Operation of Randle's Cycle in Patients With NIDDM

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It has been suggested that the insulin resistance of non-insulin-dependent diabetes mellitus (NIDDM) may be caused by substrate competition between glucose and free fatty acids (FFAs) (Randle's cycle). We measured substrate oxidation and energy metabolism in 10 nonobese untreated NIDDM patients with fasting glucose levels of 7–8 mM with indirect calorimetry in the basal state and during an isoglycemic-hyperinsulinemic (~100 mU/L) clamp without (control) and with a concomitant infusion (~0.35 mmol/min) of Intralipid, a triglyceride emulsion. In the control study, fasting rates of total glucose turnover ([3-^{3}H]glucose) and glucose and lipid oxidation (9.4 ± 1.4, 7.3 ± 1.3, and 3.0 ± 0.4 μmol · kg^{-1} · min^{-1}, respectively) were comparable with those of nondiabetic individuals. After insulin administration, lipid oxidation was normally suppressed (to 1.3 ± 0.3 μmol · kg^{-1} · min^{-1}, $P < 0.01$), as were the circulating levels of FFA, glycerol, and β-hydroxybutyrate, whereas glucose oxidation doubled (14.1 ± 1.8 μmol · kg^{-1} · min^{-1}, $P < 0.01$). Because glycemia was clamped at 7.5 mM, endogenous glucose production (EGP) was completely suppressed, and total glucose disposal was stimulated (to 25.7 ± 5.2 μmol · kg^{-1} · min^{-1}, $P < 0.01$ vs. baseline), but glucose clearance (3.6 ± 0.8 ml · kg^{-1} · min^{-1}) was 30% reduced compared with normal. With concomitant lipid infusion, FFA, glycerol, and β-hydroxybutyrate all rose during the clamp; correspondingly, lipid oxidation was maintained at fasting rates (3.6 ± 0.2 μmol · kg^{-1} · min^{-1}, $P < 0.01$ vs. control). As a consequence, the insulin-induced increase in glucose oxidation was abolished (7.9 ± 1.3 μmol · kg^{-1} · min^{-1}, $P < 0.01$ vs. control), and total glucose disposal was inhibited (21.8 ± 4.6 μmol · kg^{-1} · min^{-1}, $P < 0.05$ vs. control) by an amount almost equal to the decrement in glucose oxidation. Lipid infusion did not detectably interfere with insulin-induced suppression of EGP. Energy expenditure failed to increase during the control insulin clamp but was significantly stimulated (~10%, $P < 0.01$) by concomitant lipid administration (diet-induced thermogenesis). We conclude that in mildly hyperglycemic, nonobese NIDDM patients, excessive fatty substrate oxidation is unlikely to be responsible for the insulin resistance; increased lipid provision, however, enhances lipid oxidation and energy expenditure and inhibits glucose oxidation and total disposal. Thus, in this type of diabetes, Randle's cycle does not appear to be spontaneously overactive but can be induced acutely, with metabolic and energetic consequences similar to those observed in nondiabetic subjects. *Diabetes* 39:383–89, 1990

Substrate competition is the mechanism by which, in tissues that can use different substrates as oxidative fuel, increased availability of one substrate restrains consumption of the others. Effective competition between glucose and free fatty acids (FFAs) under conditions of insulin stimulation (Randle's cycle) was originally demonstrated in isolated rat hearts and diaphragms by Randle et al. (1) ~25 yr ago. They established the biochemical bases of glucose-FFA competition (2–4) and postulated that enhanced respiration of fatty substrates might be the origin of the insulin insensitivity of diseases such as diabetes mellitus and obesity in humans (1).

Early attempts to prove that substrate competition occurs in vivo in humans were made by Felber and Vannotti (5), who showed that infusion of Intralipid (a triglyceride emulsion) with heparin reduces tolerance to oral glucose in nondiabetic individuals. In subsequent studies with the insulin-clamp technique, lipid infusion was shown to inhibit insulin-mediated glucose disposal during insulin administration under both euglycemic and hyperglycemic conditions (6). Combining the insulin clamp with indirect calorimetry (a

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noninvasive method to measure substrate oxidation in vivo; 7) made it possible to demonstrate that lipid infusion causes increased lipid oxidation, which in turn inhibits glucose oxidation, and hence glucose uptake, in full accord with Randle's postulates (8).

