Impairment of glucose disposal by infusion of triglycerides in humans: role of glycemia

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FELLEY, C. P., E. M. FELLEY, G. D. VAN MELLE, P. FRASCAROLO, E. JÉQUIER, AND J.-P. FELBER. *Impairment of glucose disposal by infusion of triglycerides in humans: role of glycemia.* Am. J. Physiol. 256 (Endocrinol. Metab. 19): E747–E752, 1989.—The present study was designed to assess the role of hyperglycemia (150 mg/dl) vs. euglycemia (90 mg/dl) on glucose metabolism in vivo during the infusion of a triglyceride emulsion (Intralipid). Seven young healthy volunteers were studied on four occasions using the hyperinsulinemic clamp technique, twice during euglycemia and twice during hyperglycemia, without or with Intralipid. Glucose oxidation (O) was calculated from continuous respiratory exchange measurements, and glucose storage (S) was obtained as the difference between total glucose disposal (M) and O. Two-way analysis of variance with interaction term demonstrated *1*) a significant increase for M with hyperglycemia and a decrease with Intralipid; no interaction, and *2*) in euglycemia, O/M and S/M occurred in one-to-one ratios; on the other hand, during 150-mg/dl hyperglycemia, the ratio dropped roughly to 1:2. Intralipid had no effect on the ratio, and no interaction could be observed. These results suggest the existence of physiological regulatory mechanisms by which *1*) the rise in plasma free fatty acid inhibits both oxidative and nonoxidative glucose disposal, and *2*) the rise in glycemia stimulates predominantly nonoxidative glucose disposal.

glucose clamp technique; indirect calorimetry; oxidative glucose disposal; nonoxidative glucose disposal

IMPAIRED GLUCOSE TOLERANCE and type II diabetes are frequently associated with obesity (18), and obesity is considered a risk factor for diabetes. Longitudinal studies have shown an increased frequency of impaired glucose tolerance in obesity, especially when the body mass index (BMI) is >27 kg/m^2 (24, 25). The Bedford study demonstrated that a prolonged period of obesity is required for the development of type II diabetes (21).

We have recently shown that glucose storage under experimental conditions of euglycemic hyperinsulinemia, when measured as nonoxidative glucose disposal, is decreased in nondiabetic obese subjects and is markedly lowered in obese patients with impaired glucose tolerance (8). However, glucose storage is unaltered in similar groups of obese subjects during a 100-g oral glucose tolerance test (OGTT) (8). This suggests that the impairment in glucose storage observed during the euglycemic hyperinsulinemic clamp is compensated for by the rise in glycemia and insulinemia occurring in the OGTT and that, in nondiabetic obese subjects, hyperglycemia and hyperinsulinemia compensate for the defect in nonoxidative glucose disposal.

Obesity is characterized by an increase in fat mass. High levels of free fatty acids (FFA) are frequently observed in fasting obese subjects (5). Infusions of triglyceride emulsions induce an increase in plasma FFA levels and reduce glucose tolerance in normal individuals (9, 12). In a previous work, Thiebaud et al. (28) have shown that triglyceride infusion during a euglycemic hyperinsulinemic clamp decreases both glucose storage and oxidation; however, a similar lipid infusion induces no change in glucose storage during the hyperglycemia accompanying OGTT in control subjects (27). As in the obese subjects, the inhibition of glucose storage due to elevated plasma FFA levels only becomes evident during the euglycemic hyperinsulinemic clamp, but it is apparently compensated for by the hyperglycemia and hyperinsulinemia, which accompany the OGTT.

However, glucose tolerance tests are difficult to interpret because of the complexity of the interactions between plasma glucose and insulin concentrations and the variability in the intestinal absorption of glucose. This study was therefore designed to assay the effect of hyperglycemia by itself on the lipid-induced inhibition of glucose storage during steady-state conditions of glycemia and insulinemia.

