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REVIEW

Dicarboxylic acids, an alternate fuel substrate in parenteral nutrition: an update

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ABSTRACT — Dicarboxylic acids (DA) are formed from the ω-oxidation of monocarboxylic acids when the β-oxidation of free fatty acids is impaired. Medium-chain DA have the peculiar characteristic of being water soluble due to the presence of two carboxylic terminal groups in the molecule. Contrary to both long- and medium-chain triglycerides which are administered as emulsions, they can be given by a peripheral vein as inorganic salts. DA are β-oxidized at level of both peroxisomes and mitochondria via carnitine-independent pathway.

The products of β-oxidation of odd-chain DA are acetyl-CoA and malonyl-CoA, which can not be oxidized further, are used in lipogenesis. Moreover even-chain DA produce acetyl-CoA and succinyl-CoA, which is a gluconeogenetic precursor.

Azelaic acid (C9), does not show acute or chronic toxicity effects in animals but much of it is lost in urine (more than 50% of the given dose). Sebacic acid (C10) is lost in urine to a smaller extent (about 12% of the administered dose) and its energy density (6.64 Kcal/g) is greater than that of C9 (4.97 Kcal/g). Dodecanedioic acid (C12) seems to be the best candidate for parenteral nutrition, because it is eliminated in the urine only in minimal amounts (3.90% of the given dose), it is rapidly utilized by tissues, and it has a high energy density (7.20 Kcal/g).

Introduction

In 1989 we proposed the use of the salts of dicarboxylic acids (DA) in total parenteral nutrition (TPN) as an alternate energy source (1). The advantage of medium chain DA with an even number of carbon atoms over conventional lipid substrates (such as both long and medium chain triglycerides) is related to their bioavailability. DA are water soluble molecules having a various length of a linear carbon atom chain which terminates with two carboxylic groups, which confer water solubility to the molecule. The general structural formula for these molecules is indicated below:

$$HOOC - (CH_2)_n - COOH$$

On the contrary, monocarboxylic acids with the same chain length as DA are water insoluble and are called medium-chain fatty acids.

'In vivo' dicarboxylic acid synthesis

Verkade and van der Lee (2) and Verkade et al (3) were the first to acknowledge the existence of the ω-oxidation of monocarboxylic acids. They found that after administration of medium-chain (C8-C12) triacylglycerols to both animals and humans a significant dicarboxylic aciduria appeared: dicarboxylic acids present in urine were of the same chain length or had a shorter chain length than the monocarboxylic acids composing the triglycerides administered.

Concerning the degree of ω-oxidation, Bjorkhem (4) found that in physiological conditions in experimental animals 4% of palmitic acid and 8% of decanoic acid were ω-oxidized. On the contrary, Wada and Usami (5) calculated that approximately 15% of the metabolized palmitic acid in diabetic ketotic rats was ω-oxidized. Thus, the degree of ω-oxidation of monocarboxylic acids may increase substantially in some pathophysiological conditions, such as starvation, fat-feeding and diabetes (6) or in congenital or acquired defects of β-oxidation of monocarboxylic acids (7, 8).