There seems to be little doubt that by use of Intralipid plus heparin infusion as the experimental tool to simulate accelerated lipolysis, insulin-mediated glucose disposal can be acutely inhibited by exogenous lipids in nondiabetic individuals (6,8). The effect is markedly time dependent; i.e., it depends on the sequence of application of lipid and insulin stimulation (9). Whether the same is true in insulin-resistant states is unclear, however. In a group of women with moderate degrees of obesity but normal glucose tolerance, we showed that infusion of Intralipid plus heparin at the same rate and in the same sequence as previously done in nonobese subjects (6) fails to impede insulin-mediated glucose uptake but interferes with the ability of insulin to suppress endogenous glucose production (10). Thus, classic substrate competition is not acutely inducible in obese individuals, but increased availability of fatty substrates stimulates hepatic glucose production, in agreement with in vitro evidence (11–14) and suggestions from previous in vivo work (6).

Non-insulin-dependent diabetes mellitus (NIDDM) is an insulin-resistant state that shares some of the metabolic features of obesity (15). Therefore, it seemed logical to test whether Randle's cycle can be induced in nonobese NIDDM patients. In this study, lipid infusion in the same format used previously was combined with the insulin clamp and indirect calorimetry in a group of insulin-resistant moderately hyperglycemic patients (6).

RESEARCH DESIGN AND METHODS

Ten ambulatory NIDDM patients (1 woman, 9 men) were recruited from the Diabetic Clinic of the Gastroenterology Division. Their age was 54 ± 3 yr (mean ± SE), and their body weight was 78 ± 4 kg, corresponding to a mean ratio of actual to ideal body weight of 1.10 ± 0.05 (Metropolitan Life Insurance tables, 1959; 16). The patients had had diabetes for an average of 9 ± 4 yr, were being treated with oral hypogycemic agents (half of them) or diet, and were taking no other medication at the time of study. Patients were instructed to withhold oral drugs and to eat a weight-maintaining diet containing at least 200 g carbohydrate/day for 2 wk before the study. No subject habitually undertook vigorous physical exercise or suffered from any endocrine disorder other than diabetes. The nature, purpose, and potential risks of the study were carefully explained to all subjects before obtaining their consent to participate.

Experimental protocol. The experiments were carried out after an overnight (12- to 14-h) fast with the subjects lying in a quiet room. Polyethylene cannulas were inserted into an antecubital vein for infusion of test substances and retrogradely into a wrist vein for blood sampling; the latter catheter was kept patent by a slow saline drip while the hand was warmed in a heated box (~70°C) to allow arterialization of venous blood (17).

Insulin sensitivity was assessed with the use of the isoglycemic insulin-clamp technique (i.e., plasma glucose concentration was maintained at whatever level the patient presented with on the morning of the study; 18). Peripheral plasma insulin concentrations were acutely raised and maintained at ~100 mU/L by means of a primed constant infusion of regular insulin (Actrapid, Novo, Copenhagen) administered at a rate of 1 mU · kg^{-1} · min^{-1} for 2 h, whereas plasma glucose was held at the desired level by a variable exogenous glucose infusion.

Endogenous glucose production (EGP) was measured in 8 subjects by tracer dilution (19). [3-^{3}H]glucose (Amersham, Buckinghamshire, UK) was administered as a primed (40-μCi) constant (0.3-μCi/min) infusion, which was begun 3 h before the insulin clamp and continued throughout the study. The larger prime and the longer equilibration time of the tracer were adopted to ensure isotopic equilibrium in the presence of slower glucose clearance rates (19).

Substrate oxidation and energy expenditure were measured in 7 subjects by indirect calorimetry (7). Ninety minutes before the clamp, a transparent plastic ventilated hood was placed over the subject's head and made airtight around the neck. Air flow and O_2 and CO_2 concentrations in the expired and inspired air were measured by a computerized continuous open-circuit system (Metabolic Measurement Cart Horizon apparatus, SensorMedics, Anaheim, CA). Gas-exchange measurements were taken during a 45-min basal period after the subjects had adapted to the hood and stabilized their breathing pattern and were continued throughout the clamp.

Each subject was studied twice, with and without an infusion of 10% Intralipid (Pierrel, Italy; 3 ml/min, corresponding to ~1 mmol/min of FFA equivalents) plus heparin (200-U bolus + 0.4 U · kg^{-1} · min^{-1}), which was started simultaneously with the insulin infusion and continued throughout the clamp. Thus, each subject served as his/her own control. The two experiments were carried out within 2 wk of one another, the order of the lipid and control studies being randomized.

Plasma glucose was measured by the glucose oxidase method on a Beckman analyzer (Fullerton, CA). [3-^{3}H]glucose concentration in plasma samples and in tracer infusates was measured as described previously (10), and blood metabolites were measured by continuous-flow fluorimetry (10). Serum potassium was measured by flame photometry, and nonprotein urinary nitrogen was measured by the Kjeldahl method (20).

