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Plasma Clearance and Oxidation of Dodecanedioic Acid in Humans

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ABSTRACT. *Background:* Dicarboxylic acids are water-soluble, contrary to monocarboxylic acids, and have a metabolic pathway intermediate between those of lipids and carbohydrates. Our goal was to investigate the plasma turnover and oxidation rate of dodecanedioic acid (C12) in eight healthy male volunteers. *Methods:* A simultaneous infusion of both cold (0.24 mmol/min corresponding to 0.396 kcal/min) and radiolabeled (1.62 μCi/min) C12 free acid was performed. Blood specimens were sampled over a period of 360 minutes, and 24-hour urine samples were collected to measure the levels of C12 by high-performance liquid chromatography and liquid scintillation. Indirect calorimetry was continuously performed, and expired $^{14}CO_2$ was collected. Binding of C12 in human plasma was determined in separate experiments using equilibrium dialysis. *Results:*A linear one-compartment model was used to describe the kinetics of labeled C12. Its volume of distribution was 139.02 ± 10.84 mL/kg_{bw} (mean ± SE), and its plasma elimination constant was 0.01 ± 0.004 min^{-1}. The 24-hour urinary excretion of C12 was 3.14 ± 0.96 mmol, corresponding to about 7% of the administered dose. The amount of C12 oxidized, expressed as percent oxidation, was equal to 35.44 ± 1.64%. The mean basal value of npRQ (0.80 ± 0.006) significantly ($p < .02$) decreased during the infusion to 0.78 ± 0.01, which is a value close to that theoretically calculated (0.77). The oxidation of free fatty acids was significantly increased at the end of the C12 infusion, whereas the glucose oxidation was reduced to about 50%. *Conclusions:* The experimental data suggest that C12 might represent a fuel substrate immediately available for tissue energy requirements, because a relevant amount of C12 is promptly oxidized. Its prompt oxidation and its conversion to succinic acid support the use of dodecanedioic acid in parenteral nutrition, especially in insulin-resistance conditions in which glucose uptake and oxidation is impaired. (*Journal of Parenteral and Enteral Nutrition* **20:**38–42, 1996)

The introduction of dicarboxylic acids (DA) in parenteral nutrition as alternate fuel substrate has been recently advocated.[1–10] This class of substances shows a peculiar physical-chemical behavior and a metabolic pathway that is intermediate between that of lipids and carbohydrates. In fact, the presence of another end-carboxylic group in addition to that of free fatty acids (FFA) confers to the DA molecule the characteristic of being water soluble, whereas FFA are lipophilic substances because of their aliphatic chain. Therefore, FFA can not be administered directly but as esters of glycerol, that is, under triglyceride form (long-chain triglycerides [LCT] or medium-chain triglycerides [MCT]). In addition, both LCT and MCT, being water insoluble, must be administered as emulsions.

Even-numbered DA are completely oxidized in the cells to CO_2 and H_2O via succinyl-CoA formation, and it is well known that succinic acid represents a gluconeogenetic substance, because it can be directly converted to glucose.[11] Recently, we showed[8] by using the euglycemic-hyperinsulinemic clamp technique that sebacate, a DA with 10 carbon atoms, acts as a glucose-sparing substrate. Therefore, even-numbered DA like sebacate might be particularly useful in those clinical conditions in which the organism uses alternate gluconeogenetic substrates, such as amino acids, with reduction of lean body mass and potential impairment of protein-based immune processes.

The amount of urinary loss of dodecanedioic acid (C12) has been evaluated in experimental animals[9] and found to be 3.90 ± 1.62% of the administered dose. In addition, the C12 pharmacokinetic profile was studied, indicating a short half-life (about 12 minutes) and tubular reabsorption. These data appeared to be very interesting for further investigations in humans. In fact, the major problem of the DA previously studied (azelaic, C9, and sebacic, C10, acids) was their high urinary excretion.[4–6] Thus, the aim of the present study was to investigate in humans the plasma turnover of C12 and its oxidation rate using a simultaneous infusion of both cold and radiolabeled dodecanedioic acid.

MATERIALS AND METHODS

(1,12)^{14}Dodecanedioic acid (C12) (specific activity 117 mCi/mmol) was purchased from Amersham (Buckinghamshire, UK). Dodecanedioic acid and azelaic acid were from Sigma (St Louis, MO). Dodecanedioic acid was then purified by the company Real SRL (Como, Italy) and was free from pyrogens and contaminants with a degree of purification, ascertained using gas-liquid chromatography and mass spectrometry, of 99.8%.

