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Use of Even-Numbered Carbon Atom Dicarboxylic Salts in Parenteral Nutrition as Fuel Substrate

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ABSTRACT. Sebacic acid (C10), a saturated, straight-chain dicarboxylic acid with 10 carbon atoms in disodic salt form, was given intravenously to two groups of healthy male volunteers in order to evaluate its possible use in total parenteral nutrition. The first group, composed of six subjects, received 1000 mg of sebacate as a bolus; six other subjects (second group) received 10 g of sebacate dissolved in 500 mL of double-distilled water at an infusion rate of 3.33 g/h over 3 hours. The serum sebacate data for each subject were analyzed by computer, using biexponential fit corresponding to a 2-compartment open model. The distribution half-life ($t_{1/2}$) was 0.34 ± 0.06 hour and the elimination phase was rather rapid (Ke = 2.10 ± 0.38/h); the volume of the central compartment was 2.79 ± 0.54 L and the volume of tissue compartment 3.72 ± 0.14 L. These data showed a good tissue fixation of sebacate. The plasma clearance was evaluated to be 5.96 ± 2.19 L/h and the renal clearance was 19.22 ± 10.69 L/h, indicating that a tubular secretion of C10 takes place. The serum concentration of sebacate raised to the maximal value at the end of the infusion (180 minutes), corresponded to 480.50 ± 43.02 μg/mL.

Respiratory and metabolic parameters were evaluated by indirect calorimetry from the beginning of the infusion for 210 minutes. The O_2 consumption ($\dot{V}O_2$ mL/min per square meter) remained essentially unchanged throughout the experiment (from 154.3 ± 28.3 at time 0 to 155.3 ± 39.5 at time 180 minutes). The CO_2 production ($\dot{V}CO_2$ mL/min per square meter) decreased from below basal values (147.7 ± 27.3) to 123.7 ± 25.0 at the end of the infusion. Thus, respiratory quotient (RQ) decreased significantly (from 0.96 ± 0.04 to 0.81 ± 0.06) and the percentage of calories derived from lipids increased during and after the infusion (from −0.13 ± 13.3 to 52.1 ± 26.2). Metabolic rate (MR, kcal/h per square meter) remained constant during the entire study period. In conclusion sebacate seems to be a valuable new substrate for use in total parenteral nutrition and may have properties useful in special metabolic conditions. In this study, the urinary excretion of C10 and its products of β-oxidation (suberic [C8] and adipic [C6] acids) was found to be low (totaling less than 16% of the administered dose) and the energy production high (6.64 kcal/g) with C10 being completely oxidized in the organism to CO_2 and H_2O. (*Journal of Parenteral and Enteral Nutrition* **16**:32–38, 1992)

This study evaluated whether sebacic acid, a saturated straight-chain dicarboxylic acid with 10 carbon atoms, can be used as a substrate for total parenteral nutrition (TPN). In fact, this diacid could be particularly useful in patients with deranged metabolism secondary to the stress of major surgery, accidental trauma, or sepsis.

The first report of dicarboxylic acid (DA) was by Verkade et al[1,2] in 1933/1934 as a result of their general studies on fat metabolism. These authors found that the administration of medium-chain (from C8 to C12) monocarboxylic acids to humans or animals resulted in urinary excretion of the corresponding chain length DA, as well as small amounts of shorter chain length DA. Later, some cases of dicarboxylic aciduria were described as congenital or acquired defects of fatty acid (FA) oxidation.[3]

A congenital inhibition of β-oxidation with DA excretion is described in neonates who clinically display symptoms apparently caused by incomplete catabolism of FA simultaneously with carbohydrate depletion.[4–6] The site for this defect seems to be located at the acetyl-CoA dehydrogenase level due to the lack of an enzyme that cleaves two hydrogen atoms from the α and β positions of FA. Consequently, the entire β-oxidation process is impaired and therefore ω-oxidation takes place with DA production.

