Plasma free fatty acid transport during prolonged glucose consumption and its relationship to plasma triglyceride fatty acids in man

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Abstract Plasma free fatty acid (FFA) transport in human subjects has been studied during the course of prolonged ingestion of different amounts of glucose. Compared with the fasting state, hypocaloric glucose intake resulted in marked suppression of net transport of FFA with no change in (fractional) turnover rate. There was no further suppression of net transport of FFA when the intake was increased to isocaloric or hypercaloric levels, but there was a significant increase in the (fractional) turnover rate, indicating an enhancement of clearance mechanisms. During the 20–24-hr period of fasting after isocaloric glucose consumption, the (fractional) turnover rate quickly fell to that found in the fasting individual, whereas net transport remained suppressed for much longer. This suggested that ingestion of glucose maintains an influence on lipolysis longer than on esterification. During this period of fasting after glucose administration, the contribution of plasma FFA to circulating triglyceride fatty acids increased with time and was positively and significantly correlated with the changes in the net transport of plasma FFA.

Supplementary key words caloric intake · net transport · precursors of plasma triglyceride fatty acids

In the postabsorptive state the concentration of plasma FFA is determined primarily by the net inflow transport from adipose tissue, and the concentration is a measure of the lipolysis in that tissue. Clearance, under these circumstances, appears to be a function of the concentration of plasma FFA with a relatively constant fraction of the plasma FFA pool (about one-third) removed every minute (1, 2). Following an acute glucose load, the suppression of plasma FFA concentration is largely accounted for by a fall in net inflow transport (1, 3, 4), although clearance may also be enhanced (5). The ingestion of glucose also diminished the contribution of plasma FFA to endogenous plasma TGFA production in rats (6), although this has only been shown in man during more prolonged glucose intake (7).

The aim of this study was to examine the effect of prolonged rather than acute consumption of glucose on plasma FFA kinetics with particular regard to the relative roles of net transport into the plasma and clearance from the plasma in the regulation of the FFA concentration. We have designed experiments to achieve a range of FFA fluxes by varying the nutritional state from one of hypercaloric intake of glucose (when presumably adipose tissue lipolysis is maximally suppressed) through states of eucaloric and hypocaloric intake to one of fasting. We have also assessed the changes in plasma FFA kinetics throughout 24-hr periods covering the transition from glucose absorption to a late postabsorptive state. The relationship between the changes in FFA flux and the contribution of plasma FFA to TGFA production has been followed during this period.

METHODS

Subjects

Of the 11 subjects studied, all but three were healthy, lean, male volunteers aged 18–53 yr. The other three were obese and hypertriglyceridemic (subject 1, a young female weighing 87 kg, and subjects 10 and 11, young males weighing 105 and 128 kg, respectively). Alcohol consumption had been minimal in all subjects.

Experimental design

Experiment 1 (Table 1). A series of studies was performed to measure FFA kinetics during a variety of

Abbreviations: FFA, free fatty acid(s); TGFA, triglyceride fatty acid(s); VLDL, very low density lipoproteins.

TABLE 1. Net transport and concentration of plasma FFA during fasting and during glucose consumption at various caloric levels

Subject	Weight	Height	Overnight Fasted State[a]			Calorie States with Glucose Diets[b]								
						50%			100%			130%		
			Concentration	Net Transport	FTR[c]	Concentration	Net Transport	FTR	Concentration	Net Transport	FTR	Concentration	Net Transport	FTR
	kg	*cm*	*μmoles/ml*	*μmoles/min*	*min*$^{-1}$	*μmoles/ml*	*μmoles/min*	*min*$^{-1}$	*μmoles/ml*	*μmoles/min*	*min*$^{-1}$	*μmoles/ml*	*μmoles/min*	*min*$^{-1}$
1	87	165	0.719	853	0.33				0.085	185	0.59			
2	66	170	0.636	650	0.38				0.059	102	0.64			
3	54	165	1.241	790	0.26				0.094	134	0.59	0.086	128	0.62
4	66	174	0.879	859	0.36				0.064	96	0.55	0.128	203	0.58
5	64	174				0.129	118	0.34	0.068	122	0.63	0.065	112	0.61
6	58	172				0.182	185	0.38						
7	69	180	0.747	621	0.29	0.121	116	0.34	0.064	94	0.53	0.117	203	0.62
8	70	178				0.157	154	0.35	0.111	188	0.62	0.108	202	0.66
9	57	173	0.779	511	0.25				0.087	172	0.77			
10	105	177	0.636	526	0.25	0.240	262	0.33	0.120	164	0.43			
11	128	181	0.602	650	0.34				0.124	250	0.63			
Mean			0.780	683	0.31	0.166	167	0.35	0.088	151	0.60	0.101	170	0.62
SEM			±0.074	±48	±0.02	±0.021	±27	±0.01	±0.008	±16	±0.03	±0.011	±20	±0.01