Data analysis. Rates of glucose appearance and disappearance were calculated from the isotopic data with the use of a two-compartment model for non-steady-state glucose kinetics (21). This model is roughly equivalent to the monocompartmental model of Steele (22); both have been shown to underestimate glucose appearance during clamp experiments with high rates of glucose flux (23). In our studies, negative rates of EGP were in fact calculated during the 2nd h of the insulin clamp in 10 of 16 cases either with or without concomitant lipid infusion. These values, however, were taken to indicate only that endogenous glucose output was completely suppressed, and whole-body glucose disposal rates were calculated from the infusion rate of exogenous glucose (after correction for changes in glucose levels in a distribution volume of 250 ml/kg; 24). When EGP was a positive number, this was added to the exogenous glucose infusion to calculate whole-body glucose disposal.

Protein oxidation was estimated from the urinary nonprotein excretion rate by multiplying the latter value by 6.25 (7). Changes in body urea pool were calculated by multiplying the measured change in blood urea nitrogen concentration by the distribution volume of urea (600 ml/kg; 25) and were taken into account in the estimation of protein oxidation. Net whole-body rates of carbohydrate and lipid oxidation and energy expenditure were estimated from gas-exchange measurements and protein oxidation by use of equations described in detail and discussed in ref. 26. The terms *carbohydrate oxidation* and *glucose oxidation* are used interchangeably.

Nonoxidative glucose disposal (a collective term encompassing glycogen formation, anaerobic glycolysis, and lipid synthesis from glucose-derived carbons) was computed as the difference between whole-body glucose disposal and total glucose oxidation.

All data are expressed as means ± SE. For any variable, the statistical significance of changes in mean values over time was assessed by one-way analysis of variance (ANOVA) for repeated measures. Differences in mean values between the lipid and the control study were analyzed by Student's paired *t* test.

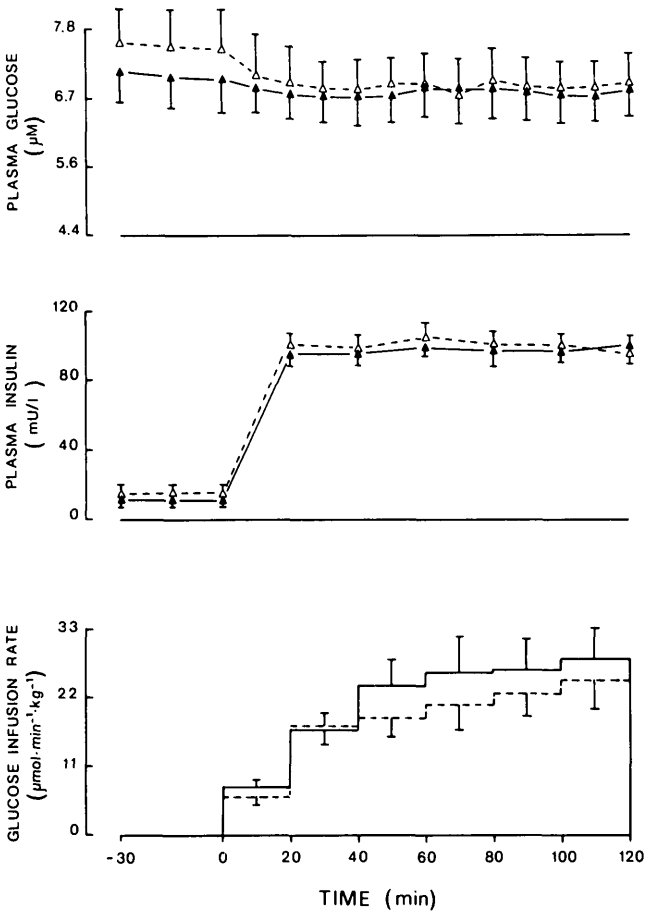

FIG. 1. Plasma glucose and insulin concentrations in basal state and during insulin clamp in 10 nonobese non-insulin-dependent diabetic patients without (*solid lines*) and with (*dashed lines*) concomitant lipid infusion. Exogenous glucose infusion rates required to maintain isoglycemia during control and lipid studies are also shown (*bottom*).