An acquired defect of β-oxidation that produces dicarboxylic aciduria is the Jamaican vomiting sickness that occurs after eating unripe akee-fruit, whose content of hypoglycine A is the cause of a Reye-like syndrome.[7–9] A possible mechanism of action of hypoglycine A metabolites is the sequestration of the cofactors, carnitine and coenzyme A, with impairment of β-oxidation and FA diversion toward the DA pathway. Also, ketotic patients who have enhanced FFA mobilization with impaired acetyl-CoA utilization in Kreb's cycle seem to excrete elevated amounts of DA adipic (C6) and suberic (C7) in the urine. On these grounds some authors proposed the hypothesis that the omega-oxidation of FA[10,11] intervenes when β-oxidation is impaired. In fact, DA produced by ω-oxidation are not toxic, but are water soluble and easily excreted in the urine thus preventing dangerous accumulation of free fatty acids (FFA) in the plasma. Consequently, omega-oxidation could be viewed

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as a detoxification process for FFA. Therefore, it seems conceivable to propose the use of DA in total parenteral nutrition as a possible alternate fuel source especially in critical conditions, such as in the advanced states of sepsis, when glucose intolerance, increased gluconeogenesis, and oxidative defects of the intermediary metabolism ensue. In these situations increased lipid fuel dependency has been shown and in fact intravenous lipid emulsion has been extensively used as a caloric supplement.[12,13] Moreover, in the critically ill, lipids provide a means of increasing the net oxidation of nutritional fuel without increasing carbon dioxide production ($\dot{V}CO_2$) that represents a significant advantage when ventilatory support for pulmonary insufficiency is required. However, there is evidence[14,15] that fat metabolism might be impaired at some stages of septic processes, allowing high levels of plasma triglycerides, which can induce cerebral microembolism and consequent injury of the nervous tissue due to anoxia. Additional studies supporting this hypothesis include the recent findings of impairment of both lipoproteinlipase (LPL) activity[16] and of carnitine deficiency in such patients.[17] Therefore, we proposed to utilize DA in TPN[18] because of the absence of toxicity, even when administered in large amounts, and because DA can be administered directly through a peripheral vein in salt form, thus circumventing the LPL hydrolysis step.

DA are β-oxidized at the level of mitochondria, yielding malonic or succinic acids as terminal products, which are derived respectively from DA with an odd or even carbon atom number.[19] Malonic acid starts the synthesis of DA while succinic enters the Kreb's cycle. In addition, there is experimental evidence that peroxisomes are capable of β-oxidizing DA.[20] It is possible that β-oxidation of DA uses the same enzyme system as monocarboxylic acids.[21] Although previous data, obtained by indirect calorimetric technique, showed that the oxidation of C9 DA, ie, azelaic acid (Az), is associated with a low cost of ATP synthesis in terms of carbon dioxide production, the major problem was that more than 50% of the administered dose of Az was excreted in the urine.[18] Thus, we studied whether sebacic acid, which is the superior homologue with 10 carbon atoms, would decrease of urine excretion and be accompanied by good tissue utilization.

MATERIALS AND METHODS

Sebacate Administration

Twelve healthy male volunteers ranging in age from 25 to 40 years (mean ± SD: 31.0 ± 5.60 years) were admitted to the present study. Six subjects (group I) received 1000 mg of sebacate (prepared as described below) dissolved in 5-mL double-distilled water injected as a bolus in a forearm vein. Six others (group II) received IV 10 g of sebacate dissolved in 500 mL of double-distilled water at a rate of 3.33 g/h over 3 hours using an electric syringe pump. Blood samples (5 mL) were collected without an anticoagulant and were centrifuged. Serum samples were frozen until analyzed. Blood sampling was taken at 0, 5, 10, 20, 30, 40, 50, 60, and 70 minutes after IV bolus of C10 and at 30, 60, 90, 120, 150, 180, 210, and 240 minutes after beginning the IV infusion of sebacate. The patients voided before the C10 infusion was started. Twenty-four-hour urine was collected together in the same container. The protocol was approved by the Ethical Committee of the Institutional Health Review Board Health of the Science Centre of the Catholic University School of Medicine in Rome. Written informed consent was obtained in all cases.

Sebacate Solutions

We prepared 1-mol/L solution of sebacic acid salified with NaOH according to the following reaction:

$$1\ \text{mol/L}\ HOOC\text{-}(CH_2)_8\text{-}COOH + 2\ \text{mol/L}\ NaOH \rightarrow 1\ \text{mol/L}\ NaOOC\text{-}(CH_2)_8\text{-}COONa + 2\ \text{mol/L}\ H_2O$$

Then 1 mol/L sebacate was diluted with double-distilled water to obtain the chosen concentration. The infusions were sterilized using a Millipore filter (Molsheim, France) before administration.