METHODS

Study Subjects

Seven healthy volunteers, one female and six males, ranging in age from 21 to 34 yr [25 ± 2 (SE)] were studied. Their ideal body weight (based on the Metropolitan Life Insurance Tables, 1979) ranged from 93 to 106% (102.0 ± 1.6%). Their BMI ranged from 19.8 to 24.1 kg/m^2 (22.9 ± 0.5 kg/m^2).

No subject had a family history of diabetes mellitus, and none was taking any medication. They were consuming a diet containing at least 250–300 g carbohydrate/day for 3 days before each study. No subject engaged in intense physical training during the 2 days preceding the test. Before their participation, the nature, purpose, and

risks of the study were explained to all subjects, and their voluntary consent was obtained. The experimental protocol was approved by the human investigation committee of the Department of Medicine at the University Hospital of Lausanne, Switzerland.

Experimental Protocol

All studies (Fig. 1) were performed in the recumbent position after a 10- to 12-h overnight fast. The glucose clamp was performed by a modification of the method of DeFronzo et al. (11). An intravenous catheter (Venflon) was placed in an antecubital vein for infusion of insulin, somatostatin, and glucose. When a triglyceride emulsion (Intralipid, Vitrum, Stockholm, Sweden) was infused, a second catheter was placed in a homolateral antecubital vein. A third catheter was inserted into a controlateral wrist vein for blood withdrawal and kept patent with an infusion of isotonic saline. The hand was kept in a heated box at 70°C to achieve arterialization of the venous blood. Each subject was studied on four occasions with an interval of at least 1 wk between each test, and the order of the studies was randomized.

Euglycemia in the absence of Intralipid (EU LIP−). After 45 min of base-line measurements, somatostatin, (Stilamin, Serono, Coinsins, Switzerland) was infused at a continuous rate (8 μg/min) for the next 135 min of the experiment. After 15 min of somatostatin infusion, a priming dose of purified pork insulin (Actrapid MC, Novo, Copenhagen, Denmark) was given in a decreasing manner (4) over a period of 10 min and then infused at a continuous rate of 1 $mU \cdot kg^{-1} \cdot min^{-1}$ for the remainder of the test. Concomitantly, a variable 20% glucose infusion was also started to maintain the plasma glucose concentration at 90 mg/dl (5.0 mmol/l) for the entire 120 min of hyperinsulinemia. Samples of plasma glucose concentration were obtained every 5 min throughout the test.

Hyperglycemia in the absence of Intralipid (HYPER LIP−). This uses the same protocol as EU LIP−, but a priming dose (4) of 20% glucose solution was infused and then varied to raise and maintain the glycemia at 150 mg/dl (8.3 mmol/l).

Euglycemia in the presence of Intralipid (EU LIP+). After 45 min of base-line measurements, a 20% Intralipid infusion (a neutral fat emulsion) was administered at 0.5 ml/min for the first 30 min then at 1.0 ml/min for the next 3 h of the experiment. After a 90-min equilibration period with the Intralipid infusion, the glucose clamp was initiated as described in protocol EU LIP−. Fifteen minutes before starting the glucose clamp, somatostatin was infused as described in protocol EU LIP−.

Hyperglycemia in the presence of Intralipid (HYPER LIP+). This uses the same protocol as EU LIP+, but a priming dose of 20% glucose solution was infused and then varied to raise and maintain the glycemia at 150 mg/dl (8.3 mmol/l), as described in protocol HYPER LIP−.

In all four protocols, somatostatin was infused to block the endogenous insulin response to hyperglycemia. All studies were performed in combination with continuous indirect calorimetry. At the end of each test, urine was collected for determination of nitrogen; its glucose content was also measured to ensure that there was no significant glucosuria. Hepatic glucose production was not measured in the present study and was assumed to be totally suppressed during glucose-insulin and somatostatin infusion (11).