[a] Subjects were fasted 16 hr overnight following their habitual diets.
[b] Pure glucose diets were given to provide 50, 100, or 130% of isocaloric requirements (see text).
[c] FTR, (fractional) turnover rate (min^{-1}) = net transport of plasma FFA (μmoles/min)/plasma FFA pool size (μmoles).

nutritional states (*a*) in subjects who were fasted for 16 hr overnight after consuming habitual diets (approximately 40% of calories from carbohydrate, 40% from fat, and 20% from protein), and (*b*) in subjects who had been eating a carbohydrate-rich diet for 4 days (15% protein, 60% glucose, and 25% other carbohydrates). This was followed by sustained glucose consumption in which glucose was the sole source of calories for 36 hr. Solutions of glucose were consumed every 3 hr for the first 24 hr until 6 AM on the morning of the study, at which time a solution was given every hour to provide $^1/_{24}$ of the calculated daily caloric requirement. The ingestion of the glucose drinks was continued until the study was completed. The effects of the glucose-enriched diets were studied during three separate nutritional states, eucaloric, hypocaloric (50%), and hypercaloric (130%).

Experiment 2 (Table 2). Kinetics of plasma FFA turnover and the incorporation of circulating FFA into TGFA of very low density lipoproteins were studied in five subjects. Measurements were made continually throughout the last 3 hr of sustained isocaloric glucose consumption (in subjects who had been prepared as described under experiment 1 [*b*]) and during a subsequent 20–24 hr of fasting.

Infusion techniques. All experiments commenced between 8 AM and 9 AM. Catheters were placed into a forearm vein on one side and into a large antecubital vein on the other and they were kept patent by slow infusions of isotonic saline without heparin. After 45 min, labeled palmitic acid complexed as the sodium salt to human albumin (5) was given as a priming injection in a volume of 15–40 ml (10–30% of total radioactivity) followed by a constant infusion at a rate of 0.1 ml/min. [1-^{14}C]-Palmitic acid (57.7 mCi/mmole) and [9,10-^{3}H]palmitic acid (500 mCi/mmole) were obtained from Radiochemical Centre, Amersham, England. Purity of radioisotopes was checked by thin-layer chromatography; more than 99% of the ^{14}C and more than 97% of the ^{3}H radioactivity was in FFA. The [1-^{14}C]palmitic acid was infused in both studies in subjects 1 and 4 (Table 1) and in the hypocaloric study in subject 6 (Table 1). In all other studies ^{3}H-labeled palmitic acid was infused. For the measurements of plasma FFA kinetics alone (experiment 1) the infusions were continued for 3–4 hr, and four blood samples were taken from the catheter in the large antecubital vein at 15-min intervals during the last hour of infusion. In five subjects (7–11, experiment 2) fed isocaloric glucose diets, the radiopalmitate infusions were started 8 hr before the last glucose drink and were then continued for a further 20–24 hr of fasting; blood samples were collected as shown in Table 2. In subjects 9–11, studies were also carried out after an overnight fast and the radiopalmitate infusions were then maintained for 9 hr.