Dicarboxylic Acid Analysis

DA were extracted from both serum and urine samples and dimethyl esters were synthesized as previously reported.[18] Then analysis of dimethyl derivatives of DA was performed by gas liquid chromatography according to our previously described method.[18]

Indirect Calorimetric Analysis

Respiratory and metabolic parameters were assessed as already described,[22,23] using a computerized monitoring system equipped with: (1) mass spectrometer for a rapid analysis of O_2, CO_2, and N_2; (2) pneumotachometer for inspiratory and expiratory flow measurement; (3) analog/digital converter; (4) microcomputer that analyzes signals and computes derived parameters. For each breath, the computer performed a complete analysis of inspiratory and expiratory gas, giving the tidal volume (V_T); O_2-end and CO_2-end tidal values; O_2 consumption ($\dot{V}O_2$); CO_2 production ($\dot{V}CO_2$); and respiratory quotient (RQ). $\dot{V}O_2$ (mL/min per square meter) and ($\dot{V}CO_2$) (mL/min per square meter) were calculated according to the conventional formulas; RQ was calculated from the $(\dot{V}CO_2)/\dot{V}O_2$ ratio and the metabolic rate (MR, kcal/m^2 per 24 hours) was obtained by a previously described method.[24]

Statistical Analysis

Data were expressed as the mean ± SD. Linear regression analysis was performed to evaluate the correlation between various parameters. Statistical analysis for the indirect calorimetric data was performed using the multiple linear-regression technique and Scheff's test for simultaneous sample variance analysis.[25] The F ratio (the ratio of explained to unexplained variability adjusted for the degrees of freedom) and the p value indicate the reliability of the data.

RESULTS

Pharmacokinetic Data

The serum sebacate data for each subject were analyzed by computer, using biexponential fit corresponding to a 2-compartment open model. In Table I the equations used for pharmacokinetic profile analysis are summarized. The serum concentrations (mean ± SD) of sebacate determined over 1 to 4 hours in two groups of subjects treated with a single intravenous dose of 3000 mg of C10, administered as a bolus (group I), and as a 3-hour infusion at a rate of 3.33 g/h (group II), are plotted in Figures 1 and 2. The lines represent the computer best fit of data. The elimination is clearly biexponential.

Individual kinetic parameters for group I are given in Table II. The amounts of both C10 and its product of β-oxidation, suberic (C8), and adipic (C6) acids, excreted in the urine over a period of 24 hours are reported in Table III; less than 16% of the administered dose of DA was eliminated in the urine.

TABLE I
Equations used for pharmacokinetic profile analysis

$C_1 = Ae^{-} + Be^{-\beta t}$	$k_{el} = \frac{A + B}{A/\mathring{a} + B/\beta}$
$k_{21} = \frac{\mathring{a}\beta}{k_{el}}$	$k_{12} = \frac{AB(\beta - \mathring{a})^2}{(A + B)^2 k_{21}}$
$V_1 = \frac{D}{A + B}$	$V_2 = V_1 \frac{k_{12}}{k_{21}}$
$V_d \text{ area} = \frac{D}{AUC_{o-\infty}\beta}$	$Vdss = \frac{\mathring{a} + \beta - K_{el}}{k_{21}} V_1$
$Cl_r = V_{d\ area}\ k_e$	$CL_p \text{ (bolus)} = \frac{D}{AUC_{o-\infty}}$

Where: C_1 is the concentration of sebacate in central compartment at time t; β is β-phase elimination rate constant; å is distribution rate constant; B is the extrapolated initial concentration in the central compartment; A is the extrapolated initial concentration in the tissue compartment; k_{el} is the first-order rate constant for elimination of sebacate from the central compartment; k_{21} is the first-order rate constant for transfer of sebacate from tissue compartment to central compartment; k_{12} is the first-order rate constant for transfer of drug from central compartment to tissue compartment; V_1 is the volume of central compartment; D is the amount of sebacate injected (dose); V_2 is the volume of tissue compartment; $AUC_{o-\infty}$ is the total area under plasma concentration curve calculated from the equation $C_1(t)$ and extrapolated to infinity; Vdss is the volume of distribution at steady state; CL_p is the plasma clearance; and CL is the renal clearance.