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All other chemicals were of the highest purity available. A 0.4 mol/L solution of dodecanedioic acid salified with NaOH was used for the infusions. The infusions were sterilized by ultrafiltration through 0.25-μm Millipore filters (Molsheim, France) before administration.

Experimental Protocol

A continuous infusion of 0.24 mmol/min (which is amount of free acid infused, corresponding to 0.396 kcal/min) unlabeled sodium dodecanedioate was administered over 195 minutes (77.22 kcal) at a constant rate, by means of an electric syringe pump (Harvard Apparatus, Southnatick, MA) in eight male healthy volunteers, aged 59.7 ± 4.8 years and with a body mass index of 25.0 ± 0.5 kg/m^2, who fasted overnight. Simultaneously with the infusion of cold dodecanedioic acid, a constant infusion of radioactively labeled C12 was given in tracer amounts (1.62 μCi/min). All patients were chosen of male sex and above 50 years of age because of the infusion of radiolabeled carbon.

Heparinized blood samples (8 mL) were taken every 15 minutes after the beginning of the infusion until 180 minutes after its end (360 minutes total) and immediately centrifuged. Plasma samples were frozen at −20°C until analysis.

Each patient voided before starting the C12 infusion and the subsequent 24-hour urine samples were collected in a container with 0.1% sodium azide to prevent bacterial growth.

The protocol was in conformity with the directives given by the Ethical Committee of the Institutional Health Review Board of the Catholic University, School of Medicine, in Rome (Italy). Informed consent was obtained in all cases.

DA Analysis

Plasma samples. Azelaic acid, 100 μg, were added to 1 mL of each plasma sample as an internal standard. Proteins were precipitated with 0.1 mL of 4 N HCl and DA acids extracted twice with eight volumes of ethylacetate maintaining the solutions at 60°C for 15 minutes. The combined extracts were dried in a GyroVap apparatus (Howe, model GV1; Gio. DeVita, Rome, Italy), operating at 60°C, coupled with a vacuum pump and a gas trap FTS System (Stone Ridge, NY).

Urine samples. Samples (0.5 mL) from 24-hour urine were added with 50 μg azelaic acid as internal standard and then treated with cation-exchange resin (50 W-X4, 100-to 200-μm mesh, H^+; Dowex, Aldrich Chimica, Milano, Italy) to remove salts, concentrated under reduced pressure, and filtered through a Millipore HV (0.45-μm) filter. The samples were acidified to pH 1 to 2 with 4 N HCl, extracted twice with ethylacetate, and evaporated in the GyroVap as previously described.

High-performance liquid chromatography (HPLC) analysis. The extracted solutes were dissolved in 0.5 mL acetonitrile and methanol (1:1, vol/vol) and added to 10 mg of *p*-bromophenacylbromide and 30 μL of *N,N*-diisopropylethylamine as catalyst. The mixture was heated to 60°C for 15 minutes. The derivatives were dissolved in a final volume of 1 mL of acetonitrile and methanol (1:1, vol/vol) and an aliquot of 10 μL automatically injected into a liquid chromatograph (Hewlett-Packard 1050) with an HP 3396A integrator and a scanning spectrophotometer operating at a wavelength of 190 to 600 nm (light source: deuterium lamp, noise < 2.5 × 10^{-5} AU peak-to-peak at 254 nm with 4-nm bandwidth, flowing water at 1 mL/min).

DA derivatives were separated on an LC-18, 4.6-mm ID, 25-cm length, 5-μm particle size, reversed-phase column (Supelco Inc, Bellefonte, PA). The HPLC conditions were as follows: solvent A, bidistilled water and methanol (1:1, v/v); solvent B, acetonitrile; after 15 minutes isocratic elution with 15% acetonitrile, a gradient elution was performed from 15% to 100% of solvent B in 80 minutes. The flow rate was 1 mL/min, ultraviolet detector operating at 255 nm, chart speed 0.2 cm/min, range of absorbance from −0.300 to 1.000 absorbance units. The eluates corresponding to the retention time of dodecanedioic acid were collected in a counting vial in the presence of standard scintillation solution (Insta-Fluor, Packard, Downers Grove, IL) and counted by a beta scintillation counter (model 1600TR; Canberra-Packard, Canberra, CT). Quenching was checked by the internal standard method.