TABLE 2. Studies spanning periods of sustained isocaloric glucose consumption and the subsequent 24 hr of fasting

Subject	Weight		Time Relative to End of Glucose Consumption (hr)												Results after 16-hr Overnight Fast after Habitual Diet
			−3	−2	−1	0	1	3	6	9	12	16	20	24	
	kg														
7	69	Plasma FFA concentration (μmoles/ml)		0.063	0.077	0.057	0.058	0.144	0.139	0.237	0.323		0.675		
		Plasma FFA net transport (μmoles/min)		94	117	82	72	115	51	158	142		287		
		Plasma FFA (fractional) turnover rate (min^{-1})		0.56	0.56	0.53	0.50	0.37	0.14	0.25	0.15		0.16		
		VLDL TGFA concentration (μmoles/ml)		1.13	0.88	1.16	1.03	1.16	1.25	2.22	2.64		2.19		
		Ratio of specific activities[a]		8	9	7	6	12	7	28	27		62		
		Plasma insulin concentration (μU/ml)		56	34	56	75	16	15	14	14		15		
8	70	Plasma FFA concentration (μmoles/ml)	0.104	0.110	0.117	0.112	0.109	0.104	0.155	0.090	0.120	0.129	0.303	0.646	
		Plasma FFA net transport (μmoles/min)	191	193	187	184	190	165	218	92	138	116	183	224	
		Plasma FFA (fractional) turnover rate (min^{-1})	0.66	0.63	0.57	0.59	0.62	0.57	0.50	0.37	0.22	0.32	0.22	0.12	
		VLDL TGFA concentration (μmoles/ml)	1.25	1.25	1.22	1.16	0.94	1.13	1.09	1.34	2.15	2.91	3.53	3.63	
		Ratio of specific activities	51	50	46	46	47	39	47	—	41	35	56	69	
		Plasma insulin concentration (μU/ml)	59	55	90	89	77	44	17	16	10	10	8	7	
9	57	Plasma FFA concentration (μmoles/ml)		0.079	0.065	0.096	0.093	0.086	0.085	0.091	0.084		0.375		0.779
		Plasma FFA net transport (μmoles/min)		183	162	170	186	162	125	110	99		264		511
		Plasma FFA (fractional) turnover rate (min^{-1})		0.86	0.92	0.66	0.74	0.70	0.56	0.45	0.44		0.26		0.25
		VLDL TGFA concentration (μmoles/ml)		3.28	3.19	3.13	3.53	3.44	3.50	4.09	4.22		4.69		0.902
		Ratio of specific activities		12	11	12	13	13	12	14	15		51		95
		Plasma insulin concentration (μU/ml)		38	46	40	41	16	17	14	14		15		16
10	105	Plasma FFA concentration (μmoles/ml)	0.127	0.112	0.119	0.124	0.123	0.140	0.293	0.280	0.453	0.446	0.566	0.875	0.636
		Plasma FFA net transport (μmoles/min)	170	165	156	159	163	170	295	260	358	339	418	562	526
		Plasma FFA (fractional) turnover rate (min^{-1})	0.42	0.46	0.41	0.40	0.41	0.38	0.31	0.29	0.25	0.24	0.23	0.20	0.25
		VLDL TGFA concentration (μmoles/ml)	12.03	13.06	14.53	13.09	13.59	11.25	14.50	16.25	18.19	19.84	19.38	17.50	12.54
		Ratio of specific activities	6	6	6	6	8	11	14	17	24	24	32	46	22
		Plasma insulin concentration (μU/ml)	207	243	194	221	214	50	28	35	32	35	29	25	29
11	128	Plasma FFA concentration (μmoles/ml)	0.130	0.119	0.115	0.132	0.139	0.512	0.802	0.595	0.840	0.746	0.796	0.860	0.602
		Plasma FFA net transport (μmoles/min)	264	251	223	261	291	820	853	664	836	798	887	935	650
		Plasma FFA (fractional) turnover rate (min^{-1})	0.63	0.66	0.61	0.62	0.65	0.50	0.33	0.35	0.31	0.33	0.35	0.34	0.34
		VLDL TGFA concentration (μmoles/ml)	6.50	6.97	6.41	6.03	6.19	6.09	6.09	6.72	7.28	8.22	6.66	5.25	4.88
		Ratio of specific activities	11	10	10	11	13	37	37	30	41	42	50	55	26
		Plasma insulin concentration (μU/ml)	165	163	102	205	214	34	36	33	25	27	33	25	24

[a] This ratio, (VLDL TGFA/plasma FFA) × 100, provides an index of the percentage of VLDL TGFA derived from plasma FFA (see text).

Whenever subjects participated more than once, consecutive studies were carried out at least 5 days apart. No subject received more than a total of 150 μCi of ^{3}H or 50 μCi of ^{14}C.

