unchanged 1 hr after a single glucose feeding. After three hourly glucose feedings the incorporation of acetate-^{14}C into liver fatty acids continued to be greatly suppressed compared to animals fed ad lib. although significantly increased compared to the fasted animals (Table 2). Similar findings were observed when hepatic lipogenesis from glucose-^{14}C was measured (Table 3).

FFA Release from Isolated Fat Pads

A single feeding of glucose resulted in suppression of net FFA release from adipose tissue into the medium, as shown in Table 4. The decrease was 84% at 30 min but only 54% at 1 hr after glucose administration. However, suppression (41%) was still evident 2 hr after one glucose feeding.

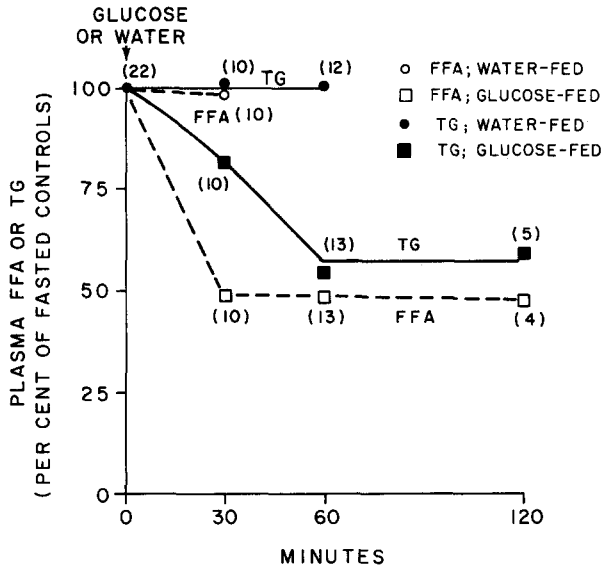

FIG. 2. Lowering of plasma TG and FFA concentrations by a single feeding with glucose. The data of Table 1 for TG have been expressed as a percentage of values in fasted controls and the mean values of all four experiments are plotted as a function of time after the feeding of either 2 ml of water or 2 ml of 50% glucose in water. Number of rats is given in parentheses; see Table 1 for standard deviations in each experiment. Serum, rather than plasma, TG concentrations were used for rats from Expt. I.

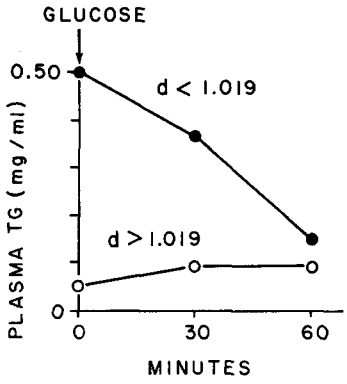

FIG. 3. Effect of a single glucose feeding on the relative distribution of plasma TG between d <1.019 and higher density proteins. See Expt. III, Table 1.

FFA Mobilization and Plasma FFA Concentration

As shown in Table 5 and in Fig. 2, 30 min after glucose feeding plasma FFA fell to a concentration which was about 50% of that found in both the fasted and water-fed controls. This effect of glucose was highly significant ($P \leq 0.01$). No further change in plasma FFA level was found at 1 or 2 hr after a single glucose feeding. The rapid fall of plasma FFA concentration in refed rats appears to be an excellent index of the fall in net FFA inflow into the circulation.

Triglyceride Secretion Rates

30 min after a single glucose feeding, at a time when the plasma TG concentration was falling, the rates of TG secretion were significantly lower than those of the controls. The decrease observed in these experiments varied from 20 to 48% (Table 6). Composite results of the experiments in which TG secretion was studied 30 min after feeding glucose are shown in Fig. 4. A significant depression in post-Triton triglyceridemia ($P = 0.05$) was found in these experiments between 30 and 60 min. In

TABLE 2 LIPOGENESIS FROM ACETATE-2-^{14}C IN LIVER SLICES OF GLUCOSE-REFED AND FASTED RATS

Condition	No. of Rats	% of Added ^{14}C Incorporated into Fatty Acids*	Relative Lipogenesis
			%
Fed ad lib.	3	50.7 ± 4.3	100
Fasted	6	2.0 ± 1.0	4
Glucose-refed (once)	6	1.6 ± 0.50	3
Fed ad lib.	2	56.2 ± 0.05†	100
Fasted	5	3.1 ± 1.7	6
Glucose-refed (3 times)	4	7.4 ± 1.8	13

* Per 500 mg of fresh tissue slices per 3 hr. Mean ± SD.
† Range.

TABLE 3 LIPOGENESIS FROM GLUCOSE-U-^{14}C IN LIVER SLICES OF GLUCOSE-REFED AND FASTED RATS

Condition	No. of Rats	% of Added ^{14}C ($\times 10^2$) Incorporated into Fatty Acids*	Relative Lipogenesis
			%
Fed ad lib.	3	41.6 ± 4.3	100
Fasted	6	0.38 ± 0.086	1
Glucose-refed (once)	6	0.43 ± 0.14	1
Fed ad lib.	2	45.8 ± 16†	100
Fasted	5	0.50 ± 0.097	1
Glucose-refed (3 times)	5	1.3 ± 0.79	2

* Per 500 mg of fresh tissue slices per 3 hr (mean ± SD). All values (in contrast to those in Table 1) have been multiplied by 100 for convenience of presentation.
† Range.