Indirect Calorimetry

During the 45-min control period and throughout the equilibration period and the glucose clamp studies, the O_2 uptake at standard temperature and pressure, dry and CO_2 production were measured by an open-circuit technique consisting of a clear plastic hood placed over the subject's head, a pump, a flowmeter, a paramagnetic O_2 analyzer (Magnos 4G, Hartmann & Braun, Frankfurt, FRG) and an infrared CO_2 analyzer (Uras 3G, Hartmann & Braun). The analyzers and flowmeter outputs were connected to a desktop computer (Hewlett Packard, 9835 A), which recorded continuous integrated calorimetric measurements over 5-min intervals.

Calculations

The total glucose disposal rate was measured as the glucose infusion rate (in $mg \cdot kg^{-1} \cdot min^{-1}$) during the sec-

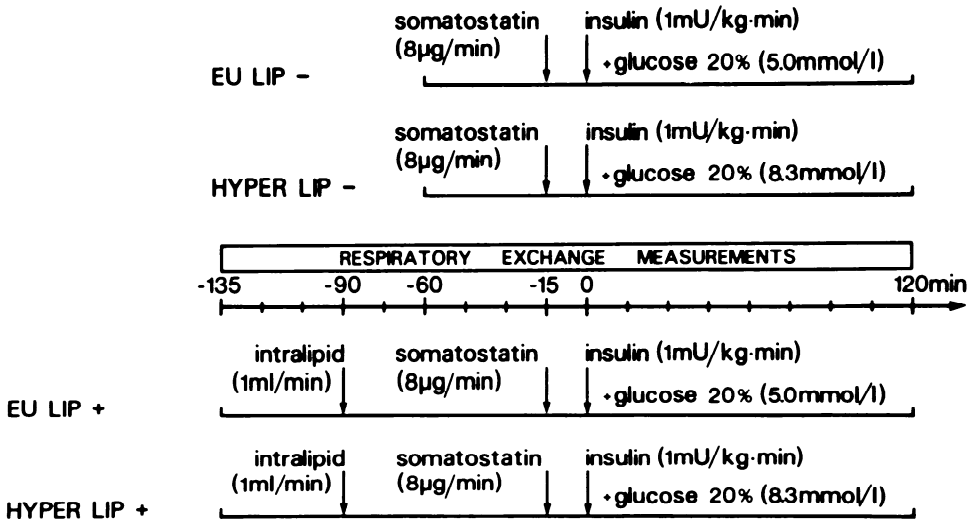

FIG. 1. Protocol of the study.

ond hour of the glucose clamp (60–120 min). Substrate oxidation rates were calculated as previously described (7, 17). The nonprotein respiratory quotient (NPRQ) was calculated from calorimetric values and urinary nitrogen. The rate of carbohydrate oxidation was obtained using the table of Lusk (23), where a NPRQ of 0.707 represents 100% fat oxidation and a NPRQ of 1.00 represents 100% carbohydrate oxidation. For each gram of glucose or fat oxidized, 746 and 2,019 ml oxygen were consumed, respectively. The insulin-stimulated carbohydrate oxidation rates were calculated from the indirect calorimetric data by averaging the values for the last 60 min of the glucose clamp. The carbohydrate storage rate was estimated by subtracting the carbohydrate oxidation rate from the total glucose disposal rate during the clamp. When the NPRQ was >1.00, the calculated lipid oxidation had a negative value equivalent to net lipid synthesis (1). When this occurred, the amount of glucose converted into lipid was subtracted from the glucose oxidation rate, and storage was then calculated as described above. Corrections were made for changes in the urea pool size induced by hyperinsulinemia (17).

Analytical Methods

Plasma glucose concentration was determined in duplicate by the glucose oxidase method on a Beckman glucose analyzer II (Beckman Instrument, Fullerton, CA). Plasma immunoreactive insulin (IRI) was determined by radioimmunoassay (RIA) as described by Herbert et al. (15). Plasma FFA were extracted using the method of Dole and Meinertz (6) and determined according to the method of Heindel et al. (14). C-peptide was determined by RIA (kit, Mallinckrodt Diagnostica, Dietzenbach, FRG). Blood lactate was determined by an enzymatic test with lactate-dehydro-genase and glutamate-pyruvate-transaminase (Lactat Monotest, Boehringer & Soehne, Mannheim, FRG) carried out with a Cobas-Biocentrifuge microanalyzer (Hoffmann-La Roche, Basel, Switzerland). Urinary nitrogen was measured by the method of Kjeldahl (13). All laboratory values were computed as one or the mean of two basal plasma concentrations and the mean of the concentration between 60 and 120 min of insulin infusion.