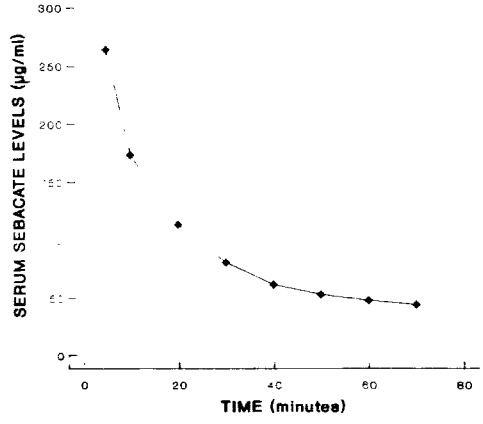

FIG. 1. Mean serum concentrations (±SD) of sebacate after a single intravenous dose of 1000 mg as bolus. The line represents the computer best fit of data (C1 is the concentration of sebacate in the central compartment at time t). The elimination is exponential.

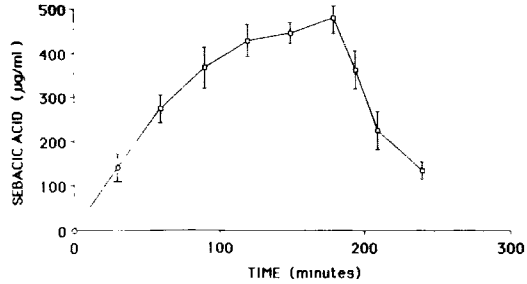

FIG. 2. Serum levels (µg/mL) (mean ± SD) of disodic sebacate (C10) after IV infusion of 10 g at a rate of 3.33 g/h over a period of 3 hour. The *solid line* indicates that C10 was infused during the first 180 minutes.

Indirect Calorimetric Data

The data were analyzed with respect to $\dot{V}O_2$, $\dot{V}CO_2$, RQ, and MR (Fig. 3). The 24-h nitrogen loss[26] determined in the group of subjects infused with sebacate (IR = 3.33 g/h) was 14.2 ± 2.0 g per 24 hour.

The basal values of O_2 ($\dot{V}O_2$ mL/min per square meter) remained essentially unchanged throughout the experiment, whereas the $\dot{V}CO_2$ (147.7 ± 27.3 mL/min per square meter at the beginning of infusion) decreased during the infusion reaching values of 123.7 ± 25.0 mL/min per square meter at 180 minutes.

RQ reflected the $\dot{V}O_2$ and $\dot{V}CO_2$ pattern; basal values decreased to 0.81 ± 0.06 at 180 minutes showing a significant drop ($p < 0.001$).

The analysis according to the de Weir equations[24] (Fig. 4) showed a marked change in the quantity of calories derived from lipid oxidation during infusion. The percentage of calories derived from lipids increased to more than 50% at 180 minutes.

The values of molecular weight, O_2 consumed, CO_2 produced (mM), RQ, kcal/g of substrate oxidized, ATP/mol, ATP/kcal, and ATP/CO_2 for glucose, palmitic acid, azelaic, and sebacic acids are comparatively reported in Table IV.

The stoichiometric analysis of sebacate oxidation is reported in the Appendix.

DISCUSSION

Recently, we proposed the introduction of DAs in TPN suggesting their use in particular conditions, such as sepsis, in that the cellular utilization of traditional fuel substrates as glucose or long-chain triglycerides (LCT) is impaired.[18] DA have the advantage of being directly available for cellular uptake because they are transported in the plasma in free form and not esterified with glycerol as long- or medium-chain triglycerides (MCT), therefore bypassing the hydrolysis step at the level of lipoprotein lipase. In addition, DA administration does not require complex and expensive pharmaceutical procedures, as in the case of lipid emulsions (LCT or MCT), because dicarboxylic salts are highly soluble in water. Another advantage of DA is that their intramitochondrial transport is probably carnitine-independent and they can also be oxidized in the peroxisomes.[27] However, as previously

TABLE II
Pharmacokinetic parameters (means ± SD) of sebacate after a single intravenous dose of 1000 mg as bolus

$\hat{a}$ (h^{-1})	$t_{1/2\hat{a}}$ (h)	β (h^{-1})	$t_{1/2\beta}$ (h)	k_{e1} (h^{-1})	k_{21} (h^{-1})	k_{12} (h^{-1})	V_1 (liter)	V_2 (liter)	Vdss (liter)	Vd_{area} (liter)	AUC (mg/L·h)	CL_p (liter/h)	$t_{1/2}$ (h)	CL_t (liter·h^{-1})
5.97 ± 1.13	0.12 ± 0.02	0.67 ± 0.10	1.05 ± 0.15	2.10 ± 0.38	1.91 ± 0.43	2.63 ± 0.99	2.79 ± 0.54	3.72 ± 0.14	6.51 ± 0.68	8.79 ± 2.01	180.02 ± 66.22	5.96 ± 2.19	0.34 ± 0.06	19.22 ± 10.69

See Table I for definition of terms.