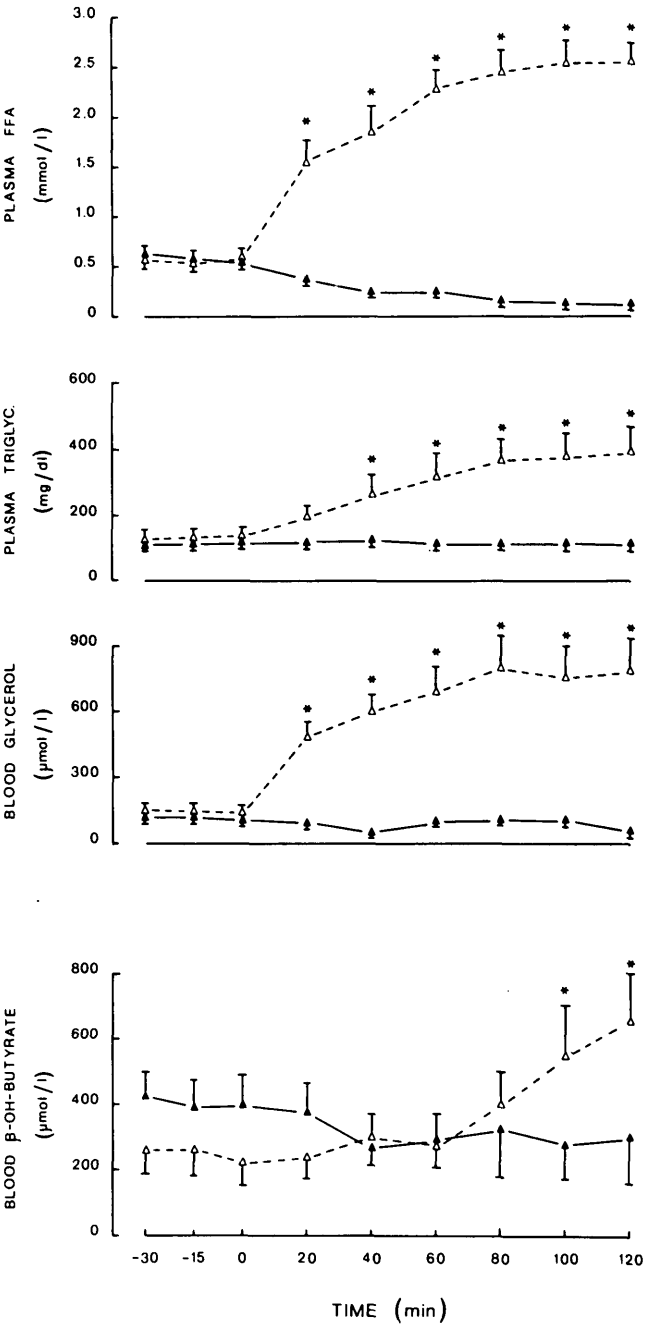

FIG. 2. Plasma concentrations of free fatty acids (FFA) and triglycerides and blood concentrations of glycerol and β-hydroxybutyrate (β-OH-butyrate) in 10 non-insulin-dependent diabetic patients in basal state and during insulin clamp without (▲) or with (△) concomitant lipid infusion. *$P < 0.05$ or less lipid vs. control studies by paired *t* test.

RESULTS

Fasting plasma glucose concentrations were 7.1 ± 0.5 and 7.5 ± 0.6 mM (NS) in the control and lipid studies, respectively. Isoglycemia (at 7 mM) was maintained satisfactorily in both studies (Fig. 1). Fasting plasma insulin concentrations were 11 ± 2 (control) and 12 ± 2 mU/L (lipid) and were raised and held constant at similar plateaus (99 ± 1 and 100 ± 2 mU/L, mean of the 2nd h) during the clamp. Less exogenous glucose was required to maintain isoglycemia during lipid infusion than in the control condition from 40 min

into the clamp on (Fig. 1). During the 2nd h of the clamp, the rate of glucose infusion was less with than without lipid infusion in 9 of 10 subjects; the corresponding mean group values (22.9 ± 4.5 vs. 27.0 ± 4.9 μmol · kg^{-1} · min^{-1}) were significantly ($P < 0.025$) different from one another.

EGP was similar in the fasting state on both occasions (9.7 ± 1.3 vs. 10.4 ± 1.1 μmol · kg^{-1} · min^{-1}, control vs. lipid, respectively; NS). During the 2nd h of the clamp, EGP was not, on average, significantly different from 0 in either study (−5.2 ± 2.4 vs. −1.6 ± 2.7 μmol · kg^{-1} min^{-1}, control and lipid, respectively).