Statistical Methods

All statistical calculations were performed using two-way analysis of variance (31). The homogeneity of the variance in the four studies were tested by a Bartlett test (30). When the variance was not equal in the four tests, a logarithmic transformation was used.

RESULTS

Plasma Glucose, IRI, C-Peptide, FFA, and Blood Lactate During Basal and Clamp Studies (Table 1)

In the two euglycemic and in the two hyperglycemic protocols, plasma glucose concentrations were ~90 and 150 mg/dl, respectively. The target plasma glucose levels were attained in all studies with a coefficient of variation <5% for each of the experiments performed. IRI was maintained stable and at a similar level during all four studies. It should be noted that Intralipid infusion maintained the postabsorptive plasma FFA levels during the glucose-clamp studies. The blood lactate concentrations are analyzed in Table 2. Endogenous insulin production measured as C-peptide was inhibited in all four protocols.

TABLE 1. *Changes in plasma glucose, IRI, FFA, and lactate concentrations during basal and glucose clamp studies*

	Basal	EU LIP−	EU LIP+	HYPER LIP−	HYPER LIP+
n	28	7	7	7	7
Glycemia, mg/dl	93±1	91±2	90±1	149±1	152±2
IRI, μU/ml	12±1	91±4	90±6	88±4	88±4
C-peptide, ng/ml	1.53±0.08	0.25±0.04	0.20±0.02	0.26±0.03	0.22±0.04
FFA, μmol/l	393±25	176±17	422±31	164±15	379±39
Lactate, μmol/l	651±30	738±31	680±34	978±54	918±79

Values are means ± SE of the concentrations between 60 and 120 min of insulin infusion. EU LIP− and EU LIP+, euglycemic clamp in absence (LIP−) or the presence (LIP+) of Intralipid. HYPER LIP− and HYPER LIP+, hyperglycemic clamp in absence (LIP−) or presence (LIP+) of Intralipid; IRI, immunoreactive insulin; FFA, free fatty acid.

TABLE 2. *Free fatty acid levels effect and glycemia effect on lactate*

	Lactate Concentration, μmol/l		
	LIP−	LIP+	Average
EU	734	674	703
		$P = 0.0002$ (glycemia effect)	
HYPER	968	898	932
	$P = 0.22$ (FFA effect)		

EU, euglycemic clamp in absence (LIP−) or presence (LIP+) of Intralipid; HYPER, hyperglycemic clamp in absence (LIP−) or presence (LIP+) of Intralipid.

Glucose Disposal (M)

Variations in the observed values of insulin-mediated M, oxidative glucose disposal (O), and glucose storage (S) are presented in Fig. 2. In the conditions of euglycemia in the absence and in the presence of Intralipid, M was 7.61 ± 0.54 and 5.85 ± 0.45 $mg \cdot kg^{-1} \cdot min^{-1}$, respectively, O was 3.76 ± 0.20 and 2.98 ± 0.15 $mg \cdot kg^{-1} \cdot min^{-1}$, respectively, and S was 3.85 ± 0.49 and 2.87 ± 0.45 $mg \cdot kg^{-1} \cdot min^{-1}$, respectively. In hyperglycemia in the absence and in the presence of Intralipid, the values were, respectively, 11.90 ± 1.45 and 8.41 ± 1.21 $mg \cdot kg^{-1} \cdot min^{-1}$ for M; 4.09 ± 0.21 and 3.50 ± 0.28 $mg \cdot kg^{-1} \cdot min^{-1}$ for O, and 7.81 ± 1.34 and 4.91 ± 0.96 $mg \cdot kg^{-1} \cdot min^{-1}$ for S.