TABLE III
Amounts of sebacic, suberic, and adipic acids excreted in 24 h urine for each of 6 healthy volunteers infused with 10 g of sebacate for a 3-h period at a rate of 3.33 g/h

Volunteer	Sebacic acid (g)	Suberic acid (g)	Adipic acid (g)
1	1.088	0.207	0.157
2	1.120	0.231	0.130
3	1.205	0.248	0.159
4	1.206	0.280	0.191
5	1.307	0.258	0.180
6	1.319	0.255	0.185
Mean ± SD	1.216 ± 0.096	0.246 ± 0.025	0.167 ± 0.023

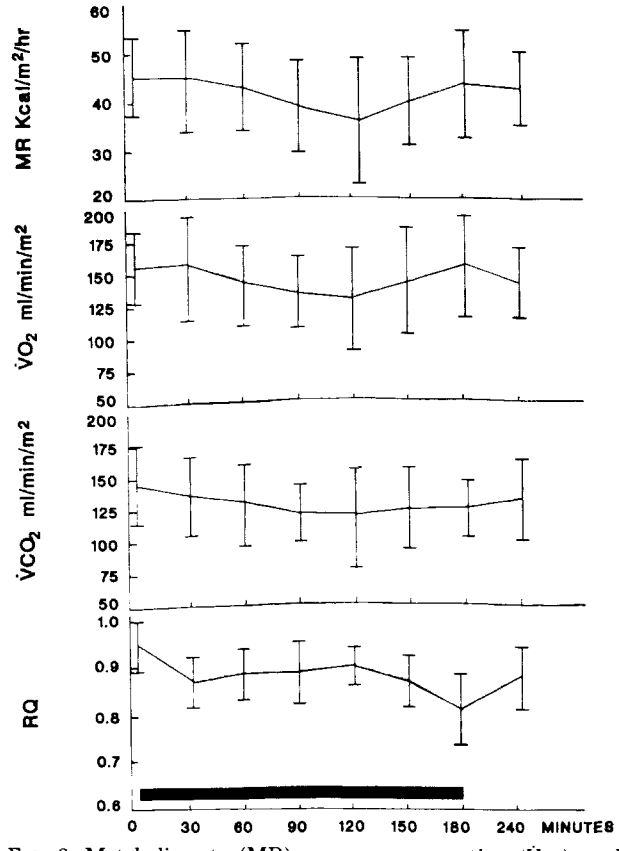

FIG. 3. Metabolic rate (MR), oxygen consumption ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$), and respiratory quotient (RQ) during the study period (mean ± SD).

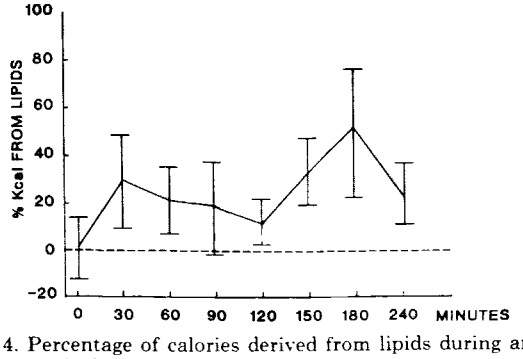

FIG. 4. Percentage of calories derived from lipids during and after the infusion of sebacate.

