Effects of Medium- and Long-Chain Fatty Acids on Whole Body Leucine and Glucose Kinetics in Man

Ulrich Keller, Igor Turkalj, Roland Laager, Daniel Bloesch, and Stefan Bilz

Elevation of plasma concentrations of nonesterified fatty acids (NEFA) has been reported to result in protein sparing and in impaired insulin-mediated glucose metabolism. To assess the influence of the chain length of fatty acids on these effects, medium-chain (MC) and long-chain (LC) fatty acid–containing lipid emulsions (2 mg/kg/min each) combined with heparin were administered during 390 minutes to 25 healthy overnight-fasted male subjects. Whole body leucine flux (a parameter of whole body protein breakdown) decreased during MC triglycerides (MCT) by 20% ($P < .005$). Irreversible leucine catabolism (oxidation of [1-^{13}C]-leucine) decreased during LC triglycerides (LCT) by 40% ($P < .01$) but not during MCT when compared to controls receiving glycerol infusions. MCT administration resulted in a marked (52 %, $P < .001$) decrease of α-ketoisocaproate (α-KIC) concentration, suggesting diminished leucine transamination and decreased leucine nonoxidative disappearance ($P < .015$). Hyperinsulinemia (30 to 40 μU/mL, euglycemic clamping) resulted in decreased leucine flux and oxidation during both lipid infusions, particularly during MCT. The increase in glucose disappearance during hyperinsulinemia in subjects receiving MCT or LCT was less than in controls, and endogenous glucose production measured by 6,6-D_2-glucose infusions was less suppressed ($P < .01$). Thus, elevation of plasma LC fatty acids (but not of MC fatty acids) results in decreased leucine oxidation (protein catabolism). This protein-sparing effect of LCT appears to be dissociated from fatty acid effects on glucose metabolism; both MCT and LCT diminished insulin's ability to increase glucose disappearance and to decrease hepatic glucose production.

CIRCULATING nonesterified free fatty acids (NEFA) serve as important source of energy. Medium-chain triglyceride (MCT)-containing lipid emulsions (8 to 10 carbon atoms) have been demonstrated to be more rapidly and more completely cleared than long-chain triglyceride (LCT) emulsions due to the fact that they do not require a carnitine-dependent transport system to cross the mitochondrial membrane barrier for β-oxidation.[1] Administration of MCT to dogs[2] has been demonstrated to diminish leucine flux and oxidation, suggesting a protein-sparing effect. A recent study in human subjects failed to detect an effect of an MCT-containing lipid emulsion containing a 1:1 mixture of MCT and LCT on leucine[3] and glucose[4] kinetics; however, the control subjects did not receive similar amounts of free glycerol as infused during administration of the lipid emulsions.

Studies in man demonstrated that acute physiological elevation of plasma long-chain (LC) fatty acid concentrations diminished insulin-stimulated glucose utilization[5-7] and glucose transport,[8] and plasma NEFA concentrations are a major regulator of hepatic glucose production.[9]

The question is therefore of importance whether the chain length of NEFA affects hepatic glucose metabolism differently. Therefore, the present studies were designed to determine the effect of elevated plasma concentrations of medium-chain (MC) and LC fatty acids on leucine and glucose kinetics in man. The MCT emulsion employed consisted of a relatively high (70%) content of MC fatty acids. The results were compared to a control group receiving glycerol in amounts matching those administered during lipid infusions. Since nutritional lipids are usually supplied with carbohydrates at elevated plasma insulin concentrations, it was of interest to assess the effect of the lipid emulsions also during a period of hyperinsulinemia and euglycemic clamping. This provided an opportunity to determine insulin sensitivity of leucine and glucose kinetics during elevated plasma NEFA concentrations.

MATERIALS AND METHODS

Subjects

Twenty-five healthy overnight-fasted male volunteers aged 24.2 ± 1.0 years (range, 20 to 43 years), with a body mass index of 22.0 ± 0.5 kg/m^2 (range, 16.7 to 26.9 kg/m^2) participated in the study after giving written informed consent. Before the investigation, a medical history, physical examination, and routine laboratory tests were performed in all volunteers in order to exclude cardiopulmonary, renal, hepatic, or metabolic diseases. In particular, fasting plasma glucose and lipid concentrations were within the normal range. The subjects were on no medication and did not perform vigorous exercise for at least 24 hours before the study. The study protocol was reviewed and approved by the Ethical Committee of the Basle University Hospital.