Indirect Calorimetry and Expired Radiolabeled Carbon Dioxide Collection

Urinary nitrogen was determined by a BUN Analyzer II (Beckman Instruments, Fullertone, CA). Indirect calorimetry was continuously performed by a ventilated hood apparatus (Deltatrac: Datex Instrumentarium, Helsinki, Finland), which automatically gives values of oxygen consumption ($\dot{V}O_2$), carbon dioxide output ($\dot{V}CO_2$), Respiratory Quotient (RQ), and energy expenditure each minute.

Expired air was collected over 2-minute periods at intervals of 15 to 30 minutes for a period of 600 minutes after starting the labeled dodecanedioic infusion by using a 20 L Douglas-bag. Because ethanol solutions of methylbenzetonium hydroxide (MH) are not yet commercially available, methylbenzetonium chloride (MC) from Sigma Chemical was used. Equal parts of a 1-M solution of MC in ethanol and of a 1-M NaOH ethanol solution were mixed at 45°C for 20 minutes. Then, the solution was filtered to eliminate the NaCl formed. Phenophtaleine, 0.1%, was added as pH indicator to the 1 mol/L MH ethanolic solution obtained. Aliquots of 3 mL each of this solution were put into graduated tubes and titrated with 0.15 N HCl. Following the above procedure, solutions containing 3 meQ of MH were obtained; these solutions are capable of trapping exactly 3 mmol of CO_2. The MH solution trapping $^{14}CO_2$ was added with 10 mL of scintillation solution.

Equilibrium Dialysis

Binding of dodecanedioic acid to normal human plasma was determined by equilibrium dialysis according to Ashbrook et al[12] as previously described for sebacic acid.[13] Briefly, we used a five-cell Spectrum Equilibrium Dialyzer (Spectrum Medical Industries Inc, Los Angeles, CA). The Teflon cells contained 1-mL compartments separated by a dialysis membrane (Spectra/Por, 47 mm diameter, molecular weight cutoff 12,000 to 14,000; Spectrum Medical Industries, Inc). Albumin and heavier plasma proteins do not cross the dialysis membrane. C12 reached equilibrium within 2 hours at 37°C in the absence of albumin. We therefore chose a 3-hour incubation period.

Binding was assessed at varying concentrations of C12 (from 5 × 10^{-5} to 2.5 × 10^{-2} M in the injection cell) in phosphate buffer, at pH 7.4. Amounts of ca 20,000 dpm of (1,12)^{14}C-dodecanedioic acid were added to the cold concentrations of C12.

Dodecanedioic acid was added to one side of the chamber and human plasma was added to the other side. The rotation speed of the dialysis cells was 30 rpm, and the temperature of the solution was kept at 37°C by a thermostatic bath (Haakes, Karlsruhe, Germany). At the end of the incubation period, aliquots of 500 μL were removed from each side of the equilibration chamber, and the radioactivity was measured by a Canberra-Packard beta scintillation counter. The recovery of radioactivity ranged from 95% to 100%. Albumin concentration was determined in the pool of normal human plasma used.

Mathematical Model Used and Statistics. The following linear (L) and nonlinear (NL) models were fitted to the experimental data:

$$\text{L:} \quad \frac{dC}{dt} = \frac{R_I}{VW} - kC, \quad C(0) = 0,$$

$$\text{NL:} \quad \frac{dC}{dt} = \frac{R_I}{VW} - \frac{TC}{M + C}, \quad C(0) = 0,$$

where R_I is the infusion rate, V the volume of distribution in mL/kg$_{BW}$, and W is the weight of the subject. The use of the nonlinear (carrier-limited) model for describing the C12 plasma curves did not significantly improve the estimates of the parameters, as evidenced by the average value of the loss function, at the additional price of more parameters to be estimated. This indicates that either no significant carrier mechanisms are involved in the transport of C12 out of plasma or that in the observed range of plasma C12 concentrations, the carrier processes are observed in the near-linear region of their action. Therefore, the final model used is a one-compartment model with a linear exit to tissues and urine (differentiated by the known percent urinary elimination).

The model was fitted separately on each experimental subject by unweighed nonlinear least squares, using a quasi-Newton minimization algorithm.[14] The asymptotic SE of each parameter estimate was computed by inverting the Hessian matrix at the minimum and using Cramer-Rao inequality.

Because the theoretical respiratory quotient from the combustion of dodecanedioic acid is intermediate between those of glucose and FFAs, it is not possible, by measuring only two parameters ($\dot{V}O_2$ and $\dot{V}CO_2$) to derive simultaneously the amounts of C12, glucose, and lipids instantaneously oxidized. In this case, the commonly used equations do not hold. The average increase of $\dot{V}O_2$ over the basal values during

the infusion was computed and expressed as percentage of the basal V_{O_2}. The npRQ values observed during the infusion were compared with those recorded before the C12 infusion was started by paired Student's *t* test. All results are reported as means ± SE, unless specified otherwise.