Insulin-mediated M. A Bartlett's test (30) of homogeneity of variance was first performed and gave a chi-square value of 9.85 with three degrees of freedom. Con-

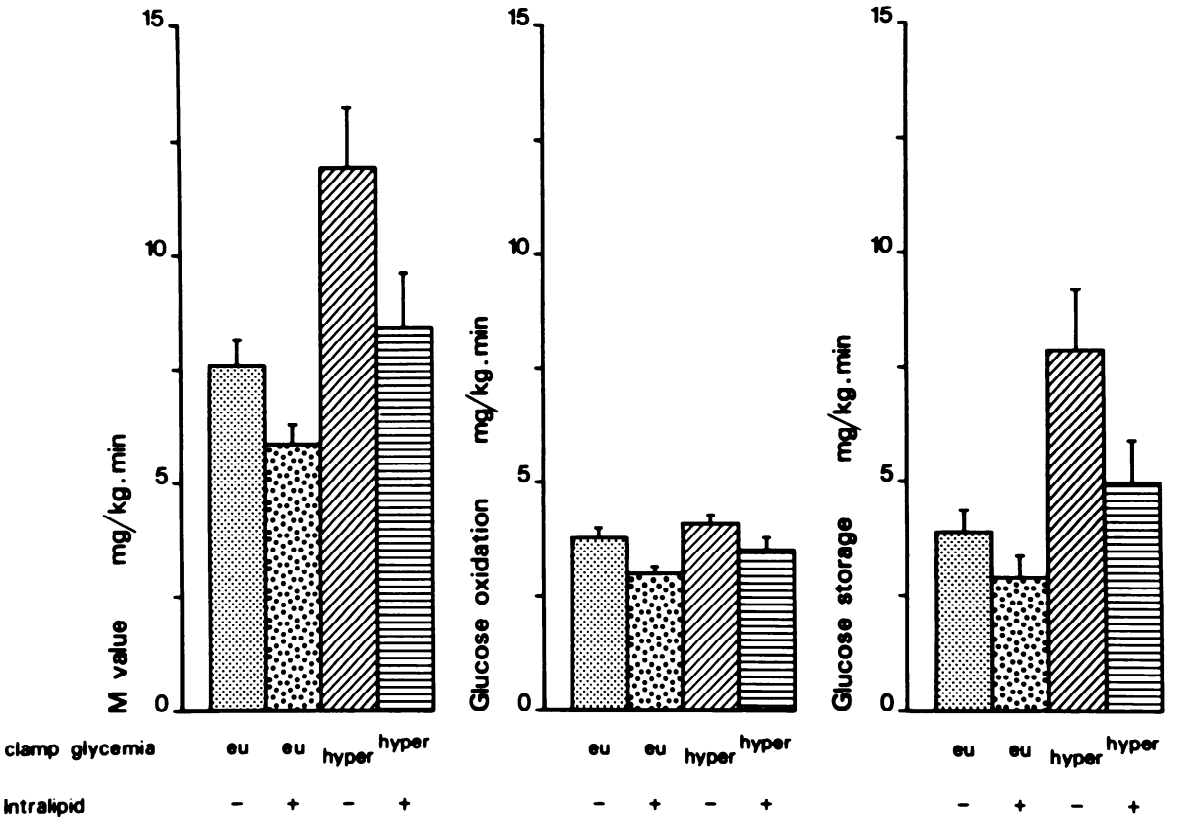

FIG. 2. Variations in insulin-mediated glucose disposal (M), oxidative glucose disposal, and glucose storage during glucose clamp studies, in presence or absence of Intralipid, in euglycemia or hyperglycemia. All data are means ± SE. Overall comparison of 4 means yielded for M: F 3,24 = 7.1, P = 0.001; for glucose oxidation: F 3,24 = 5.4, P = 0.005; for glucose storage: F 3,24 = 5.0, $P < 0.01$.