Analytical techniques. Blood samples were collected without tourniquet into chilled heparinized tubes and kept on ice for no more than 60 min before the plasma was separated at 4°C. An aliquot of the extracted lipids (equivalent to those contained in 1.5 ml of plasma) was separated by thin-layer chromatography, using hexane–diethyl ether–methanol–acetic acid 180:40:6:4 as solvent. The concentration of the isolated FFA was determined by the colorimetric method of Duncombe (8). Because the plasma FFA concentrations were very low during glucose consumption, two-thirds of the isolated FFA, equivalent to 1 ml rather than the recommended 0.5 ml of plasma, was used for mass determination in such studies. An aliquot of the isolated FFA was also assayed for radioactivity using 0.3% 2,5-diphenyloxazole (PPO) in toluene as scintillator in a Packard Tri-Carb liquid scintillation counter. Quenching was minimal. Although these determinations permitted an accurate calculation of the plasma FFA specific activity, it was found that the recovery of radioactivity in FFA after chromatography varied from about 80% when plasma concentrations were very low to greater than 90% when concentrations were in the normal range. Consequently, to obtain the true plasma FFA concentration it was necessary to correct for the FFA recovery in every sample as follows. To a separate aliquot of the lipids contained in the heptane phase after the initial extraction (9), 0.5 μmole of carrier palmitic acid was added. The neutral and acidic lipids were then separated by the method of Borgström (10), with a consistent recovery of total radioactivity in excess of 96%. More than 97% of the radioactivity in acidic lipids was found to be in FFA even after 30-hr infusions of radiopalmitate. Consequently, the measurement of acidic lipid radioactivity permitted calculation of the recovery of FFA after chromatography in each sample, and the appropriate correction factor could be applied to obtain the true plasma concentration.[1]

VLDL were isolated by ultracentrifugation (11) and extracted with Dole's solution (9). Radioactivity was determined in an aliquot of the VLDL lipids as above without further separation since it was found that more than 95% of the radioactivity was in the triglyceride fraction, even after the 30-hr infusions. Triglyceride concentration was determined in a Technicon Auto-Analyzer, using pure triolein as a reference standard. Plasma insulin was also measured (12).

Plasma volume (ml) was estimated from the formula: body surface area (m^2) $\times$ 1534 (Ref. 13).

Calculations

Net transport of plasma FFA. Once the plasma FFA has reached a constant specific radioactivity during a continuous infusion of labeled palmitic acid, the net transport of plasma FFA in μmoles/min can be calculated from the ratio

$$\frac{\text{infusion rate (dpm/min)}}{\text{plasma FFA specific activity (dpm/}\mu\text{mole)}}$$

(Fractional) turnover rate of plasma FFA. This represents the fraction of the plasma FFA pool cleared per unit time. It can be calculated in min^{-1} from the ratio

$$\frac{\text{plasma FFA net transport (}\mu\text{moles/min)}}{\text{plasma FFA pool size (}\mu\text{moles)}}$$

In experiment 1, despite the hourly glucose drinks, the FFA concentrations and specific activities were steady throughout the periods of measurement. "Steady state" conditions did not prevail in the studies that included the transition from absorptive to postabsorptive periods (experiment 2). However, in the presence of a slowly changing state, the use of the constant infusion technique, coupled with frequent sampling, was thought to be able to provide a reasonable approximation of prevailing FFA net transport.

Estimate of proportion of VLDL TGFA derived from plasma FFA. Specific activities of FFA and VLDL TGFA were expressed as dpm/μmole after correcting for efficiency of counting. In the studies carried out after overnight fasting and during the last 8 hr of glucose consumption, the priming injection and the constant infusion of labeled palmitic acid that followed ensured that specific activity of VLDL TGFA reached a constant level after 2–5 hr, with less than 10% variation during the subsequent 4–7 hr. Once a constant VLDL TGFA specific activity was achieved, the ratio of the specific activities, VLDL TGFA/plasma FFA, gave an estimate of the contribution of plasma FFA to TGFA[2] (7), bearing in mind that forearm venous FFA specific activity is not necessarily equal to that of FFA in the hepatic circulation (14). The assumptions made in this approach have

[1] We had previously found that, during glucose consumption when FFA concentrations are very low, the values obtained in whole plasma as measured by the method of Dole and Meinertz (29) were 0.08–0.14 μmole/ml higher using a single wash and 0.04–0.05 μmole/ml higher with a double wash than the values obtained by the method described above. These discrepancies can probably be ascribed to contamination by lactate, pyruvate, and acidic phospholipids that can be corrected only partly with a double wash (29).