In the fasting state, plasma FFA concentrations were similar in the two studies, averaging 0.56 ± 0.06 (control) and 0.56 ± 0.07 mM (lipid) (Fig. 2). After insulin administration in the control study, plasma FFA fell to a mean level of 0.14 mM during the 2nd h ($P < 0.001$). In contrast, lipid-plus-heparin infusion resulted in a marked, gradual increase in FFA levels, which leveled off at 2.4 mM between 60 and 120 min ($P < 0.001$ vs. control). Parallel changes were seen in plasma triglyceride concentration (which did not change from baseline in the control study, although increasing 3- to 4-fold [$P < 0.001$] during lipid infusion) and blood glycerol levels, which plateaued at ~0.07 and ~0.8 mM ($P < 0.001$) in the control and lipid studies, respectively (Fig. 2). Similarly, blood β-hydroxybutyrate concentrations decreased by 25–30% during the control clamp, whereas they nearly doubled during the lipid clamp ($P < 0.03$ control vs. lipid), thereby documenting enhanced lipid oxidation by the liver. Blood lactate and pyruvate concentrations were similar in the fasting state in both groups of experiments (Fig. 3). After insulin infusion, blood lactate rose by ~25% in the control group and slightly, although not significantly, less (~15%) in the lipid group. Blood pyruvate, on the other hand, remained stable in the control study but declined by 20% with lipid infusion. As a consequence, the lactate-pyruvate ratio remained unchanged from baseline in controls (10 ± 1 to 12 ± 1, NS) but was significantly increased during the 2nd h of the lipid clamp (10 ± 1 to 15 ± 2, $P < 0.02$) (Fig. 3). Fasting blood alanine levels were similar in the control and lipid studies (371 ± 32 and 410 ± 34 μM, respectively) and did not show any consistent change during either clamp. Plasma potassium concentrations were superimposable in the two groups of experiments in the basal state and fell to similar extents (by ~1 meq/L) during insulin administration.

The results of indirect calorimetry are depicted in Fig. 4. Basal O_2 consumption (244 ± 15 vs. 258 ± 17 ml/min) and CO_2 production (199 ± 12 vs. 209 ± 12 ml/min) were similar in the control and lipid studies. Consequently, the mean basal *RQ*s (ratio of CO_2 production to O_2 consumption) also were superimposable (0.82 ± 0.02 vs. 0.81 ± 0.01). During the clamp, however, O_2 consumption remained at baseline in the control group, whereas it rose to 270–300 ml/min after lipid infusion. CO_2 production, on the other hand, showed a small gradual increase throughout the 120 min of insulin infusion in both groups of studies. Consequently, *RQ* rose progressively (to 0.91 ± 0.02, $P < 0.01$) during the control clamp but failed to do so in the lipid study ($P < 0.01$ control vs. lipid; Fig. 4).

Urine nonprotein nitrogen concentrations (~0.4 mM) and urine flow rates (~1.5 ml/min) were similar in the two groups of studies; thus, whole-body protein oxidation was estimated to be 5.6 ± 0.7 and 6.5 ± 0.8 μmol · kg^{-1} · min^{-1} (NS) for the control and lipid groups, respectively. From these data and the gas-exchange measurements, whole-body rates of substrate utilization could be calculated (Table 1). Basal rates of total glucose disposal, glucose oxidation, nonoxidative glucose uptake, and lipid oxidation were similar for both studies. Insulin administration (control study) stimulated total glucose utilization 2.5-fold by doubling glucose oxidation and increasing nonoxidative glucose disposal five times; at the same time, lipid oxidation was reduced by >60%. In contrast, with insulin administration and concomitant lipid infusion, lipid oxidation persisted at a rate slightly higher than baseline; correspondingly, glucose oxidation failed to be stimulated, and total glucose uptake was 15% less than in the control condition. Note that nonoxidative glucose disposal was not significantly affected by lipid administration.

Energy expenditure averaged 4.8 ± 0.3 kJ/min in the fasting state during the control study and remained at this level throughout the insulin clamp (4.9 ± 0.3 kJ/min between 60 and 120 min; Fig. 5). In contrast, basal energy expenditure in the lipid study (5.1 ± 0.3 kJ/min) increased gradually during insulin administration; its mean value over the 2nd h of the study was significantly higher (5.6 ± 0.4 kJ/min, $P <$