For the end-infusion period, assuming that C12 oxidation proceeds at steady state, the rate of C12 oxidation can be taken as known (equal to the percent oxidation times the infusion rate) and the following metabolic equations can be written (from the stoichiometric reaction of oxidation of C12 under the hypothesis of complete oxidation):

$$\text{M:} \quad V_{O_2} = 0.746\,G + 2.029\,L + 6.04\,N + 1.509\,D,$$

$$V_{CO_2} = 0.746\,G + 1.430\,L + 4.89\,N + 1.169\,D,$$

where V_{O_2} and V_{CO_2} (mL/min) are given in terms of oxidized glucose, lipids (except C12), excreted urinary nitrogen, and oxidized dodecanedioic acid, respectively (mg/min). An average chain length of 17 carbon atoms has been used for FFAs in the metabolic computations, corresponding to a molar weight of 270 g.

Two-way analysis of variance (ANOVA), using subjects as blocks and period (basal *vs* end-infusion) as factor, was used to assess the significance of differences in nutrient usage between the preinfusion dodecanedioic acid–free situation and the stable dodecanedioic end-infusion period.

Oxidation Rate of Dodecanedioic Acid. The amount of dodecanedioate oxidized was calculated, according to Nordenstrom et al[15] as the ratio between the total radioactivity excreted with expired air and the amount of labeled C12 infused (percent oxidation). The total radioactivity excreted was determined as the area under the curve (AUC) of the rate of expired radioactivity (as $^{14}CO_2$) *vs* time (AUC_e). The AUC_e was calculated using the trapezoidal approximation from 0 to 600 minutes and extrapolating the $^{14}CO_2$ profile after 600 minutes with an exponential decay whose time constant was determined from the data recorded after 415 minutes.

RESULTS

The mean number of binding sites per albumin molecule, as determined by equilibrium dialysis, was 2.93 ± 0.12 with an affinity constant K of 8.76 ± 1.82 × 10^3 M^{-1}. The 24-hour urinary excretion of C12 in the eight subjects under study was 3.14 ± 0.96 mmol, corresponding to about 7% of the administered dose and ranged from a minimum value of 0.47 mmol to a maximum value of 8.26 mmol. The urinary nitrogen loss over 24 hours was 4.77 ± 0.36 g and, therefore, within a normal range. The time course of unlabeled C12 plasma concentration is represented in Figure 1; the levels of C12 gradually rose to the peak that was reached at the end of the infusion. The labeled C12 concentration in plasma *vs* time is plotted in Figure 1, showing that the shape of the curve was similar to the time course of plasma unlabeled C12 concentration. Figure 2 shows plasma labeled C12 (μCi/mL) time-concentration points for one experimental subject, together with the fitted model curve.

The volume of distribution of labeled C12 estimated by the model was 139.02 ± 10.84 mL/kg_{bw}, and the plasma elimination constant of C12 was 0.01 ± 0.004 min^{-1}. The rate of excretion of $^{14}CO_2$ is reported in Figure 3. In all examined subjects, there was a rapid increase of expired radioactivity that peaked about 40 minutes after the end of the labeled C12 infusion. The amount of C12 oxidized, expressed as percent oxidation, was equal to 35.44 ± 1.64%. The average increase of V_{O_2} over the basal values was 3.25%, indirectly indicating that the thermogenic effect of the administered dose of C12 was small.

Because the average V_{O_2} and V_{CO_2} in the end-infusion phase (minutes 90 through 180) were, respectively, 277.14 and 212.62 mL/min, the nitrogen excretion rate was 3.3 mg/min, the constant infusion rate of C12 was 0.24 mmol/min, and its oxidation was 0.085 mmol/min (19.56 mg/min, 35.44%), we can solve equations M for L and G, giving an average lipid and glucose consumption of 0.334 and 0.331 mmol/min (90.28 and 59.66 mg/min) in the steady-state end-infusion phase. The corresponding computation done on the average basal values of V_{O_2} and V_{CO_2} in the absence of C12 administration (respectively, 258.46 and 206.86 mL/min) shows an average minute fuel consumption of 0.296 mmol/min for lipids and 0.571 mmol/min for carbohydrates (respectively, 79.80 mg/min and 102.71 mg/min). Two-way ANOVA shows a highly significant difference between basal and dodecanedioic acid–associated glucose consumption (about 40% decrease with dodecanedioic acid, $p < .001$) and a significant difference in lipid consumption (about 10% increase with dodecanedioic, $p = .032$). Taking into account that V_{O_2} shows a highly significant increase (about 10%, $p < .001$), whereas V_{CO_2} does not change significantly with dodecanedioic acid administration, the increase in lipid consumption appears determined by the increase in energy expenditure, whereas the decrease in glucose consumption appears determined by the fuel preference with shift to dodecanedioic acid oxidation.