sequently we transformed our data, and a suitable choice was logarithmic transformation. After that manipulation the chi-square value was 2.29. This transformation implies that we will consider relative changes rather than absolute changes. Therefore, we took the insulin-mediated glucose disposal obtained during the first protocol (EU LIP−) and considered it as 100% of insulin mediation. All other values are expressed as a percentage of it. There was a significant effect of glycemia (F ratio = 12.4; df = 1, 24; P = 0.002) and a significant effect of Intralipid (F = 8.7; df = 1, 24; P = 0.007) on M (Table 3). No interaction between the two treatments (F = 0.2; df = 1, 24; $P > 0.50$) could be detected.

Carbohydrate oxidation and storage vs. M. Similarly, the ratio of O over M (O/M) was analyzed. There was a significant effect of glycemia (F = 8.3; df = 1,24; P = 0.008) on O/M (Table 4). On the other hand, there was no effect of Intralipid (F = 1.7; df = 1,24; P = 0.20) and no interaction between the two treatments (F = 0.8; df = 1, 24; $P > 0.30$). By subtraction, the stored part was obtained and presented in Table 4. Because there was no significant effect of Intralipid, the average values were also presented (recalling that we used a logarithmic scale).

TABLE 3. *Free fatty acid levels effect and glycemia effect on insulin-mediated glucose disposal*

	LIP−	LIP+	
EU	100%	73.1%	P = 0.002 (glycemia effect)
HYPER	145.4%	106.3%	
	P = 0.007 (FFA effect)		

EU, euglycemic clamp in absence (LIP−) or presence (LIP+) of Intralipid; HYPER, hyperglycemic clamp in absence (LIP−) or presence (LIP+) of Intralipid.

Lactate

Here again, the logarithmic transformation was appropriate. In hyperglycemia there was a very significant increase in blood lactate levels (F = 19.7; df = 1, 24; P = 0.0002), but there was no effect of Intralipid (F = 1.6; df = 1, 24; $P > 0.20$) and no interaction between the two treatments (F = 0.007; df = 1, 24; $P > 0.90$) (Table 2).

Because there was no significant effect of Intralipid, the average values were also presented.

DISCUSSION

This investigation was designed to study the effect of hyperglycemia, with or without lipid infusion, on glucose metabolism. Intracellular glucose disposal occurs through both oxidative and nonoxidative mechanisms. By the former pathway, glucose is completely degraded to carbon dioxide and water either via the citric acid cycle or via the pentose shunt. Nonoxidative glucose

TABLE 4. *Free fatty acid levels effect and glycemia effect on breakdown of glucose disposal*

	LIP−	LIP+		Average
Percent oxidative				
EU	49.8%	51.7%		50.7%
			$P = 0.008$ (glycemia effect)	
HYPER	35.6%	43.3%		39.3%
		$P = 0.20$ (FFA effect)		
Percent nonoxidative				
EU	50.2%	48.3%		49.3%
			$P = 0.008$ (glycemia effect)	
HYPER	64.4%	56.7%		60.7%
		$P = 0.20$ (FFA effect)		

EU, euglycemic clamp in absence (LIP−) or presence (LIP+) of Intralipid; HYPER, hyperglycemic clamp in absence (LIP−) or presence (LIP+) of Intralipid.

disposal corresponds to storage as glycogen, anaerobic glycolysis, conversion to fat, or transformation of intermediary products of glucose utilization to amino acids. Quantitatively, glycogen synthesis is the most important pathway.