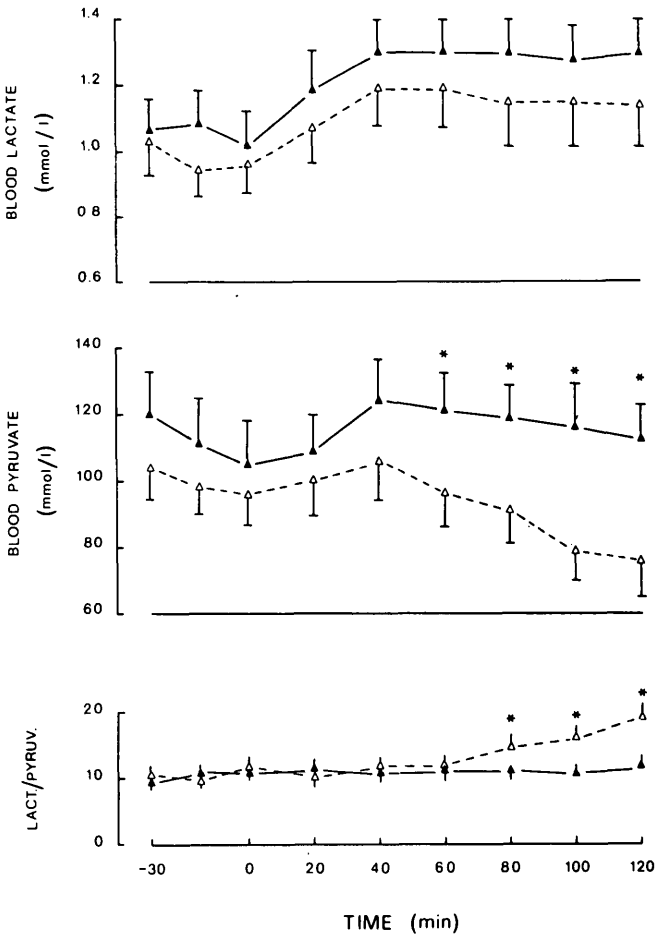

FIG. 3. Blood lactate and pyruvate concentrations and their molar ratio in 10 non-insulin-dependent diabetic patients in basal state and during insulin clamp without (▲) or with (△) concomitant lipid infusion. *$P < 0.05$ or less lipid vs. control studies by paired *t* test.

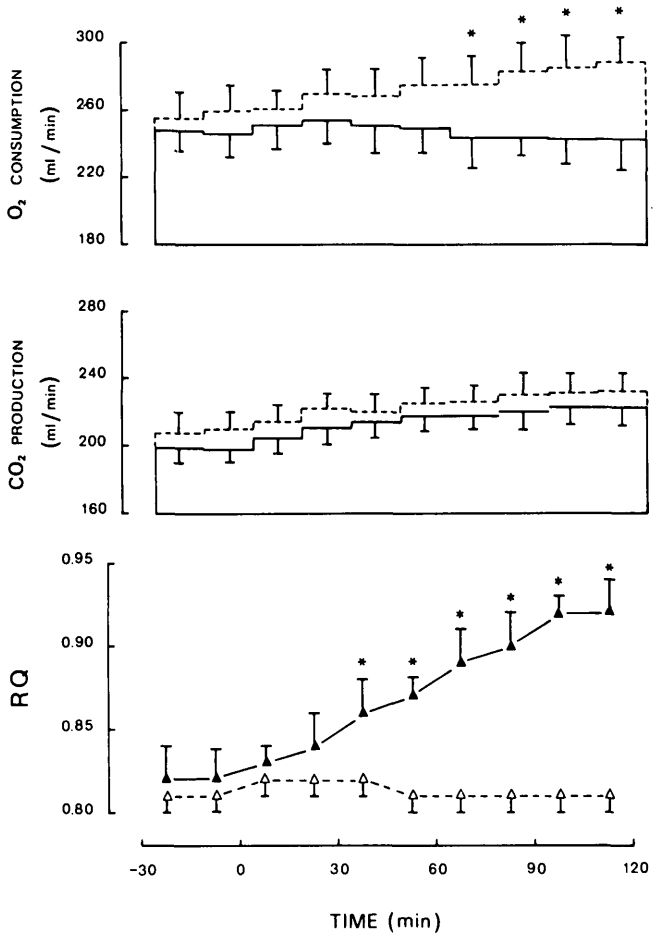

FIG. 4. Rates of O_2 consumption, CO_2 production, and total *RQ* (ratio of O_2 consumption to CO_2 production) in 10 non-insulin-dependent diabetic patients in basal state and during insulin clamp without (*solid lines*) or with (*dashed lines*) concomitant lipid infusion. *$P < 0.05$ or less lipid vs. control studies by paired *t* test.

0.01) than at baseline or during the corresponding period of the control experiment. In either study in the basal state, carbohydrate and lipid oxidation contributed 32 and 50%, respectively, to total energy production (Fig. 6). These proportions were reversed during insulin administration (62% of energy from carbohydrate, 21% from lipid) but were conspicuously maintained during combined insulin and lipid administration.

DISCUSSION

The diabetic patients in this study were nonobese, middle aged, mildly hyperglycemic, and untreated at the time of study. The approach used to test for Randle's cycle was the same as that previously applied in our laboratory to healthy individuals (6) and nondiabetic obese subjects (10). The reasons for choosing an isoglycemic rather than euglycemic insulin-clamp protocol were *1*) to study the diabetic patient in his/her native (i.e., hyperglycemic) condition and *2*) to avoid the confounding effect of an insulin preinfusion (to achieve euglycemia) because of the strong time dependence of the glucose-FFA interaction (9).