β-oxidation of dicarboxylic acids at peroxisomal and mitochondrial level

Dicarboxylic acids given to humans or animals (2, 3,

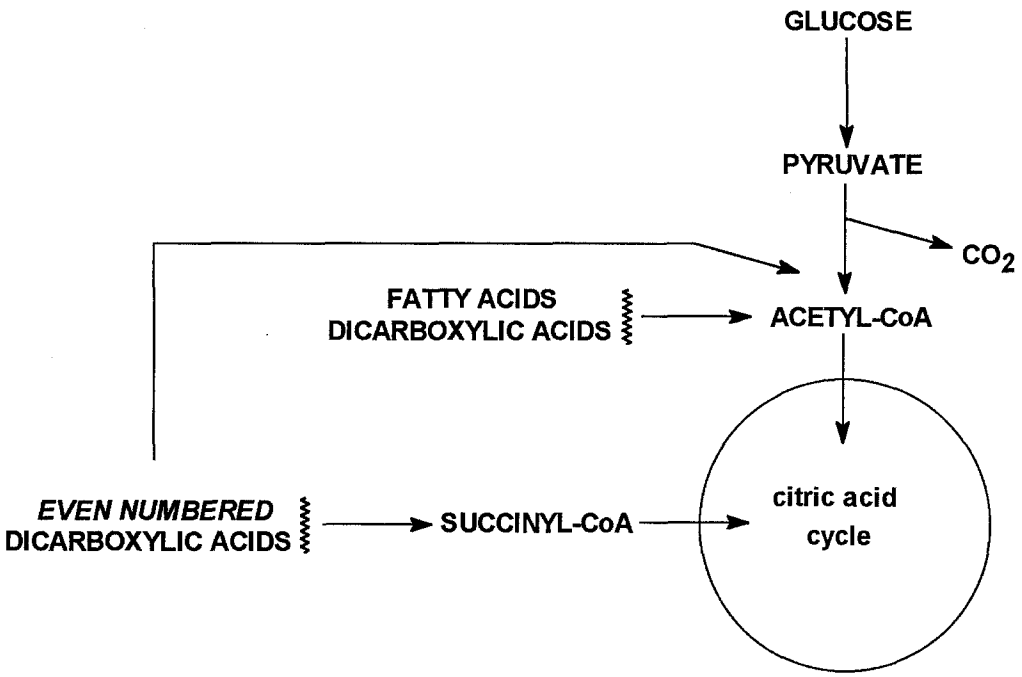

Fig. Metabolic pathway of dicarboxylic acids.

9) are rapidly β-oxidized. While odd-chain DA produce malonyl-CoA which is not further oxidized, it is used for de novo lipid synthesis. Even-chain DA give rise to succinyl-CoA, which is channeled in the tricarboxylic acid cycle and subsequently the gluconeogenetic pathway (5, 10) (Fig.). Therefore, the gluconeogenetic properties of even-chain DA are very important particularly in those conditions in which there is a ketosis. The energy produced during the cellular oxidation of DA is higher than that deriving from glucose, but lower than that from both long- or medium-chain fatty acids as shown in the Table. However, the ATP/CO_2 ratio of azelaic acid (DA with 9 carbon atoms) is equivalent to the ratio of palmitic acid (8.2 vs 8.1), and is certainly higher than that of glucose (6.3). Stoichiometric calculations give similar values of the ATP/CO_2 ratio for other DAs, such as sebacic acid and dodecanedioic acid (DAs with 10 and 12 carbon atoms respectively), taking also into account that even-number carbon atoms DAs are more efficiently oxidized than odd-number DAs. In addition, the production of CO_2 from DAs – administered as sodium salts – is lower than that from glucose as indicated by the values of respiratory quotient (RQ). This can represent an advantage in patients with respiratory diseases, where the pulmonary exchanges of CO_2 is impaired and lead to hypercapnia and respiratory acidosis.

Table Characteristics of energy substrates

Substrate	MW	Kcal/g	RQ
Glucose	180	3.7	1.00
Palmitic Acid	256	9.0	0.70
Azelaic acid	188	5.0	0.66
Sebacic acid	202	6.6	0.77
Dodecanedioic acid	230	7.2	0.77

Ketotic dicarboxylic aciduria may result from the ω-oxidation of monocarboxylic acids, in conditions such as starvation or diabetes (4, 11–13). Moreover Mortensen et al (14) suggested that dicarboxylic aciduria might also be explained by accelerated β-oxidation of medium-chain dicarboxylic acids, with subsequent partial excretion of short-chain DA.

Studies on the chain length-dependency of DA β-oxidation showed both in vivo and in vitro the optimum for chain length is 12. Shorter and longer DA are β-oxidized more slowly (15). The longer the chain-length of dicarboxylic acids the higher the caloric energy density and the higher the energy equivalent of ATP and O2/ATP ratio (mitochondrial metabolism).