[2] It has been shown that the fractions of palmitate in plasma FFA and TGFA increase by approximately similar proportions in subjects consuming high sugar diets (30), making labeled palmitate a valid marker during both fasting and sustained glucose consumption.

been presented in detail elsewhere (7) and are discussed later. We have calculated this ratio in the relatively "steady state" conditions following an overnight fast (subjects 9–11, Table 2) and during the last 3 hr of sustained glucose consumption when FFA and VLDL TGFA concentrations and specific activities varied little (all subjects, Table 2). We have also made less reliable estimates in the non-steady state studies spanning the transition from glucose consumption to fasting, bearing in mind the delay that must occur before changes in the specific activity of FFA will be reflected in the VLDL TGFA specific activity. Consequently, conclusions should be drawn from progressive changes in the ratio rather than from individual values.

RESULTS

Plasma FFA kinetics in relation to caloric intake

Table 1 presents the values for concentration and net transport of plasma FFA after an overnight fast and during sustained glucose consumption at various caloric intakes. The plasma FFA concentrations represent the means of at least four samples.

Both concentration and net transport of plasma FFA were significantly lower during glucose consumption at all caloric levels than in the fasted state ($P < 0.001$ for each comparison). When the intake of glucose was 50% isocaloric, the plasma FFA concentration was significantly higher than during the higher caloric intakes ($P < 0.05$), but FFA concentrations were not significantly different at 100% and 130% of isocaloric requirements. There was no significant difference in the net transport of plasma FFA between any of the three glucose diets. In the five hypocaloric studies, the (fractional) turnover rate was 0.35 min^{-1} ± 0.01 SEM. This was not significantly different from that found in the overnight fasted subjects (0.31 min^{-1} ± 0.02 SEM), but was significantly lower than that found in subjects with isocaloric glucose (0.60 min^{-1} ± 0.01 SEM [$P < 0.001$]). The (fractional) turnover rates in subjects with these higher caloric intakes were significantly greater than when the subjects were fasted overnight ($P < 0.001$).

Plasma FFA as precursors of plasma TGFA

Table 2 shows the plasma FFA kinetics data and the relative incorporation of FFA into VLDL TGFA during the last 3 hr of 36 hr of continual glucose intake (in isocaloric amounts) and during the subsequent 20–24 hr of fasting. The data obtained in subjects 9, 10, and 11 after overnight fasts (after habitual diets) are shown for comparison. Subjects 7, 8, and 9 were healthy, lean, young males, and subjects 10 and 11 were obese, hypertriglyceridemic, but otherwise healthy, males.

In all subjects, while glucose was being consumed the plasma FFA concentration and net transport were markedly suppressed, and the (fractional) turnover rate was raised. In two of the three lean subjects, 8 and 9, the plasma FFA concentration showed no tendency to increase until after 12 hr of fasting, whereas in the obese men, 10 and 11, this occurred by the sixth hour. Similarly, the net transport of plasma FFA remained suppressed in all three lean subjects for at least 12 hr after stopping glucose and in fact fell, rather than rose, in subjects 8 and 9; even after 20 hr it was only of the order found during glucose consumption. By contrast, net FFA transport rose rapidly in both obese subjects within 3–6 hr of fasting. In all subjects the (fractional) turnover rate of plasma FFA began to fall after 3–9 hr of fasting, irrespective of whether or not the FFA concentration had changed.

In all subjects the VLDL TGFA concentration was relatively stable for the first 6 hr after glucose intake had ceased, and it then began to rise, reaching a peak after 12–16 hr in subjects 7, 10, and 11. In subjects 8 and 9 the concentrations were apparently still increasing after 20–24 hr of fasting. Although changes in TGFA and FFA concentration and in FFA net transport were all in the same direction, these changes did not appear to be closely interrelated. Thus, the increase in VLDL TGFA concentration preceded the increase in plasma FFA concentration in subjects 8 and 9, while in subject 11 the TGFA concentration failed to rise convincingly despite very large increases in FFA concentration and net transport.