Our study confirms that the infusion of Intralipid (a triglyceride emulsion) induces a resistance to insulin-mediated glucose disposal in normal volunteers (28). This resistance can be defined as a state in which a normal amount of insulin produces a subnormal biological response (19). Although hyperinsulinemia induced a decrease in plasma FFA levels, infusion of Intralipid maintained plasma FFA concentrations during the glucose clamp at values similar to the basal concentrations. Thus by preventing the fall in FFA from accompanying hyperinsulinemia, it is possible to bring about a significant impairment in insulin-mediated glucose disposal. However, we cannot exclude that it is the metabolic state induced by FFA levels that determines the sensitivity to insulin during the clamp. This impairment in glucose metabolism can be explained in part by the inhibitory effect of sustained lipid oxidation on glucose oxidation, as described by Randle et al. (26). However, the inhibition of glucose storage observed during the experimental rise in plasma FFA (28) and in obesity (10, 22) appears as a quantitatively more important phenomenon. Its precise biochemical mechanism is not yet elucidated. As in another similar study (16) the insulin-mediated glucose disposal was markedly increased during hyperglycemia. The increased concentrations of glucose (~150 mg/dl) and insulin (~90 μU/ml) employed in this study were chosen because they approximate the physiological levels after oral glucose loading. Furthermore, the use of somatostatin enabled us to study the effect of hyperglycemia per se while maintaining constant IRI levels. In euglycemia, the oxidative and nonoxidative glucose disposal occurred in a one-to-one ratio. On the other hand, during the 150-mg/dl hyperglycemia the oxidative and nonoxidative disposal ratio dropped roughly to 1:2. As demonstrated by Thiebaud et al. (29) glucose oxidation saturates under conditions in which storage can still increase, and these data demonstrate that, at physiological insulinemia, hyperglycemia is a potent stimulus of nonoxidative glucose disposal. This explains the fall in the ratio of oxidative over nonoxidative glucose disposal. This potent effect of hyperglycemia confirms the initial hypothesis that an increase in glycemia can compensate for the decrease in glucose storage induced by Intralipid infusion.

Intralipid had no effect on these ratios but nevertheless diminished the insulin-mediated glucose disposal significantly. This shows that Intralipid inhibits both glucose oxidation and glucose storage.

Analysis of variance showed no interaction between the two treatments (Intralipid and hyperglycemia) on insulin-mediated glucose disposal, the part that is oxidized, and the part that is stored. This is very consistent with the hypothesis of two separate metabolic pathways. If the Intralipid infusion as used in the present study can represent a model for the increase in lipid metabolism observed in obesity (11), then this would show that the slight rise in glycemia resulting from the inhibition of glucose disposal would compensate for this inhibition as a positive-feedback mechanism. It would follow that glucose intolerance frequently observed in obesity is not only the result of a resistance to insulin-mediated glucose disposal but also a regulatory mechanism by which glucose storage can still proceed, but at higher glycemia.

Lactate levels were also significantly increased during hyperglycemia. In fact, the variations of lactatemia paralleled those of nonoxidative glucose disposal, which was markedly increased by hyperglycemia, suggesting that lactate may be a good marker of glucose storage. As was shown by Katz and McGarry (20), it now seems that, even in the presence of a glucose load, most liver glycogen arises from C3 compounds, such as lactate. A major question is whether lactate was produced from glucose in extrahepatic organs, such as skeletal muscle (3), or in the liver itself, as suggested by Jackson et al. (16).

Somatostatin was reported to produce a transient fall

in glucose oxidation (2). In the present case this effect would be of no consequence, since somatostatin was used in the four protocols.

In summary, a resistance to insulin-mediated glucose disposal can be induced in normal subjects by maintaining the postabsorptive FFA levels during a glucose clamp. The triglyceride emulsion Intralipid decreased both oxidative and nonoxidative glucose disposal, but it did not modify the oxidative-to-nonoxidative disposal ratio. Conversely, hyperglycemia at physiological insulinemia acted as a potent stimulus on nonoxidative glucose disposal. This study suggests the existence of physiological regulatory mechanisms in which *1*) the rise in plasma FFA inhibits both oxidative and nonoxidative glucose disposal and *2*) the rise in glycemia resulting from the inhibition of glucose disposal stimulates predominantly nonoxidative glucose disposal.

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