Procedures

The subjects reported to the metabolic ward at 7 AM after a 10-hour overnight fast. Thereafter, a teflon cannula was placed into a right antecubital vein for infusions. A superficial dorsal hand vein was cannulated in retrograde fashion using a 21-g butterfly needle for blood sampling. The hand was kept in a thermostat-controlled warming chamber at a temperature of approximately 58°C to allow arterialization of venous blood.[10] After obtaining 3 blood and breath samples drawn at 10-minute intervals to determine background enrichments of plasma [1-^{13}C]-leucine, [1-^{13}C]-α-ketoisocaproate (α -KIC), [6,6-D_2]-glucose, and of breath $^{13}CO_2$, priming doses of 2 μmol/kg [1-^{13}C]-leucine (99% enriched, Tracer Technology, Cambridge, MA), 0.3

From the Departments of Research and of Internal Medicine, University Hospital, Basel, Switzerland.

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Address reprint requests to Ulrich Keller, MD, Division of Endocrinology, Diabetology and Clinical Nutrition, Kantonsspital Basel, 4031 Basel, Switzerland.

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mg/kg $NaH^{13}CO_3$ (90% enriched, KOR Isotopes, Cambridge, MA), and of 3 mg/kg [6,6-D_2]- glucose (98% enriched, Tracer Technologies, Somerville, MA) were injected. Thereafter, continuous infusions of [1-^{13}C]-leucine (0.04 μmol/kg/min) and [6,6-D_2]-glucose (0.04 mg/kg/min) were administered using Harvard (Holliston, MA) syringe pumps throughout the study. After 120 minutes of tracer equilibration, blood and breath samples were obtained in frequent intervals during a 30-minute baseline period and during a 390-minute infusion period. All blood samples were collected in tubes containing EDTA as anticoagulant. Plasma was rapidly obtained by refrigerated centrifugation (4°C) and stored at -70°C until later assay. Expired air was collected from a mixing bag connected to a mouth piece into Douglas bags for determination of $^{13}CO_2$ production ($\dot{V}CO_2$) and O_2 consumption ($\dot{V}O_2$) by infrared gas analysis (E. Jäger, Würzburg, Germany). Respiratory volume per unit of time was measured using a respirometer (Spiroflo III; Rotamed, Port Talbot, UK). Expired air was also collected during 2-minute breathing equilibration periods from a mixing bag connected to a mouth piece using gas-tight 100-mL glass flasks for later $^{13}C0_2$ analysis.

The subjects were allocated in random order to receive either glycerol (10% wt/vol; 0.25 mg/kg/min; control group, n = 8) to match the free glycerol content (2.5% wt/vol) in both lipid emulsions, or a MCT-containing emulsion (20% wt/vol; special preparation of Lipofundin MCT [Braun, Melsungen, Germany] consisting of approximately 70% MCT and 30% LCT), infused at 2 mg/kg/min (n = 9), or a LCT-containing emulsion (20% wt/vol; n = 8; 2 mg/kg/min Lipofundin-S [Braun]). The amount of esterified glycerol infused was slightly different (0.2 mg/kg/min during MCT, and 0.1 mg/kg/min during LCT). To all lipid and glycerol infusions, 2,000 U of heparin was added to increase lipolysis of infused lipids. During the last 120 minutes of the study, an euglycemic hyperinsulinemic clamp was performed[11] by infusing insulin (Actrapid HM; NovoNordisk, Küsnacht, Switzerland) mixed in 2 mL albumin 20% per 50 mL saline at 20 mU/m^2/min after administration of a priming dose of 80 mU/ m^2/min during the initial 4 minutes. All infusates were sterile and pyrogen-free.

Analytical Methods

[^{13}C] enrichments and concentrations of plasma leucine and α-KIC, and D-enrichment of plasma glucose were measured by selected ion monitoring during gas chromatography–mass spectrometry (Hewlett-Packard GC-MS HP 5890/5970) using D_{10}-leucine and D_3-α-KIC, respectively, as internal standards.[12] $^{13}CO_2$ content of expired air was measured by isotope ratio mass spectrometry (Finnigan MAT 251 Spectrometer, Bremen, Germany). Background ^{13}C-enrichment of plasma leucine, α-KIC, and expired CO_2 were subtracted from all subsequent measurements. In order to account for possible changes in background $^{13}CO_2$ enrichment during the lipid or glucose infusions, 7 volunteers (2 glycerol-controls, 2 LCT, 3 MCT) were examined in the same fashion but without [1-^{13}C]-leucine tracer infusion. In glycerol-controls background $^{13}CO_2$ production did not change during the entire study. Mean background $^{13}CO_2$ enrichment decreased slightly during LCT until 270 minutes by 1%, and during the glucose clamp period (at 390 minutes) by 0.7%, respectively. These changes of background enrichments were used in the calculation of $^{13}CO_2$ production of the respective groups. Plasma total NEFA were determined by microfluorometric enzymatic assay,[13] and individual NEFA by gas chromatography after separation with thin-layer chromatography.[14] Plasma glycerol,[15] total ketone bodies (sum of acetoacetate and β-OH-butyrate),[16] and triglyceride concentrations were determined microfluorometrically (enzymatic assays). Plasma insulin, C-peptide, and glucagon were determined by radioimmunoassays as described previously.[17] Hand-venous plasma glucose concentrations were measured using a Glucose Analyser (Yellow Springs Instruments, Yellow Springs OH; Model 23 AM).