TABLE 4 EFFECT OF A SINGLE FEEDING OF GLUCOSE TO FASTED RATS ON IN VITRO RELEASE OF FFA BY EPIDIDYMAL FAT PADS

Condition	No. of Rats	Time Killed*	Net FFA Released	Per Cent Decrease
		min	*μeg/g tissue/hr*	%
Fasted	5	60	2.8 ± 0.65†	—
Glucose-refed	6	30	0.46 ± 0.44	84
" "	6	60	1.3 ± 0.82	54
Fasted	5	120	3.7 ± 1.6	—
Glucose-refed	6	120	2.2 ± 0.81	41

* In case of fasted rats, time interval is that following gastric intubation of water.
† Mean ± SD.

TABLE 5 EFFECT OF A SINGLE GLUCOSE FEEDING UPON PLASMA FFA CONCENTRATIONS

Expt.	Treatment	No. of Rats	Time after Feeding	Plasma FFA Concentration
			min	*μeg/ml*
III	Fasted control	5	0	0.76 ± 0.11
	Water-fed	5	30	0.73 ± 0.063
	Glucose-fed	3	30	0.32 ± 0.058*
	" "	8	60	0.36 ± 0.099*
IV	Fasted control	5	0	0.79 ± 0.059
	Water-fed	5	30	0.79 ± 0.10
	Glucose-fed	7	30	0.41 ± 0.063*
	" "	5	60	0.41 ± 0.12*
	" "	4	120	0.36 ± 0.077*

FFA concentrations are mean ± SD.
* Significantly different from fasted or water-fed controls; $P < 0.01$.

TABLE 6 INHIBITION OF TRIGLYCERIDE SECRETION RATES BY GLUCOSE REFEEDING (MEASURED BY TRITON-INDUCED HYPERTRIGLYCERIDEMIA)

Expt.		Time Interval After Glucose Refeeding	No. of Animals	Control TG Secretion Rate	Per Cent Inhibition
		min		*mg TG/min/ 100 g body wt*	*%*
I		60–90	(5, 5; 5, 5)*	0.025	0
II		60–90	(6, 6; 6, 6)	0.057	37
III	1	30–60	(5, 3; 3, 3)	0.17	48†
	2	30–120	(5, 3; 3, 2)	0.12	35
	3	30–60	(5‡, 3; 3‡, 3)	0.13	32†
	4	30–120	(5‡, 3; 3‡, 2)	0.10	20
IV	1	30–60	(5‡, 7; 3‡, 3)	0.11	30†
	2	30–120	(5‡, 7; 3‡, 3)	0.096	23

* Numbers in parentheses indicate number of animals in controls and glucose-refed rats, pre-Triton before semicolon, post-Triton after it.
† Probably significant; $P = 0.05$.
‡ Indicates control animals fed water; other controls were untreated.

the animals studied 60 min after a single glucose feeding one of the experiments showed the same lowering of TG secretion rate, whereas in the other experiment glucose feeding had no effect. A wide range of values for rates of hepatic TG secretion in fasted and water-fed control rats was found (Table 6). In most of the experiments TG was secreted at between 0.096 and 0.17 mg/min per 100 g body weight, rates similar to previously published values. However, in two experiments (I, II) the secretion rates were far lower than those hitherto reported for fasted animals (1, 9, 14, 28, 30–33). No correlation between initial plasma TG level and rate of TG secretion was observed. Several attempts were made to account for the low rates of TG secretion. Among the variables studied were the effects of brief ether anesthesia (Table 7) and of Triton obtained from various sources. No effect of ether

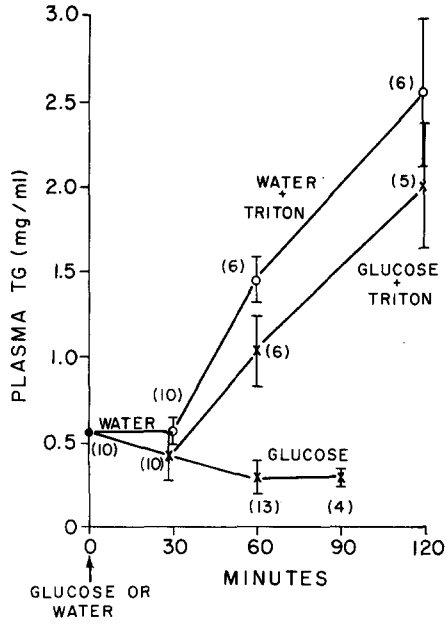

FIG. 4. Effect of a single glucose feeding on post-Triton hypertriglyceridemia in fasted rats. The data are a composite of two experiments (III and IV, Table 6) performed on consecutive days. Vertical bars = ± SD. Number of rats used at each time are given in parentheses.

anesthesia was observed, and at present, we have no explanation for the very low rates.