The ratio of specific activities, VLDL TGFA/plasma FFA, had reached constant values in all subjects during the last 3 hr of glucose consumption and was less than 13% in all but subject 8, in whom it was around 50%. This ratio began to increase after 3 to 20 hr of fasting; the highest value reached was 69% in subject 8 after 24 hr of fasting. In subject 9 the ratio had been 95% after a 16-hr overnight fast following his habitual diet, but had reached only 51% after a 20-hr fast following several days of a carbohydrate-rich diet. Interestingly and unexpectedly, in the two obese subjects the ratios after an overnight fast following a habitual diet were only 22 and 26%, respectively. Yet 12 hr after stopping the high glucose intake these ratios had already exceeded these values, and by 24 hr after glucose they had achieved values of 46 and 55%, respectively. In all five subjects this ratio tended to increase with time during the period of fasting after glucose consumption, and while there was no apparent relationship to the changes in the concentration of VLDL TGFA, it showed the same trend as was observed with the net transport of plasma FFA. When values during the 20–24 hr after glucose were expressed in terms of percentage change from those during glucose

consumption, there was a positive and significant correlation between the net transport of plasma FFA and the ratio of specific activities ($r = +0.819$, $P < 0.001$, $y = 59.2 + 1.50x$).

In all subjects plasma insulin levels fell rapidly when glucose intake ceased. In the two obese subjects, 10 and 11, the insulin responses to glucose as well as the subsequent fasting values were higher than in the lean subjects.

DISCUSSION

In man, the suppression of plasma FFA concentration by the acute ingestion of glucose may be achieved solely by a suppression of net inflow transport from adipose tissue (3), although it has been reported that clearance may also be enhanced (5). Employing multicompartmental analysis, Waterhouse, Baker, and Rostami (3) concluded that in both the fasting and glucose-fed states the irreversible disposal rate was directly proportional to the plasma FFA pool size. Similar conclusions have been drawn from studies in rats (4) and dogs (1). Fredrickson and Gordon (5) calculated the FFA (fractional) turnover rate from the initial, single exponential decay of radioactivity following a pulse injection of labeled FFA and found that during glucose consumption the (fractional) turnover rate was increased. These results, however, do not necessarily conflict with those of Waterhouse, et al. (3) because the initial decline in plasma FFA specific radioactivity is influenced by both the reversible and the irreversible disposal of plasma FFA.

In contrast to these studies describing the effects of acute glucose ingestion, we have examined the consequences of more prolonged glucose consumption on plasma FFA kinetics. When the intake was hypocaloric we found a marked fall in the net transport of plasma FFA, although clearance (fractional turnover rate) was not significantly greater than that found after overnight fasts. An increase to isocaloric or hypercaloric glucose consumption failed to further reduce net transport, but resulted in significant enhancement of clearance. When isocaloric glucose ingestion ceased, a reduction in clearance was apparent several hours before the restoration of net transport in all but one of the subjects, who was obese.

When insulin is infused in human subjects, the suppression of plasma FFA concentration is accounted for solely by a reduction in net inflow transport from adipose tissue with no change in clearance (1, 15, 16). In vitro studies of isolated fat cells have shown that insulin inhibits the hydrolysis of triglyceride (17, 18) while the presence of glucose and insulin greatly enhances the esterification of FFA in adipose tissue (19). Although we have found apparently maximal suppression of net inflow transport of FFA from adipose tissue during hypocaloric glucose ingestion, it was only at eucaloric or hypercaloric intakes that clearance from the plasma was enhanced, possibly due to increased esterification in adipose tissue. Under such conditions it is perhaps surprising that any FFA at all is released from adipose tissue. It is tempting to speculate that, during high intakes of glucose, plasma FFA may be derived from sources other than adipose tissue, possibly from the hydrolysis of plasma triglycerides. It has been shown that lipoprotein lipase activity may be stimulated by insulin (20, 21).