Fasting rates of EGP were normal in absolute terms, as expected on the basis of the mild fasting hyperglycemia (27), and were similarly suppressed by insulin during the clamp. Thus, hepatic insulin resistance was not prominent in this group of diabetic subjects. The peripheral tissues, on the other hand, were definitely resistant to the stimulatory action of hyperinsulinemia. For comparison purposes in a previously reported group of age- and weight-matched nondiabetic individuals (28), total glucose uptake during the 2nd h of a euglycemic (5.3 ± 0.2 mM)-hyperinsulinemic (93 ± 6 mU/L) clamp averaged 28.9 ± 1.3 μmol · kg^{-1} · min^{-1}, corresponding to a glucose clearance rate of 5.4 ± 0.2 ml · kg^{-1} · min^{-1}. Because insulin-stimulated glucose clearance in diabetic patients is independent of glycemia over a wide range (29), the observed total rate of glucose uptake in the patients in this study (Table 1) at a mean glucose concentration of 7 mM (Fig. 1) corresponds to a clearance rate of 3.7 ± 0.8 ml · kg^{-1} · min^{-1}, i.e., a 30% reduction vis-à-vis the nondiabetic group. Furthermore, in the diabetic patients, insulin administration failed to induce any increase in energy expenditure (diet-induced thermogenesis); this abnormality is another characteristic of insulin-resistant states (30). Notably, both the basal rate of lipid oxidation and its suppression by insulin were similar to those of nondiabetic individuals (28), as were the fasting and insulin-stimulated rates of glucose oxidation. Nonoxidative glucose disposal, on the other hand, was somewhat diminished in these patients (11.6 μmol · kg^{-1} · min^{-1}; Table 1) compared with previous control subjects (17.2 ± 1.3 μmol · kg^{-1} · min^{-1}; 28). It can therefore be concluded that in nonobese mildly diabetic subjects *1*) lipid oxidation is normal (as is also the case in more severely diabetic nonobese individuals; 31,32), *2*) glucose oxidation is not grossly impaired (in contrast to more severe degrees of diabetes; 15,32), and *3*) total glu-

TABLE 1
Substrate utilization in non-insulin-dependent diabetic patients during isoglycemic insulin clamp without (control) or with concomitant lipid infusion

	Control		Lipid	
	Basal	Clamp	Basal	Clamp
Lipid oxidation	3.0 ± 0.4	1.3 ± 0.3*	3.2 ± 0.3	3.6 ± 0.2*†
Glucose oxidation	7.3 ± 1.3	14.1 ± 1.8*	7.2 ± 0.8	7.9 ± 1.3†
Nonoxidative glucose uptake	2.1 ± 1.8	11.6 ± 4.1*	3.1 ± 1.7	13.9 ± 3.4*
Total glucose uptake	9.4 ± 1.4	25.7 ± 5.2*	10.2 ± 1.2	21.8 ± 4.6*†

Values are rates (μmol · kg^{-1} · min^{-1}) during 30 min of baseline (basal) and during the 2nd h of the insulin clamp in 7 diabetic patients.
*$P < 0.05$ or less vs. respective mean basal value.
†$P < 0.05$ or less vs. control.

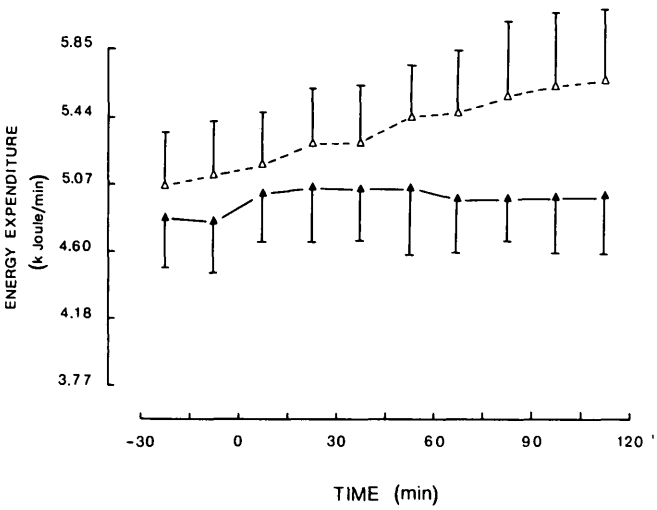

FIG. 5. Energy expenditure in basal state and during insulin clamp in 10 non-insulin-dependent diabetic patients without (▲) or with (△) concomitant lipid infusion.

cose uptake is maintained at near-normal levels by the hyperglycemia, which apparently is capable of restoring glucose oxidation more effectively than nonoxidative glucose disposal. Thus, mild diabetes is an insulin-resistant condition for which excessive utilization of fatty substrates cannot be held responsible.

Lipid infusion raised plasma FFA, blood glycerol, and serum triglyceride concentrations to the high physiological range (Fig. 2). This augmented fatty substrate supply forced lipid oxidation to levels slightly in excess of fasting rates (Table 1). The marked elevation of the lactate-pyruvate ratio in the systemic circulation (Fig. 3) reflected enhanced lipid oxidation at the whole-body level (3), whereas the relative increase in blood β-hydroxybutyrate concentrations indicated that at least part of such increment occurred in the liver (Fig. 2).