Calculations

Whole body leucine flux of 3 periods (baseline, 240 to 270 minutes, 360 to 390 minutes) was calculated by dividing the isotope infusion rate by the average of 3 or 4 consecutive plasma [1-^{13}C]-α-KIC tracer-tracee ratios (TTR) using the reciprocal pool model.[18] Near steady-state was present in these periods as there was no significant change of [1-^{13}C]-α-KIC with time during these periods by repeated-measures analysis (ANOVA). Leucine oxidation rate was calculated as: $IE_{CO2} \times \dot{V}CO_2$/TTR α-KIC $\times$ 0.81, where IE_{CO2} was the ^{13}C-isotopic enrichment of expired $^{13}CO_2$, $\dot{V}CO_2$, the rate of total CO_2 production, and $TTR_{\alpha\text{-KIC}}$, the ^{13}C-enrichment in arterialized plasma α-KIC, the transamination product of leucine which equilibrates with intracellular α-KIC.[18] The value 0.81 was used to correct for CO_2 retention and other losses.[19] Leucine nonoxidation rate was calculated by subtracting the rate of leucine oxidation from whole body leucine flux. Glucose rate of disappearance and endogenous rate of appearance (Ra) was calculated by dividing the isotope infusion rate by the steady-state plasma [6,6-D_2]-glucose TTR, subtracting the amount of [6,6-D_2]-glucose infused. Endogenous glucose Ra during clamping was obtained by subtracting the rate of unlabelled glucose from total Ra. The fact that we did not use a variable glucose tracer infusion as proposed by others [20,21]might have resulted in an overestimation of the actual rate of endogenous glucose production; however, as the same tracer infusion procedure was applied to all 3 groups, this error would have similarly occurred in all 3 groups. Moreover, since glucose disappearance increased only moderately, we observed only a moderate decrease of [6,6-D_2]-glucose plasma TTR, which should have yielded reliable rates of glucose appearance.[21]

Statistical Analyses

For evaluation of kinetic parameters, the mean values of the baseline period (-30, -15, 0 minutes), the lipid infusion period (240, 250, 260, 270 minutes), and the clamp period (360, 370, 380, 390 minutes) were compared between protocols using ANOVA. For comparing individual protocols, Fisher' s paired least significant difference tests were performed. For evaluation of plasma concentrations, all time points during the infusions were assessed by 2-way repeated-measures ANOVA (Macintosh, Statview II, Berkeley, CA). All data are presented as means $\pm$ SEM.

RESULTS

Leucine Kinetics

Plasma leucine concentrations (Fig 1, top panel) decreased during MCT administration by 10% until 270 minutes ($P < .05$ *v* baseline period; $P < .04$ *v* glycerol-controls) and by 7% during LCT (NS *v* glycerol-controls). Elevation of plasma insulin concentrations resulted in a further decrease of plasma leucine concentrations by 30% in all 3 groups ($P < .001$). Plasma α-KIC (Fig 1, bottom panel) decreased by 52% ($P < .001$) to 16 $\pm$ 1 μmol/L after 270 minutes of MCT infusion ($P < 0.001$ *v* LCT and *v* controls), whereas it remained stable during LCT and glycerol-controls. Elevation of plasma insulin concentrations resulted in a similar and significant ($P < .05$ or less) decrease of plasma α-KIC concentration in all 3 protocols. Whole body leucine flux (Fig 2, top panel) decreased during MCT at 240 to 270 minutes by 0.52 $\pm$ 0.14 μmol/kg/min ($P < .005$) or by 22% from baseline ($P < .03$ *v* glycerol-controls). During LCT infusion, leucine flux decreased by 14% ($P = .08$); the difference to glycerol-controls and to the MCT group was not significant. During hyperinsulinemia (360 to 390 minutes), leucine flux decreased in all 3 protocols on average by 18%