Medium-chain DA are activated with CoA before being β-oxidized both in the mitochondria and in the peroxisomes, with the same enzyme system as used

for oxidation of monocarboxylic acids (11–13, 16). The β-oxidation of DA in the peroxisomes ceases, is less complete since, like monocarboxylic acids, it ceases when 6 C atoms remain (adipic). The adipic acid is then liberated from the peroxisomes to enter the cytosol, where it is taken up by mitochondria, activated to adipyl-CoA and oxidized to succinyl-CoA (14).

Dicarboxylic aciduria

Some years ago Mortensen (17) stressed the concept of non-ketotic dicarboxylic aciduria. This term was employed to indicate the presence of DA in the urine of subjects affected by congenital or acquired defects of fatty acid β-oxidation: Reye's syndrome; glutaric aciduria type II (18–22); neonatal lactate acidosis (7, 8, 20, 23) or subsequently hypoglycemic attacks. Reye's syndrome was first described as a distinct clinical and pathological entity in 1963 (24). This multifactorial syndrome is characterized by encephalopathy and cellular fatty degeneration. In a study on the causative role of DA in Reye's syndrome, Tonsgard and Getz (25) showed that, when sebacic acid was added to normal serum to obtain concentrations of 0.4 mM and mitochondria were incubated in this medium, a reduction in ATP formation was observed (from 454 to 365 nmol) and the oxygen consumption was stimulated (77% compared to 33% in the presence of normal serum alone). Therefore, in those pathological conditions in which the normal oxidative pathway of monocarboxylic acids is blocked, they accumulate in the cells and also increase in plasma, where they bound on albumin. When the binding capacity of albumin for FFA is saturated, a detoxification reaction takes place with ω-oxidation of monocarboxylic acid and formation of dicarboxylic acids. Although DA are β-oxidized both in mitochondria and peroxisomes (26, 27) the rate of production (or exogenous supply) exceeds the oxidative capacity of the organism, and DA accumulate in blood and are excreted in urine.

DA could be a protective mechanism for the organism, since it is well known that long chain monocarboxylic acids, particularly if unsaturated, are highly toxic for mitochondria due to their uncoupling effect (28, 29). Ω-oxidation, which lead to the production of DA, can be regarded as a detoxification process that reduces the level of circulating polyunsaturated FFA.

Use of dicarboxylic acids in parenteral nutrition

DA are a promising new fuel substrate for parenteral nutrition for a series of theoretical reasons:

1. DAs are highly soluble in water and, compared to both long and medium chain fatty acids, are bound less avidly to albumin (30–32).
2. DAs undergo high rate of β-oxidation at the level of both mitochondria and peroxisomes (6, 11, 14, 26, 27).
3. DAs do not induce ketogenesis (5, 33) unlike medium chain triglycerides (34, 35), but rather promote gluconeogenesis during their β-oxidation via succinate production (36).
4. DAs do not require hydrolysis prior to tissue uptake and therefore they could represent a form of energy that is immediately available.
5. DAs can be easily and inexpensively prepared since they are water soluble.

Some of these properties make DA have attractive for potential use in parenteral nutrition.

Azelaic acid

It was reported (2, 3, 9, 14) that experimental animals and humans are able to shorten dicarboxylic acids with a chain length between 6 and 10 carbon atoms. However, the opinions about the oxidizable amount of these diacids were contrasting. Since there was no data in the literature concerning the toxicity and teratogenicity of dicarboxylic acids, a study on the toxicity of the shorter investigated DA, azelaic acid (C9) was performed in experimental animals (37): no lethal dose (LD50) was found after acute oral administration of 4000 mg/kg_{bw} in experimental animals and no teratogenic effect was observed. The safety of the use of azelaic acid was confirmed also in humans (38). In healthy volunteers, who received 5 g or 10 g of C9 as either an oral bolus or a short (1 h) intravenous infusion, the profile of azelaic acid plasma concentrations showed a peak at 3 h after oral administration; a rapid decline of azelaic acid in plasma was observed immediately after both oral bolus and IV infusion. No side-effects were found in spite of the very high levels of the drug reached (up to 1400 μg/ml). In 1989 the first study which evaluated whether azelaic acid could be used as an energy substrate in man was performed (1). Although azelaic acid has a caloric density of 4.97 Kcal/g, which is higher than the caloric value of 1 g of glucose (3.7 Kcal/g), the amount of C9 lost with urine was very high (more than 50% of the given dose). During the infusion of disodium azelate in humans the respiratory quotient (RQ) values decreased significantly (to 0.67) with respect to those obtained during LCT infusion, suggesting that C9 was readily oxidized and that it further promoted endogenous lipid oxidation (39).