The mean basal value of npRQ (0.80 ± 0.006) significantly ($p < .02$) decreased during the infusion to 0.78 ± 0.01, which is a value close to the theoretical RQ value calculated for C12 oxidation

$$C12O_4H_{22} + 15.5O_2 \longrightarrow 12CO_2 + 11H_2O$$

with

$$\frac{CO_2}{O_2} = \frac{12}{15.5} = 0.77.$$

DISCUSSION

Preliminary studies in Wistar rats[9] showed that the urinary loss of C12 is very small, ranging from 3% to 5% of the given dose, and that its tissue uptake is rapid: the rate of C12 plasma clearance being 5% per minute.[9] In addition, Bergseth et al[16] demonstrated that the oxidation of dodecanedioic acid in rats ranged from 28% to 39% depending on the dose of C12 administered.

Although different methodologic approaches were used in the rat experimental protocol[9] with respect to this study (IV bolus in a rat population *vs* a continuous IV infusion in single subjects), we found a relatively rapid C12 plasma clearance rate (1% min^{-1}). In particular, the most relevant observation is that the oxidation of C12 was very high, corresponding to about 35% of the administered amount. The urinary excretion of C12 was relatively small, about 7% of the given dose, compared with that of other shorter-chain DA. In fact, from 50% to 76.9% of azelaic acid was excreted in the urine depending on the infusion rate used,[14] and sebacic acid was lost with urine to a minor extent, from 16% to 46%, again depending on the amount of C10 infused.[5–7] In any case, the loss of C10 with urine was too high to support the use of pure sebacic acid in parenteral nutrition. Therefore, C12 with a much lower urinary excretion represents a valid candidate substrate for use in parenteral nutrition. In addition, it should be pointed out

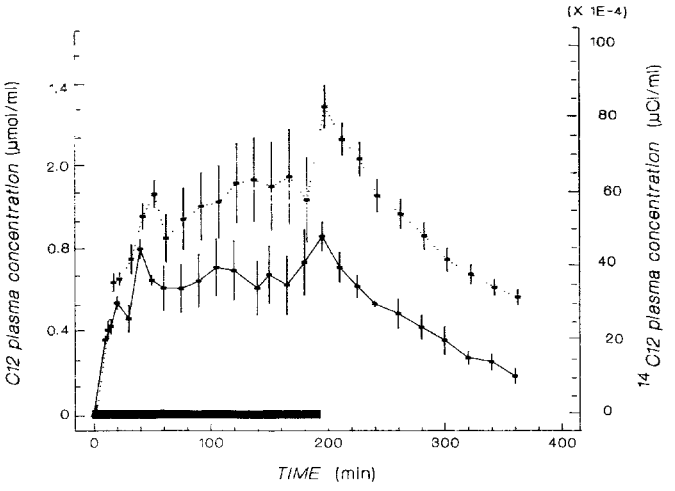

FIG. 1. Plasma-unlabeled C12 average concentration time course (—) and plasma-labeled C12 average concentration time course (– –) during and after IV infusion. Bars, SD at each time point. C12 infusion is indicated by a solid bar.

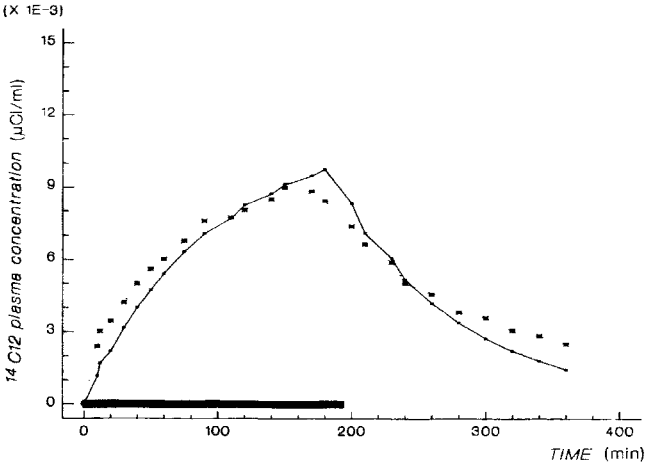

FIG. 2. Plasma-labeled C12 concentration time course of experimental subject 1 (– –), together with the model-predicted time course (—). C12 infusion is indicated by a solid bar.

that the amount of sodium provided by C12 is much smaller than that administered with infusion of lower carbon atoms DA for the same caloric content. However, although electrolytic or acid-base alterations never ensued, other strategies may be needed to further reduce the sodium load.