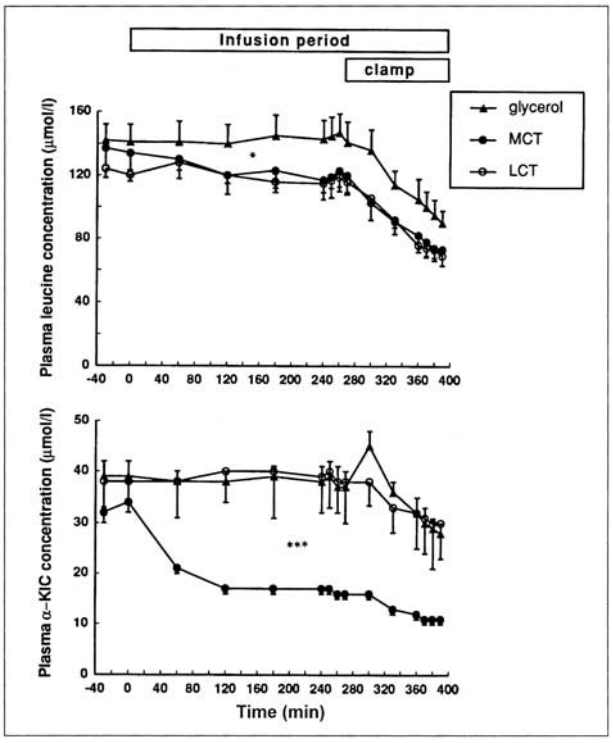

Fig 1. Plasma leucine and α-KIC during administration of glycerol- (0.25 mg/kg/min; controls) (n = 8), during infusion of MCT- (n = 9), and LCT- (n = 8) containing lipid emulsions (2 mg/kg/min), + 2,000 U heparin. Only P values of comparisons between experimental groups. *$P < .05$: MCT *v* glycerol-controls; ***$P < .001$: MCT *v* glycerol-controls and *v* LCT. Results are means ± SEM.

($P < .025$). Leucine oxidation rate (Fig 2, middle panel) decreased during LCT by 40% from baseline ($P < .02$; $P < .025$ *v* MCT and $P < .02$ *v* glycerol-controls), whereas MCT had no effect. Elevation of plasma insulin concentrations resulted in a decrease of leucine oxidation during LCT ($P < .05$) and during MCT ($P < .025$), but not in glycerol-controls. The decrease of leucine oxidation was more pronounced during LCT than during MCT ($P < .01$). Leucine nonoxidation rate (Fig 2, bottom panel) decreased during MCT administration by 25% ($P < .01$) to 1.56 ± 0.21 μmol/kg/min at 270 minutes ($P < .015$ *v* glycerol-controls). Elevation of plasma insulin concentrations decreased nonoxidative leucine flux in both lipid groups ($P < .015$ during LCT, $P < .025$ during MCT).

Glucose Kinetics

Glucose infusion rate during euglycemic clamping (Fig 3, top panel) was lower in the LCT group (by 58%, $P < .05$) and in the MCT group (by 52%, $P < .01$) than in glycerol-controls. Glucose disappearance (Rd; Fig 3, middle panel) decreased during the infusion period of all 3 groups ($P < .05$ or less). During elevated plasma insulin concentrations, glucose Rd increased less during LCT and during MCT ($P < .01$ compared to glycerol-controls). Endogenous rate of appearance (Ra; Fig 3, bottom panel) decreased by 25% in glycerol-controls ($P < .001$) and by 20% during LCT ($P = .06$). During hyperinsulinemia, endogenous glucose Ra decreased in glycerol-controls to values that were not significantly different from zero. During LCT infusion, glucose Ra was significantly less suppressed than in controls ($P < .01$); glucose Ra during MCT adminutesistration was slightly more suppressed, but the difference to the other 2 groups was not significant.

Plasma Hormones and Metabolic Substrates

Plasma insulin (Fig 4, top panel) remained unchanged until 270 minutes in all groups; insulin infusion at 20 mU/m^2/min resulted in modest hyperinsulinemia of approximately 40 μU/mL; during LCT, plasma insulin seemed to increase less than in the other 2 groups ($P = .071$; NS). Plasma C-peptide concentrations (Fig 4, bottom panel) decreased by 40% to 50% ($P < .01$) during hyperinsulinemia in all groups, indicating similar suppression of insulin secretion.