The subsequent study of the pharmacokinetics of azelaic acid (40) – using a two-compartment non-linear model, which described both tubular secretion and cellular uptake in Michaelis-Menten terms, assuming that the binding of azelaic acid to albumin was negligible – showed that the average C9 cellular uptake was 58.51 μmol/min, which is a low value to adequately support cellular energy requirements.

Sebacic acid

A study with sebacic acid (C10) was undertaken (41) to assess whether the amount of C10 lost with the urine was smaller than that of C9, and whether it was toxic in experimental animals (41). After intraperitoneal administration the LD50 ± SE was found to be 5500 ± 830 mg/kg_{bw} for rats and 6000 ± 850 mg/kg_{bw} for rabbits. However, similar toxic effects were obtained when equivalent amounts of the sodium present in the disodium sebacate were administered as sodium chloride in animals, suggesting that sodium caused the toxic effects. Sebacic acid did not show any teratogenic effect and the development of fetuses was normal. These data supported the use of C10 for further experiments in humans.

A study in healthy human volunteers (42), in which disodium sebacate was continuously infused over 480 min with an infusion rate of 41.258 mg/min, showed that the overall rate of tissue uptake was quite high (180.89 ± 4.50 μmole/min) with a percent oxidation of 6.14 ± 0.44%. The average 24-h urinary excretion of C10 (energy density, 6.64 Kcal/g) was about 12% of the administered dose.

Another study on the use of even-numbered carbon atom dicarboxylic salts in parenteral nutrition as fuel substrate (43) proved that C10 had a short half-life (0.34 ± 0.06 h), a distribution volume of 2.79 ± 0.54 L in the central compartment and of 3.72 ± 0.14 L in the tissue compartment. The renal clearance was 19.22 ± 10.69 L/h. Since the 24-h C10 urinary excretion was low (less than 16% of the administered dose) and its energy production high (6.64 kcal/g), this could prove to be a promising fuel substrate for parenteral nutrition in man.

Studies on the metabolic effects and disposition of sebacate in rats (44) and in humans (33) suggest that it is largely utilized without significant metabolic side effects.

The binding of C10 to defatted human serum albumin was studied by equilibrium dialysis (45). The albumin binding was not taken into account in the case of azelaic acid, since we supposed that, being a short chain dicarboxylic acid, it was ionized in the plasma and had a good water solubility. However, we determined the binding of sebacic acid to albumin in order to obtain a better understanding of the kinetics of this diacid. One binding site on defatted human serum albumin was found with affinity constant for sebacate of $3.69 \times 10^4 M^{-1}$; 4–5 secondary sites showed affinity constant of $7.14 \times 10^2 M^{-1}$. We also studied the competition of C10 with decanoic acid, a medium chain monocarboxylic acid present on medium chain triglycerides (MCT). The data showed that part of plasma sebacate was bound to albumin, while the relevant portion was free (the association constant was reduced to $7.14 \times 10^2 M^{-1}$) and thus immediately available for nutritional purposes. Sebacic acid is, thus, bound to albumin to a lesser extent than the correspondent monocarboxylic acid with 10 carbon atoms, decanoic acid, contained in the MCT. This means that sebacic acid is more available for tissue uptake than decanoic acid.