The effect of raising FFA availability was as expected on the basis of Randle's cycle; carbohydrate oxidation was inhibited, and total glucose uptake was diminished to almost precisely the same extent (Table 1). Note that lipid infusion abolished the insulin-induced stimulation of glucose oxidation but did not decrease carbohydrate oxidation below the basal fasting values. This suggests that substrate competition by FFA occurs in those tissues that insulin recruits to increase glucose utilization; i.e., the peripheral tissues (6). Also of interest, lipid infusion had no detectable stimulatory effect on EGP, at least at the insulin dose used in these studies and within the limits of accuracy of the tracer method (23). In keeping with this result, blood alanine concentrations were not lower with lipid than with saline, as was the case in the obese individuals in whom lipid infusion did cause an increased EGP (10). Nonetheless, it cannot be excluded that a lower degree of insulinization might let the stimulatory action of lipid on EGP become evident by releasing inhibition on the liver.

From the viewpoint of energy metabolism, two facts emerged. First, lipid infusion increased whole-body energy expenditure (Fig. 5) in this group of diabetic patients. This increment amounted to ~4% of the infused energy (12 kJ/min) over the 2nd h of the study. Remarkably, the difference in lipid oxidation between the control and test studies was ~12 mmol over 2 h, which corresponds to ~10% of the infused lipid load. This indicates that most of the Intralipid was stored (as reflected by the severalfold increments in the circulating levels of FFA and triglycerides; Fig. 2) and that the small fraction of Intralipid that was oxidized was sufficient to induce a thermogenic effect. It can therefore be concluded that at least in mildly diabetic individuals, the characteristic lack of diet-induced thermogenesis is limited to glucose, with the response to fat being preserved (30). Second, the overall effect of lipid infusion on the pattern of substrate oxidation was to clamp the fasting state (at a slightly higher energy level) for 2 h despite the hyperinsulinemia (Fig. 6). In other words, the classic insulin-induced shift in substrate oxidation for energy production was deleted despite other actions of insulin (suppression of EGP, stimulation of nonoxidative glucose disposal, promotion of potassium uptake) being kept intact. This observation speaks in favor of a primacy of substrate effects over hormone action in determining the pattern of fuel utilization, at least under the experimental circumstances explored herein.

In summary, inhibition of glucose metabolism by enhanced use of fatty substrates does not seem to explain the insulin resistance of nonobese NIDDM patients. In these patients, nevertheless, Randle's cycle can be induced acutely: insulin effectively lowers circulating FFA (i.e., control study), whereas increased provision of exogenous lipids restrains glucose utilization (i.e., Intralipid infusion). In this respect, mildly hyperglycemic individuals behave like nondiabetic subjects (6). It appears that only when insulin resistance is more severe the inhibitory effect of fat oxidation on the oxidative disposal of glucose by peripheral tissues disappears and its stimulatory action on EGP becomes prominent. This was observed in the obese subjects in our previous study (10), who were profoundly insulin resistant both at the level of the liver and in the peripheral tissues and during an acute experimental circumstance (marked hyperglycemia with hy-

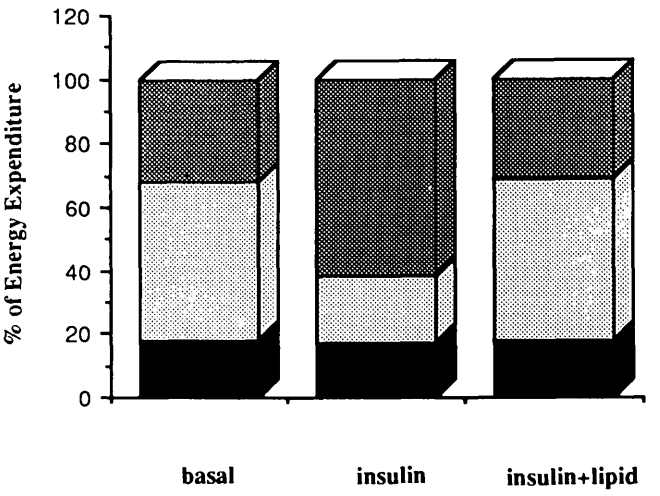

FIG. 6. Relative contributions of protein (*solid bars*), lipid (*lightly shaded bars*), and glucose (*darkly shaded bars*) oxidation to total energy expenditure in basal state and during hyperinsulinemia without or with concomitant lipid infusion.

poinsulinemia) simulating severe diabetes (6). On the basis of the latter finding, it can be supposed that NIDDM patients with fasting hyperglycemia >10 mM may respond to lipid administration with no further impairment in insulin-mediated glucose uptake but with an enhanced output of endogenous glucose. This prediction, however, remains to be verified.

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