TABLE IV
Stoichiometric comparison of substrates

Substrate	MW* Reaction	Products	O_2 consumed ($mmol \cdot L^{-1} \cdot kcal^{-1}$)	CO_2 produced ($mmol \cdot L^{-1} \cdot kcal^{-1}$)	RQ	kcal/g	ATP/mol	ATP/kcal	ATP CO_2
Glucose	180 Oxidation	$CO_2 + H_2O$	9.0	9.0	1.0	3.7	38	0.057	6.3
Palmitic acid	256 Oxidation	$CO_2 + H_2O$	10.0	6.9	0.7	9.0	129	0.056	8.1
Azelaic acid	188 Oxidation	$CO_2 + H_2O$ + malonic acid	9.56	6.38	0.66	4.97	49	0.052	8.17
Sebacic acid	202 Oxidation	$CO_2 + H_2O$	9.31	7.45	0.8	6.64	70	0.052	7.0

* MW, molecular weight.

reported[18] the sodium salt of Az, a saturated DA with a straight-chain of nine carbon atoms, is excreted in the urine in great amounts, exceeding 50% of the infused Az. Considering the additional urinary loss of pimelic acid, a seven-carbon product of the β-oxidation of Az, the total amount of Az utilized by the organism when 10 g of Az are administered IV over 80 minutes is only 2.5 g. Therefore, in the present study we investigated whether the superior homologue of Az, ie, sebacic acid (C10), permits a better utilization of this fuel substrate causing a lower urinary loss.

As expected, the pharmacokinetic profile of sebacate shows that the distribution phase in the subjects who received a bolus injection was short ($t_{1/2}$ = 0.34 + 0.06 hours) and the elimination phase was rather rapid (Ke = 2.045 + 0.38 per hour). The volume of the central compartment corresponded to the hematic volume, although the volume value of the tissue compartment indicates that a cellular fixation results. The salts of sebacic acid, having the dissociation constants of C10 $K_1 = 2.6 \times 10^{-5}$ and $K_2 = 2.6 \times 10^{-6}$, are completely dissociated in ionic form at the physiological pH and thus easily soluble in plasma and interstitial fluid. Therefore, it can be deduced that an active DA transport system exists and is involved in their passage across the cellular membrane, which is permeable only to liposoluble molecules. A similar active transport system has been recently described by Saint-Macary and Foucher[28] in the mitochondrial inner membranes; it is involved in the dicarboxylate-dicarboxylate and dicarboxylate-phosphate exchanges. The high value of the renal clearance seems to indicate that a tubular secretion of C10 takes place in agreement with Ullrich et al.[29] These authors, in fact, demonstrated that three different anion transport systems exist at the contraluminal cell side of the proximal renal tubule of the rat kidney: (1) a sulfate-oxalate transporter, (2) a sodium-dependent dicarboxylate transporter, and (3) a para-aminohippurate transporter. The para-aminohippurate transport system accepts dicarboxylates with chain lengths longer than 0.75 nm, which is the distance between the two terminal oxygen atoms, while the dicarboxylate transport system interacts with dicarboxylic acids having a chain length in a range form 0.65 to 1.0 nm (ie, C6 to C10). The tubular secretion rate of DA seems to be inversely correlated to the number of carbon atoms in their molecules: the higher the number of carbon atoms up to C12, the lower the urinary excretion.[29] In fact, sebacate and its β-oxidation products were eliminated in the urine to a much lower extent than Az and its by-products (16% *vs* 75%).

As far as the calorimetric data is concerned, the RQ dropped significantly under basal values in all the subjects studied during the sebacate infusion (Fig. 3), with a peak at 180 minutes. During the infusion of sebacate there was a significant shift toward lipid oxidation; suggesting that C10 had been oxidized to produce energy. The protein catabolism was stable throughout the study period, the lipid oxidation rate (g/h) increased as an absolute value, but there was a marked depression of glucose utilization. It has been shown that the administration of LCT or MCT without a simultaneous infusion of glucose suppresses glucose oxidation, probably by reducing the insulin secretion rate. This would also seem to have happened when DA was administered. In addition, the stoichiometric analysis showed that the absolute CO_2 production per kcal of sebacate was low (7.45 mmol/L per kilocalorie) and this could represent an advantage in patients with respiratory distress. The kcal/g and ATP/mol ratios of C10 were higher than those of glucose (6.64 *vs* 3.70 and 70 *vs* 38, respectively), but lower than those of long-chain fatty acids (Table IV).

The energy balance of oxidative reactions of even-numbered carbon atom DA seems to be more advantageous than that of odd-chain DA for TPN. Contrary to odd-chain DA that yield malonyl-CoA and acetyl-CoA as terminal products of β-oxidation, DA, having an even number of carbon atoms, are totally oxidized giving CO_2 and H_2O as terminal products, as shown in Figure 5.