In five subjects (Table 2) the ratios of equilibrated specific activities, VLDL TGFA/plasma FFA, have been determined during sustained glucose consumption and during a subsequent 20–24-hr period of fasting and, in three of the subjects, also in the postabsorptive state after habitual diets. On the assumption that the plasma FFA extracted by the liver has a specific activity that does not differ appreciably from that found in peripheral venous plasma, it is suggested that this ratio provides an estimate of the proportion of VLDL TGFA derived from plasma FFA. During constant infusions of labeled palmitic acid, the FFA specific activity in the hepatic venous plasma is lower than that in arterial plasma by up to 25%, presumably because of dilution by nonlabeled FFA released from splanchnic fat stores (14). In the studies described here, plasma samples were collected from a peripheral superficial vein in which the FFA specific activity would have been lower than that in arterial plasma and hence closer to that in the hepatic circulation. It should be noted, however, that we are assuming that the discrepancy between hepatic venous and peripheral venous FFA specific activity is no greater during sustained glucose consumption than it is in the fasted state. The following discussion should be considered in the light of these assumptions.

When subject 9 was studied in the postabsorptive state after his habitual diet, plasma FFA was virtually the sole precursor of VLDL TGFA (Table 2). On the basis of other studies in normal subjects (7) this would have also been likely in subjects 7 and 8. Under similar conditions the two obese, hypertriglyceridemic subjects, 10 and 11, derived only about one-fourth of VLDL TGFA from circulating FFA. We have previously found such results in subjects with alcoholic fatty liver and in those treated with clofibrate (7), and we have since observed this in additional male subjects in whom obesity was the only abnormality.[3] Continuing lipogenesis from glucose, even after a 16-hr fast, or the presence of fatty liver, which has been reported in obesity (22), may account for these findings.

During glucose consumption, plasma FFA accounted for only about 10% of VLDL TGFA in four of the five subjects. These values are lower than we have reported

[3] Barter, P. J., and P. J. Nestel. Unpublished data.

before (7) probably because the methods previously used may have overestimated the plasma FFA concentration and consequently underestimated the FFA specific activity during glucose consumption (see Methods section). While the contribution of plasma FFA to VLDL TGFA increased when glucose consumption ceased, it could still account for only one-half to two-thirds 20–24 hr later, although this represents a minimum estimate as described under Methods. In contrast to the lean subjects, the obese subjects, 10 and 11, derived a greater fraction of VLDL TGFA from plasma FFA when fasted after glucose than after habitual diets. While our results provide no explanation for this, it is possible that the period of glucose consumption resulted in a diminution of fat stores in the liver.

The interrelationships among plasma FFA, plasma TGFA, and dietary carbohydrates are complex. In fasted humans there is a significant correlation between the hepatic uptake of plasma FFA and the secretion rate of TGFA (14). The acute ingestion of glucose not only reduces FFA concentrations, but in man (23) and in the rat (24) the plasma TGFA concentration may also be lowered. The fall in TGFA concentration after glucose consumption in previously fasted rats is a consequence of the diminished availability of plasma FFA for TGFA production (24). In man, the intermittent consumption of sucrose is accompanied by a fall in TGFA levels during the absorptive period with a postabsorptive rise (25). Although these changes in TGFA concentration were significantly and inversely correlated with changes in insulin levels, they were less clearly related to changes in plasma FFA (25). On the other hand, a significant correlation has been reported between changes in FFA net transport and in the rate of incorporation of FFA into plasma TGFA during the infusion of physiological amounts of insulin in man (15). During more prolonged glucose consumption in man, when TGFA levels have risen and plasma FFA are no longer the sole precursor of plasma TGFA (7), a relationship between plasma FFA and plasma TGFA may be less evident. In fact, during the period of fasting after prolonged glucose consumption we have been unable to demonstrate a relationship between changes in VLDL TGFA concentration and the net transport or concentration of plasma FFA. We have found, however, that the changing percentage of VLDL TGFA derived from circulating FFA during this period was positively and significantly correlated with changes in plasma FFA net transport, although a decreasing rate of hepatic lipogenesis with fasting may also have contributed. In previous studies in which FFA kinetics were repeatedly measured on consecutive mornings after overnight fasts in subjects eating carbohydrate-rich diets, the FFA net transport was significantly correlated with FFA incorporation into VLDL TGFA (26).

Although FFA net transport was suppressed during glucose ingestion in both lean and obese subjects, the restoration of adipose tissue lipolysis after glucose occurred much earlier in the obese than in the lean subjects despite higher postabsorptive insulin levels in the obese individuals. These observations support the concept of "insulin resistance" in obesity (27, 28).

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