Plasma NEFA concentrations (Table 1) increased during

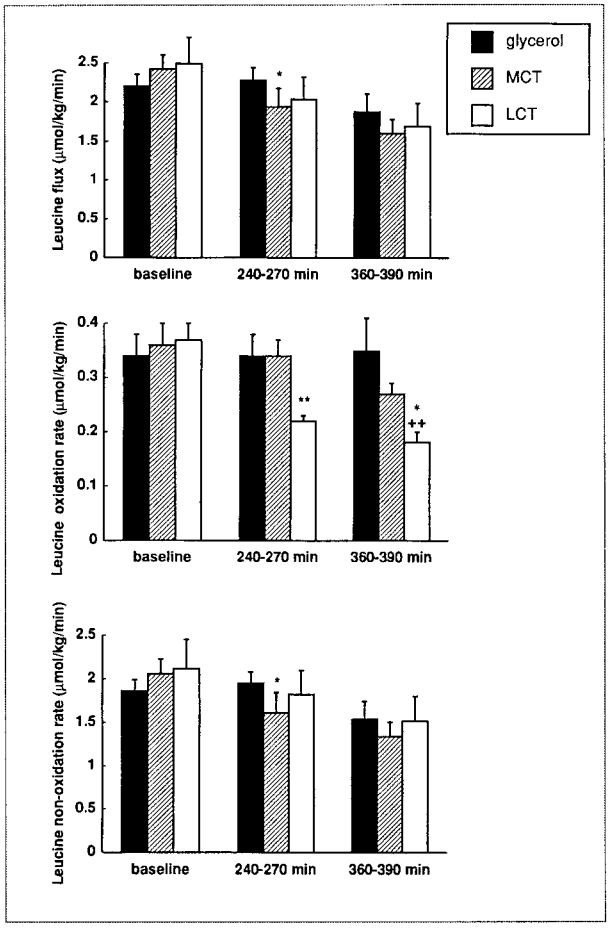

Fig 2. Whole body leucine flux leucine, leucine oxidation, and nonoxidative rate of leucine disappearance in subjects receiving glycerol, MCT, or LCT infusions. The bars represent mean data of the baseline period, the infusion period (240-270 min) and the infusion period with euglycemic clamping (360-390 min). Only *P* values of comparisons between experimental groups. *$P < .05$ *v* glycerol-controls; **$P < .01$ *v* glycerol-controls; ††$P < .01$ *v* MCT. Results are means ± SEM.

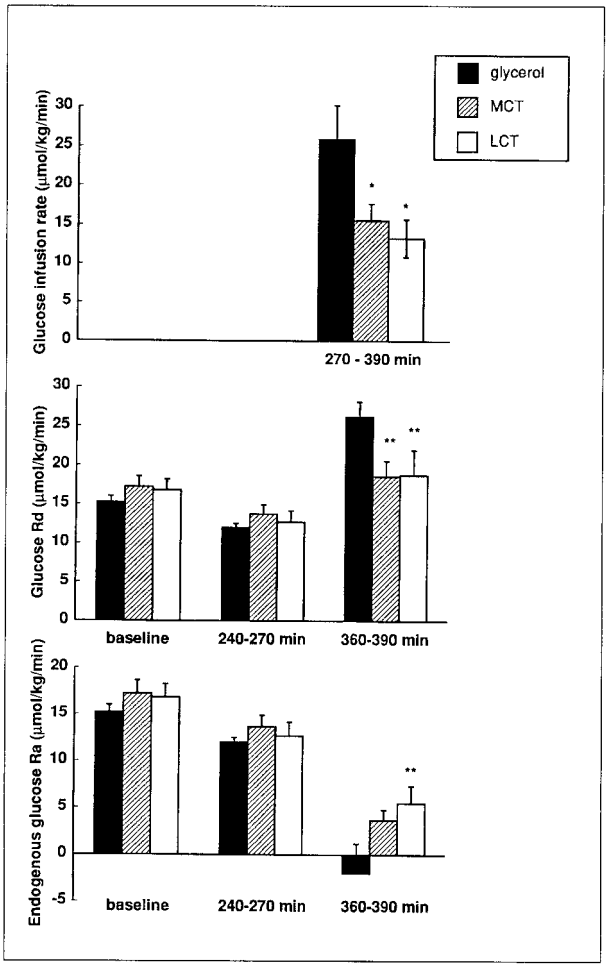

Fig 3. Glucose infusion rates during euglycaemic clamping (270-390 min), glucose rate of disappearance (Rd) and hepatic glucose production (endogenous rate of glucose appearance, Ra) in the 3 groups. Data during the infusion period are presented before (240-270 min) and after (360-390 min) euglycemic clamping. Results are means ± SEM. *$P < .05$ *v* glycerol-controls; **$P < .01$ *v* glycerol-controls.

MCT to higher levels (2,064 ± 245 μmol/L) than during LCT (955 ± 163 μmol/L; $P < .04$). Plasma NEFA concentrations were lowered during insulin infusion by 69% in glycerol-controls ($P < .001$), and less in the LCT and MCT groups ($P < .005$, $P < .02$ *v* glycerol-controls).

MCT infusion resulted in a 60-fold increase in C_8 (to 457 ± 30 μmol/L) and a 240-fold increase in C_{10} (to 349 ± 33 μmol/L). C_{16} increased by 20%, $C_{18:1}$ by 70% and $C_{18:2}$ 2-fold. C_{14}, C_{18}, and $C_{18:3}$ remained unchanged. LCT administration resulted in a 5-fold increase in $C_{18:2}$ (to 794 ± 44 μmol/L) and a 4-fold increase in $C_{18:3}$ (to 55± 6 μmol/L), respectively. C_{16} and C_{18} increased by 80% each, and $C_{18:1}$ increased by 50%. The other NEFA remained unchanged. During hyperinsulinemia, only $C_{18:2}$ and $C_{18:3}$ increased by 20% while all other NEFA did not change. In glycerol-controls, $C_{18:2}$ increased 3-fold. C_{18}, $C_{18:1}$, and $C_{18:3}$ increased by 60%, 50%, and 80% at 270 minutes, respectively. C_8, C_{10}, C_{14}, and C_{18} remained unchanged. During hyperinsulinemia, all fatty acids decreased similarly.