A more detailed study on the pharmacokinetics of sebacate (32, 46) demonstrated that the calculated clearance of sebacic acid was markedly reduced with respect to the glomerular filtration rate in all the subjects examined. These investigations suggested that a tubular reabsorption of sebacic acid occurred. The tissue uptake, evaluated by the average value of the individual estimates of maximal transport of sebacate (Tm) was 66.6 mg/min, which means that a high amount of sebacic acid (about 90 g/day) could be taken up by tissues.

The kinetics and thermogenic effects of medium-chain monocarboxylic and dicarboxylic acids have been studied in man (47). The effects on oxygen consumption and carbon dioxide production during a constant IV infusion of 0.15 g/kg_{bw} per hour over a 5 h period of C10 and isocaloric amount of a 50% mixture of medium-chain (MCT) and long-chain triglycerides (LCT) were compared in 10 healthy volunteers. Sebacic acid in contrast to MCT induced no ketone body formation, elevation of insulin levels or a significant increase in oxygen consumption. On the contrary, medium-chain monocarboxylic acids derived from hydrolysis of MCT induce uncoupling effects on the respiratory chain and increase of oxygen consumption without a corresponding rise in ATP production. The average apparent volume of distribution of MCT was 167 mL/kg of body weight (bw) and that of C10 was 112 mL/kg_{bw}. The t1/2 of MCT was 50 min and that of C10 was 78 min. Formation of ketone bodies and adverse effects on glucose metabolism were avoided by the administration of C10.

The metabolic effects of a continuous IV infusion of C10 on insulin-dependent glucose metabolism was studied in control subjects, IDDM patients and

obese subjects. After 3 h of C10 infusion (6.6 g/h), a 120-min euglycemic-hyperinsulinemic clamp was performed (48). C10 administration was associated with a glucose-sparing effect as shown by the reduced glucose uptake in all patients studied. This might represent a relevant advantage in those clinical conditions, such as sepsis, in which glucose oxidation is impaired because of insulin resistance.

Dodecanedioc acid

The last DA which was studied in experimental animals was dodecanedioic acid (49): C12 was eliminated with the urine only to a small extent (3.90 ± 1.62% of the administered dose). From the pharmacokinetic point of view dodecanedioic appears to be the best DA studied until now since it is well cleared from plasma by the tissues, it is scarcely eliminated in urine, and it has a high energy density in addition (7.20 Kcal/g). The C12 half-life was 12.47 min and the renal clearance was 0.00051 $L/kg_{bw}/min$, which is much less than the value of rat inulin clearance reported in the literature, indicating a reabsorption of C12 at the level of renal tubules. The calculated tissue uptake of C12 in rats was 14.69 $\mu moles/kg_{bw}/min$. Since rats have a much higher metabolism/kg_{bw} than man, it is necessary to use a relationship on $weight^{0.75}$. Therefore, in a subject weighing 70 kg the average cellular uptake of C12 is 771.225 μmoles/min (45). This uptake corresponds to a maximum energy supply of 24.37 $cal/min/kg_{bw}$, which compares favourably with the energy supplied in rat by glucose and free fatty acids. For glucose uptake in rats, a value of 2.28 $mg/min/kg_{bw}$ was found, corresponding to 8.46 $cal/min/kg_{bw}$. For palmitic acid, tissue uptake is 1.92 $mg/min/kg_{bw}$, with a caloric equivalent of 17.28 $cal/min/kg_{bw}$ (46). If the high value of tissue uptake of dodecanedioic acid is confirmed in humans, this dicarboxylic acid might represent a suitable energy substrate for parenteral nutrition.

Preliminary data on pharmacokinetics of C12 in humans suggested a rapid plasma clearance (2.17 + 0.86 L/min) and a very low renal clearance (0.0256 + 0.0155 L/min) which is due to very efficient renal tubular reabsorption.

Conclusions

Both biochemical considerations and experimental evidence point to a possible role of medium-chain, even-numbered dicarboxylic acids in human TPN. They can effectively substitute either carbohydrates or lipids when their metabolism is impaired, like in decompensated diabetes mellitus, sepsis, severe dyslipidemia, cirrhosis, or inborn errors of metabolism. In fact dicarboxylic acid beta-oxidation leads to succinic acid and acetyl-CoA as end-products, with evident advantage because of increased availability of both Krebs' cycle intermediate compounds and of gluconeogenetic precursors. To this end, dicarboxylic acids show intermediate characteristics between lipids and carbohydrates, and represent therefore promising molecules for nutritional purposes.