In fact, oxaloacetate, which originates from succinate via the citric acid cycle, can be decarboxylated to produce pyruvic acid, which loses another CO_2 group giving acetic acid, the last completely oxidized compound in Kreb's cycle.

In conclusion, sebacate seems to be more useful than Az for TPN. Sebacate and its β-oxidation by-products (C8 and C6) are excreted in the urine at a significantly rate than Az and pimelic acid (16% *vs* 75%) and therefore, the amounts of C10 available as cellular fuel substrate are very high. In addition, the energy production from sebacate is greater than that from azelate (6.64 *vs* 4.97 kcal/g) because C10 is totally oxidized in cells and C9 is not. Therefore, the respective β-oxidation terminal products are acetyl-CoA and malonic acid, with the former undergoing further metabolization for energy whereas malonic acid does not.

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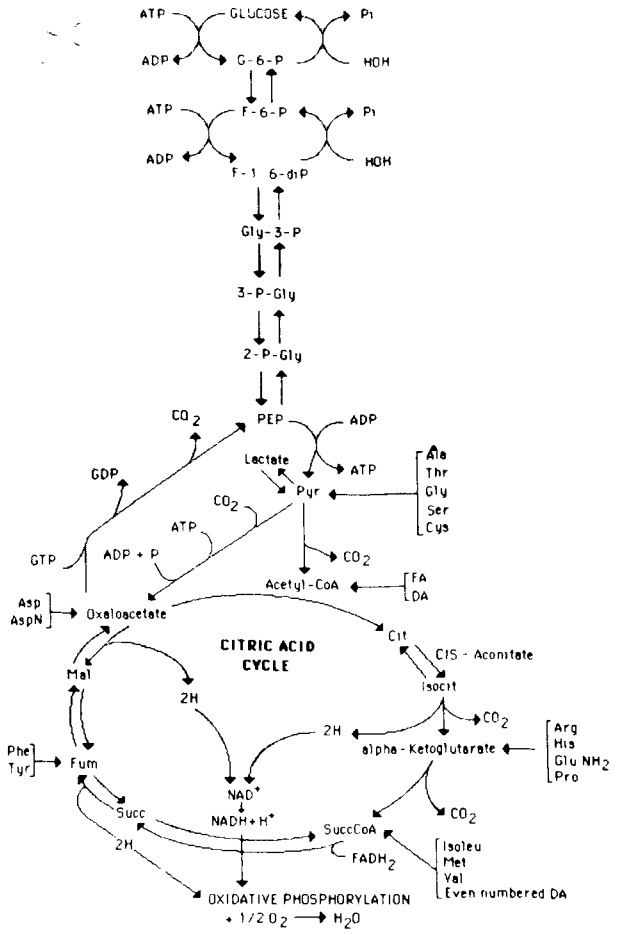

FIG. 5. Oxidative metabolic pathways. *G-6-P* = glucose-6-phosphate; *F-6-P* = fructose-6-phosphate; *F-1, 6-diP* = fructose-1, 6-diphosphate; *Gly-3-P* = glyceraldeide-3-phosphate; *3-P-Gly* = 3-phosphoglycerate; *2-P-Gly* = 2-phosphoglycerate; *PEP* = phosphoenolpyruvate; *Pyr* = pyruvate; *Cit* = citrate; *Isocit* = isocitrate; *Succ CoA* = succinyl-CoA; *Succ* = succinate; *Fum* = fumarate; *Mal* = malate; *Arg* = arginine; *His* = histidine; *Glu* NH_2 = glutamine; *Pro* = proline; *Isoleu* = isoleucine; *Met* = methionine; *Val* = valine; *Phe* = phenylalanine; *Tyr* = tyrosine; *Asp* = aspartic acid; *Asp* NH_2 = asparagine; *FA* = fatty acids; *DA* = dicarboxylic acids.

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APPENDIX

The reaction that describes the complete oxidation of sebacate is:

$$COOH\text{-}(CH_2)_8\text{-}COOH + 12.5\ O_2 \rightarrow 10\ CO_2 + 9\ H_2O$$

The respiratory quotient (RQ), defined as the ratio between moles of CO_2 produced and moles of O_2 consumed, is 0.8.

To oxidize 1 g of C10, equivalent to 0.00495 mol/L, 1.3870 L of O_2 are necessary, which corresponds to 0.0619 mol/L of this gas.