Individual ketone body concentrations (Table 2) demonstrated that plasma acetoacetate concentrations increased during MCT ($P < .01$ *v* glycerol-controls) and LCT $P < .01$ *v* glycerol-controls). Plasma β-hydroxybutyrate concentrations increased during LCT ($P < .04$ *v* glycerol-controls) and during MCT ($P < .03$ *v* glycerol-controls); elevation of plasma insulin concentrations resulted in a significant decrease of acetoacetate and β-hydroxybutyrate in glycerol-controls and in the LCT but not in the MCT group ($P < .03$ *v* glycerol-controls). Plasma triglyceride concentrations increased during MCT to 1.35 ± 0.11 mmol/L and to 1.46 ± 0.23 mmol/L during LCT infusion ($P < .001$). Hyperinsulinemia resulted in a decrease of plasma triglycerides in glycerol-controls by 36% ($P < .05$ *v* MCT, $P < .015$ *v* LCT). Plasma glycerol concentrations increased during the infusion period in all 3 groups ($P < .002$). Elevation of plasma insulin concentrations decreased plasma glycerol in all 3 groups ($P < .01$ in glycerol-controls, $P < .02$ in MCT, $P < .04$ in LCT).

Plasma glucose concentrations decreased slightly during the infusion period of all 3 groups ($P < .01$); during glucose clamping, they remained unchanged. Plasma glucagon increased during MCT by 19% ($P < .01$); during hyperinsulinemia, plasma glucagon decreased by 27% ($P < .015$) in glycerol-controls and by 20% ($P < .05$) during LCT. Plasma lactate concentrations increased during insulin-glucose clamping in glycerol-controls ($P < .05$). During MCT or LCT administration, there was no significant change of plasma lactate.

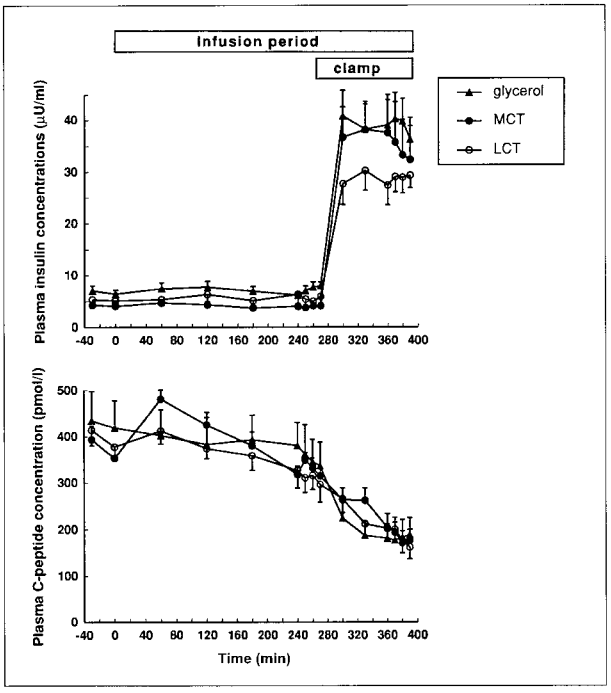

Fig 4. Plasma insulin and C-peptide concentrations before and during lipid infusions. During the clamp period, insulin was administered (20 mU/m_2/min) while plasma glucose concentrations were maintained at euglycemic by variable glucose 20% infusion. Results are means ± SEM.

Table 1. Individual Plasma NEFA Concentrations

	Glycerol (n = 8)			MCT (n = 9)			LCT (n = 8)		
	Baseline	Infusion Period		Baseline	Infusion Period		Baseline	Infusion Period	
	−30-0 min	240-270 min	360-390 min (clamp)	−30-0 min	240-270 min	360-390 min (clamp)	−30-0 min	240-270 min	360-390 min (clamp)
$C_{8:0}$	1 ± 0	1 ± 1	1 ± 0	6 ± 6	456 ± 37	544 ± 101	0 ± 0	0 ± 0§	3 ± 2
$C_{10:0}$	0 ± 0	0 ± 0	0 ± 0	1 ± 1	384 ± 40	420 ± 71	8 ± 7	2 ± 1§	1 ± 1
$C_{14:0}$	3 ± 1	4 ± 2	0 ± 0	18 ± 7	16 ± 6	14 ± 5	6 ± 5	8 ± 4	8 ± 5
$C_{16:0}$	210 ± 18	274 ± 25	159 ± 22	294 ± 37	373 ± 48	338 ± 39	344 ± 29	466 ± 49	466 ± 71*
$C_{18:0}$	79 ± 14	92 ± 21	67 ± 14	78 ± 14	104 ± 27	67 ± 11	69 ± 16	119 ± 13*	115 ± 23
$C_{18:1}$	207 ± 34	309 ± 57	128 ± 30	327 ± 36	354 ± 47	363 ± 44†	341 ± 41	514 ± 65	456 ± 82
$C_{18:2}$	107 ± 18	168 ± 31	88 ± 22	183 ± 32	329 ± 54	332 ± 52	164 ± 21	776 ± 117‡	906 ± 149*
$C_{18:3}$	3 ± 1	5 ± 2	3 ± 1	5 ± 2	5 ± 2	5 ± 2	7 ± 3	49 ± 10‡	61 ± 15
Sum of NEFA	611 ± 56	853 ± 102	418 ± 31	911 ± 101	2,019 ± 138‡	2,081 ± 142*	938 ± 82	1,934 ± 232‡	2,016 ± 313†