DISCUSSION

Our data show that within 1 hr after a single glucose feeding to fasted rats, the serum TG concentration falls to about half the level of controls. Similar effects on plasma circulating TG levels have been reported after the feeding of sucrose to fasted rats (7) or glucose to fasted human subjects (4, 5). The decrease in serum TG concentration 1 hr after carbohydrate feeding is as pronounced as that seen 1 hr after oral administration of CCl_4, one of the most rapid inhibitors of hepatic TG secretion (1–3). The percentage decrease in plasma VLDL-TG concentration, as in the case of CCl_4 poisoning (3), was even more

TABLE 7 EFFECT OF ETHER ANESTHESIA DURING INJECTION OF TRITON WR 1339 ON RATES OF HEPATIC TG SECRETION

Condition	Serum TG Concentration		Rate of TG Secretion
	Pre-Triton	Post-Triton	
	mg/ml		*mg TG/min/ 100 g body wt*
Fasted–anesthetized*	0.35 ± 0.08†	0.78 ± 0.16	0.057
Fasted–unanesthetized	0.38 ± 0.11	0.83 ± 0.15	0.060

* Light ether anesthesia, 3–5 min prior to and during Triton injection.
† Mean ± SD.

pronounced than the change found in the total TG level. The latter observation is in accord with earlier studies[4] that showed that VLDL-TG is the most rapidly turning over component of the heterogeneous plasma TG pool (34, 35).

In considering how plasma TG concentration can be lowered so markedly by glucose ingestion, we hypothesized that the rate of hepatic TG secretion into the circulation is decreased by glucose feeding in fasted rats. The rationale for the hypothesis was based upon the possibility that two major sources for the synthesis of hepatic TGFA might be relatively unavailable in a fasted animal shortly after refeeding glucose. One potential source, plasma FFA derived from adipose tissue, is known to be diminished by prolonged glucose feeding (19, 20). The other potential source of hepatic TGFA, fatty acids newly synthesized in liver, might be diminished since hepatic lipogenesis from both glucose and acetate is known to be inhibited in livers of fasted rats (15–17).

The present experiments lend strong support to our hypothesis. As anticipated, mobilization of FFA from adipose tissue was promptly inhibited by a single feeding of glucose, but hepatic lipogenesis remained impaired throughout the experiment. In all but one instance, the rate of hepatic TG secretion was lowered enough to account for the observed hypotriglyceridemia 1 hr after glucose feeding.

Although other workers have reported that the rate of hepatic TG secretion may fall when FFA mobilization is inhibited (30, 36)[5] and that TG secretion may be enhanced when FFA mobilization is increased (18), the correlation between FFA mobilization, or more specifically, the inflow of FFA into hepatic TG, and the rate of hepatic TG secretion is not regularly observed. For example, the rates of hepatic TG secretion in rats chronically fed glucose are high (28) even though FFA mobilization is reduced. Hydrazine may increase the inflow of FFA into hepatic TG without increasing the rate of TG secretion (37) even though hydrazine is thought (30) to have no direct influence on liver. In the present study, ether anesthesia, which also has been shown to increase the incorporation of labeled FFA into hepatic TG (38), did not increase the rate of hepatic TG secretion.

Even more germane to the present discussion was the observation, in one experiment, that glucose refeeding could cause a 43% decrease in plasma TG concentration within 1 hr without lowering the rate of TG secretion. In this one experiment, hepatic TG secretion after glucose refeeding continued at an unchanged but slow rate, despite the decreased mobilization of FFA produced by glucose refeeding. In this exceptional case glucose refeeding seemed to produce hypotriglyceridemia by a mechanism unrelated to inhibition of hepatic TG secretion. A similar interpretation may be extended to studies which have been reported in human subjects. For example, several workers have observed that the feeding of a single glucose load to fasted humans causes a prompt fall in plasma TG levels (4, 5). Although it has been stated that this phenomenon may be due either to an increased uptake of TG by extrahepatic tissues or to an inhibition of hepatic TG secretion induced by glucose feeding (4), we think the latter explanation may be ruled out simply because the rate of hepatic TG secretion in fasted humans is so slow (39, 40) that no degree of inhibition of this process could account for the rapid fall in plasma TG concentrations. It seems highly probable that insulin, secreted in response to various agents, almost instantaneously increases the rate of VLDL-TG removal from the circulation by a mechanism which is still undiscovered (41).

We may conclude from the present experiments that refeeding a large load of glucose to fasted rats usually reduces the rate of hepatic TG secretion promptly. The inhibition is sufficiently large, in most instances, to account for the observed fall in plasma VLDL-TG concentrations which accompanied glucose refeeding. However, the possibility remains that insulin, secreted in response to alimentary hyperglycemia, may also alter the rate of VLDL-TG removal from the circulation of fasted rats by a rapidly acting mechanism as it apparently does in humans (42).

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[4] M. C. Schotz and N. Baker, unpublished experiments.

[5] Trout has observed that a single feeding of glucose lowers both plasma FFA concentration and the rate of hepatic TG secretion (30); however, no lowering of plasma TG concentrations was reported to follow the glucose load. According to a personal communication from Dr. Trout, plasma TG level was lowered only slightly by glucose feeding.

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