Therefore:

$$0.00495 \text{ mol sebacate} + 0.0619 \text{ mol } O_2 \rightarrow 0.0495 \text{ mol } CO_2 + 0.0445 \text{ mol } H_2O$$

ie,

$$1 \text{ g C10} + 1.3870 \text{ L } O_2 \rightarrow 1.108 \text{ L } CO_2 + 0.801 \text{ g } H_2O.$$

The caloric value per gram of C10 is calculated using the following equations:

$$3.91 + (1.10 \times RQ) = 3.91 + (1.10 \times 0.8) = 4.79 \text{ kcal/L } O_2$$

$$1.3870 \text{ L } O_2 \times 4.79 \text{ kcal/}CO_2 = 6.643 \text{ kcal/g C10}.$$

Thus, 1 kcal C10 is equivalent to 0.000745 mol.

$$\text{Sebacic acid} + 4 \text{ CoA} + \text{ATP} + 3 \text{ FAD} + 3 \text{ NAD}^+ + 3H_2O \rightarrow \text{Succinyl-CoA} + \text{AMP} + \text{PPi} + 3FADH_2 + 3 (NADH + H^+) + 3\text{acetyl-CoA}$$

Three ATP are generated when each NADH is oxidized by the respiratory chain, whereas two ATP are formed for each $FADH_2$. The oxidation of acetyl-CoA by the citric acid cycle yields 12 ATP. Hence, the number of ATP formed in the oxidation of sebacic acid up to succinyl-CoA is 6 from the 3 $FADH_2$, 9 from the 3 NADH + H^+, and 36 from the 3 molecules of acetyl-CoA, which gives a total of 51 ATP. Two high-energy phosphate bonds are consumed in the activation of sebacate, in which ATP is split into AMP + 2 Pi. Thus, the net yield from the partial oxidation of sebacate is 49 ATP. But,

$$\text{Succinyl-CoA} + \text{Pi} + \text{GDP} \rightarrow \text{succinate} + \text{GTP} + \text{CoA}$$

This reaction is catalyzed by succinyl-CoA synthetase. The phosphoryl group in guanosine triphosphate (GTP) is readily transferred to adenosine diphosphate (ADP) to form ATP, in a reaction catalyzed by nucleoside diphosphokinase:

$$GPT + ADP \rightarrow GDP + ATP$$

Succinate is converted into oxaloacetate in three steps (Fig. 6).

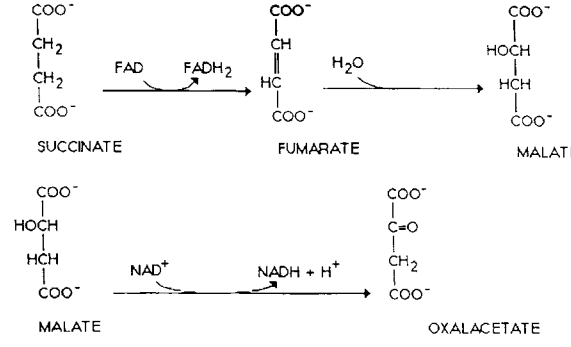

FIG. 6. Steps in conversion of succinate in oxalacetate.

Oxalacetate can be decarboxylized to produce pyruvic acid. Then acetyl-CoA is formed inside mitochondria by the oxidative decarboxylation of pyruvate:

$$\text{Pyruvate} + NAD^+ + \text{CoA} \rightarrow \text{acetyl-CoA} + CO_2 + NADH + H^+$$

The number of ATP formed when sebacate is completely oxidized can be calculated by:

$$\text{Sebacate} + 70 \text{ ADP} + 70 \text{ Pi} + 12.5 \text{ } O_2 \rightarrow 10 \text{ } CO_2 + 9 \text{ } H_2O + 70 \text{ ATP}$$

The oxidation of 1 mol/L of sebacate yields −1,341 kcal under standard conditions. The free energy stored in 70 ATP is 511 kcal, because ΔG° for the hydrolysis of ATP is −7.3 kcal. Hence, the thermodynamic efficiency of ATP formation from sebacic acid is 511/1,341, or 38.11% under standard conditions. The ATP/CO_2 molar ratio is 7 (ie, 70/10), 1000 kcal of sebacate produces 166.79 L of CO_2, whereas 1000 kcal of glucose and 1000 kcal of soybean emulsion produce 202 and 157 L of CO_2, respectively.