Studies using indirect calorimetry demonstrate that in normal lean subjects approximately 60% of a 100-g oral glucose load is stored during the 3 hours that follow the administration of glucose, with only 20% being oxidized in excess of basal glucose oxidation.[17] Approximately 75% of glucose administered per os[18] and 85% of glucose administered intravenously[19] is initially stored in muscle or in the liver.

In healthy postabsorptive subjects, the fraction of $^{14}CO_2$ derived from FFA oxidation was found to be around 23%,[15,20] whereas this value increases up to 34.7% in patients who undergo major abdominal surgical operations or in septic patients[15] before total parenteral nutrition is started.

Metges and Wolfram[21] compared the rate of conversion of MCT and LCT to CO_2 after parenteral or oral administration in humans associated with a 100-mg dose of [^{13}C]trioctanoate or [^{13}C]trioleate. They found that the oxidation rate for [^{13}C]trioctanoate was on the average 31% after parenteral administration and for [^{13}C]trioleate, 24.9%. The data obtained after oral administration were slightly higher than after parenteral administration, respectively, 34.7% and 25.3%.

Compared with the above results, C12 might represent an effective alternate fuel substrate immediately available for tissue energy requirements, because a substantial amount of C12 is promptly oxidized. In addition, the formation of succinic acid during the oxidation of C12[11] indicates that this compound, besides being a gluconeogenetic substrate by itself, may favor the use of other conventional substrates as well by increasing the availability of Krebs cycle intermediates.

Our data on substrate oxidation during dodecanedioic acid administration indicate that C12 compete with glucose for oxidation, as observed by Randle et al[22] in the

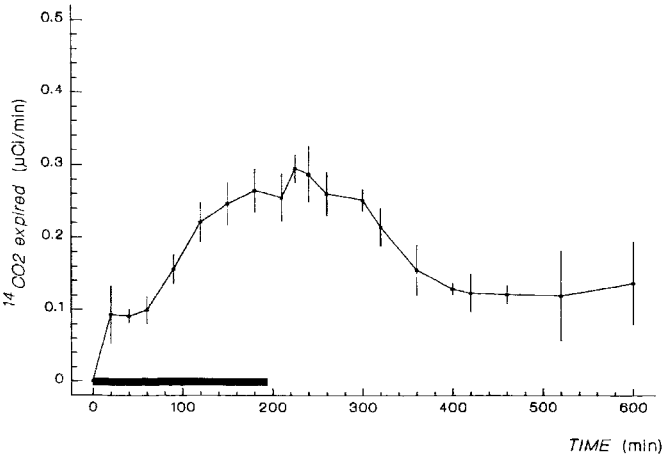

FIG. 3. Labeled expired Co_2 average time course. Bars, SD at each time point. C12 infusion is indicated by a solid bar.

glucose-fatty acid cycle. The theory of Randle et al[22] states that because both lipids and glucose are metabolized to acetyl-CoA before entering the citric acid cycle, they compete for entry in the citric acid cycle and thus for the aerobic pathway. This means that when FFA are oxidized in excess, the glucose oxidation is reduced, and conversely, when glucose enters the cells in large amounts, the lipid oxidation decreases. The infusion of a substrate like C12, which produces metabolizable substrates (acetyl-CoA) and intermediates of the Krebs' cycle (succinyl-CoA), reduces the oxidation of glucose while increasing the amount of FFAs to be oxidized in the cells. This glucose-sparing effect of C12 was also observed during the infusion of another even-numbered carbon atoms DA, sebacic acid, with a chain length of 10 carbons,[8] suggesting that these DA and, in particular, C12, which is excreted with urine at a lower extent, might be useful in those clinical condition in which a reduced use of glucose is present because of an insulin-resistance state. This is the case of diabetes mellitus,[23,24] obesity,[24] trauma, and sepsis.[-]

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