NOTE. Values are means ± SEM (μmol/L).
*$P < .05$ *v* glycerol.
†$P < .01$ *v* glycerol.
‡$P < .001$ *v* glycerol.
§$P < .001$ *v* MCT.

DISCUSSION

The results of the present study demonstrated that an increase in plasma LC fatty acids, but not in MC fatty acids, resulted in decreased whole body leucine oxidation, indicating diminutesished irreversible amino acid catabolism. Previous studies on the effect of fatty acids on leucine metabolism were conflicting; MC[22] and LC[23-25] fatty acids have been reported to decrease leucine oxidation in rat liver and heart and in human muscle.[26] In vivo studies performed in dogs demonstrated that leucine flux decreased during MCT and LCT administration. In contrast, a previous study in humans observed similarly to the present study a decrease of leucine oxidation during infusion of LCT but not during MCT. However, in the latter study less MC fatty acids were given, and the effects of lipid emulsions were assessed without a control group receiving glycerol infusions alone. In addition, the present data demonstrated a decrease of nonoxidative leucine disappearance during MCT, suggesting diminutesished protein synthesis; this emphasizes a smaller protein-sparing effect of MCT compared to LCT. It cannot be ruled out that increased transamination and oxidation of leucine did not occur in the same body protein pools, and certain tissues would not show diminutesished protein synthesis; the isotopic method used in this study was unable to clarify this issue.

The present findings are compatible with previous data ob-

Table 2. Plasma Concentrations of Glucose, Glucagon, Acetoacetate, β-Hydroxybuyrate, Triglycerides, Glycerol, and Lactate

	Glycerol (n = 8)			MCT (n = 9)			LCT (n = 8)		
	Baseline	Infusion Period		Baseline	Infusion Period		Baseline	Infusion Period	
	−30-0 min	240-270 min	360-390 min (clamp)	−30-0 min	240-270 min	360-390 min (clamp)	−30-0 min	240-270 min	360-390 min (clamp)
Glucose (mmol/L)	5.2 ± 0.2	4.7 ± 0.2	4.6 ± 0.2	5.2 ± 0.2	4.8 ± 0.2	4.7 ± 0.2	5.5 ± 0.1	5.0 ± 0.1	4.9 ± 0.1
Glucagon (pg/mL)	146 ± 14	141 ± 13	103 ± 8	182 ± 7	216 ± 17§	198 ± 5	160 ± 26	156 ± 9	128 ± 10
Acetoacetate (μmol/L)	38 ± 5	65 ± 12	29 ± 3	67 ± 25	152 ± 10*	141 ± 6	46 ± 12	126 ± 13‡	99 ± 16
β-OH-butyrate (μmol/L)	129 ± 59	334 ± 115	39 ± 23	146 ± 55	527 ± 61	435 ± 38	161 ± 156	503 ± 154	226 ± 310¶
Triglyceride (mmol/L)	0.82 ± 0.06	1.03 ± 0.17	0.66 ± 0.05§	0.86 ± 0.07	1.40 ± 0.00	1.32 ± 0.11	1.06 ± 0.18	1.40 ± 0.21	1.50 ± 0.25‡§
Glycerol (μmol/L)	62 ± 9	147 ± 11	96 ± 10	101 ± 8	195 ± 20	180 ± 21	60 ± 9	111 ± 9	96 ± 11¶
Lactate (mmol/L)	0.53 ± 0.05	0.59 ± 0.05	0.71 ± 0.07	0.59 ± 0.08	0.53 ± 0.08	0.56 ± 0.09	0.63 ± 0.13	0.51 ± 0.09	0.61 ± 0.12

NOTE. Values are means ± SEM.
*$P < .05$ *v* glycerol-controls.
†$P < .01$ *v* glycerol-controls.
‡$P < .001$ *v* glycerol-controls.
§$P < .05$ *v* MCT.
¶$P < .01$ *v* MCT.

tained in vitro demonstrating even increased amino acid oxidation during adminutesistration of MC fatty acids[25]; octanoate was observed to activate branched-chain ketoacid dehydrogenase (BCKDH) by direct inhibition of BCKDH kinase, keeping BCKDH in its active form.[27] On the other hand, long chain fatty acids have been reported to inhibit branched-chain amino acid dehydrogenase,[28] presumably by depleting the coenzyme A pool.

The increase in ketone body concentrations as observed during MCT administration in this study has been assumed to lead to protein sparing[29]; however, other studies failed to observe a decrease of protein breakdown during β-hydroyxbutyrate infusion in man.[30] In spite of the more pronounced increase in ketone body concentrations, MCT adminutesistration did not result in increased fatty acid oxidation when compared to LCT.[31]

Hyperinsulinemia during euglycemic clamping resulted in a decrease of leucine oxidation during both lipid emulsions, and this effect was enhanced by LCT compared to MCT.

Plasma α-KIC concentrations decreased during MCT but not during LCT administration. At the same time, plasma leucine concentrations decreased slightly during MCT due to a decrease of leucine flux. This observation and the fact that oxidation of leucine (and therefore of α-KIC) was unimpaired during MCT administration were the reasons for the decrease of α-KIC concentrations.

The interaction between elevated NEFA and glucose metabolism was first described by Randle et al.[32] According to these investigators, oxidation of fatty acids results in decreased oxidation of glucose. Studies in man showed that acute elevation of plasma LC fatty acids increased fatty acid oxidation and impaired the ability of insulin to stimulate glucose utilization and storage by extrahepatic tissues.[5,6,8] Recently, an inhibitory effect of NEFA on glucose transport in muscle has been demonstrated.[7] A significant correlation between NEFA concentrations and gluconeogenesis has been demonstrated in human subjects.[33]

Previous investigators[5,6] found no effect of raised plasma NEFA concentrations on basal glucose flux, in agreement with the present data. Only during hyperinsulinemia was an impairment of glucose disappearance evident. The present findings indicated that the decrease of glucose uptake was independent of the chain length of circulating NEFA. The present studies were the first to compare the effects of MC and LC fatty acids on hepatic glucose production using glycerol-infused subjects as controls. During LCT, insulin-mediated suppression of endogenous glucose production was significantly diminished compared to controls and to MCT. Thus, insulin action on endogenous glucose production was differently affected by fatty acids of different chain length.

The findings with LC fatty acids were in agreement with those of Saloranta et al[34] but at variance with those of Ferrannini et al.[6] The latter study used considerably higher plasma insulin concentrations (≈100 μU/mL), resulting in complete suppression of hepatic glucose production. The fact that insulin decreased hepatic glucose output in the present study even during fixed elevation of plasma NEFA (achieved by pretreatment with lipid and heparin infusions) suggests a NEFA-independent effect of insulin on hepatic glucose production.[8] The present data are at variance with those of Broussolle et al[4] who studied the effects of MCT and LCT infusions in the absence of hyperinsulinaemia.

Saloranta et al suggested that the liver plays a central role in NEFA's effects on glucose disposal.[34] NEFA oxidation in liver with consecutive ketone body formation would inhibit hepatic glucose oxidation. However, the present data demonstrated increased ketogenesis and presumably increased fatty acid oxidation in the liver during MCT; nevertheless, insulin's effects on hepatic glucose production were unimpaired. This suggests that fatty acid–induced impairment of insulin sensitivity of hepatic glucose metabolism was not mediated by increased β-oxidation, in agreement with a previous observation demonstrating impaired oxidation of LC fatty acids but not of MC fatty acids during insulin-glucose adminutesistration.[35]

Ketone body concentrations were significantly higher in the MCT studies during the clamp period. Since ketone bodies have been reported to diminutesish lactate removal and thereby glucose production by hepatocytes,[36] it is possible that ketone bodies were responsible for the modestly lower glucose production rates during MCT compared to LCT.

During MCT, total plasma NEFA concentrations increased more rapidly to higher levels than during LCT. This is not surprising as MCT are known to be more rapidly and more completely hydrolysed to NEFA than LCT[1] and since the same amounts of MCT and LCT (in grams) were infused; the number of moles of fatty acids was approximately 1.4 times higher during MCT than during LCT infusions.

In conclusion, the present data demonstrate that short-term adminutesistration of an LCT-containing lipid emulsion results in decreased amino acid oxidation. This effect is maintained during hyperinsulinemic glucose clamping; on the other hand, leucine catabolism is not diminutesished during MCT adminutesistration, suggesting that MCT-containing lipid emulsions during parenteral nutrition may not be as advantages as has been proposed.[1] In contrast, LCT and MCT exert similar effects on insulin-mediated glucose disposal.

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