However, a considerable amount of further work is needed to assess possible tolerance and toxicities of DA in various clinical studies.

References

1. Mingrone G, Tacchino R M, Greco A V et al. Preliminary studies of a dicarboxylic acid as an energy substrate in man. JPEN 1989; 13: 299–305.
2. Verkade P E, van der Lee J. Researches on fat metabolism II. Biochem J 1934; 28: 31–40.
3. Verkade P E, van der Lee J, Elzas M. Researches on fat metabolism. XII. The influence of carbohydrate on diaciduria. Biochim Biophys Acta 1948; 2: 38–56.
4. Bjorkhem I. On the quantitative importance of omega-oxidation of fatty acids. J Lipid Res 1978; 19: 585–590.
5. Wada F, Usami M. Studies on fatty acid omega-oxidation. Antiketogenic effect and gluconeogenecity of dicarboxylic acids. Biochim Biophys Acta 1977; 487: 261–268.
6. Mortensen P B, Gregersen N. The biological origin of ketotic dicarboxylic aciduria. In vivo and in vitro investigations of the ω-oxidation of C6-C10-monocarboxylic acids in unstarved, starved and diabetic rats. Biochim Biophys Acta 1981; 666: 394–404.
7. Borg L, Lindstedt S, Steen G. Aliphatic C6-C14 dicarboxylic acids in urine from an infant with fatal congenital lactic acidosis. Clin Chim Acta 1972; 41: 363–366.
8. Lindstedt S, Norberg K, Steen G, Wahl E. Structure of some aliphatic dicarboxylic acids found in the urine of an infant with congenital lactic acidosis. Clin Chem 1976; 22: 1330–1338.
9. Bernhard K, Andreae M. Stoffwechselversuche mit Dicarbonsauren. Z Physiol Chem 1937; 245: 103–106.
10. Tserng K Y, Jin S J. Metabolic conversion of dicarboxylic acids to succinate in rat liver homogenates, a stable isotope tracer study. J Biol Chem 1991; 226: 2924–2929.
11. Pettersen J E, Aas M. ATP-dependent activation of dicarboxylic acids in rat liver. Biochim Biophys Acta 1973; 326: 305–313.
12. Pettersen J E. In vitro studies of the metabolism of hexadecanedioic acid and its mono-L-carnitine ester. Biochim Biphys Acta 1973; 306: 1–14.
13. Pettersen J E, Aas M. Subcellular localization of hexadecanedioic acid activation in human liver. J Lipid Res 1974; 15: 551–556.
14. Mortensen P B, Kolvraa S, Gregersen N, Rasmussen K. Cyanide insensitive and clofibrate enhanced β-oxidation of dodecanedioic acid: evidence of peroxisomal beta-oxidation of dicarboxylic acids. Biochim Biophys Acta 1982; 713: 393–397.
15. Passi S, Nazzaro-Porro M, Picardo M, Mingrone G, Fasella P.

Metabolism of straight, saturated medium chain-length (C9-C12) dicarboxylic acids. J Lipid Res 1983; 24: 1140–1147.
16. Leighton F, Bergseth S, Rortveit T, Christiansen E N, Bremer J. Free acetate production by rat hepatocytes during peroxisomal fatty acid and dicarboxylic acid oxidation. J Biol Chem 1989; 264: 10347–10350.
17. Mortensen P B. Dicarboxylic acids and the lipid metabolism. Thesis, Aarhus University, 1983.
18. Przyrembel H, Wendel U, Becker K et al. Glutaric aciduria type II: report on a previously undescribed metabolic disorder. Clin Chim Acta 1976; 66: 227–239.
19. Dusheiko G, Kew M C, Joffe B I, Lewin J R, Mantagos S, Tanaka K. Recurrent hypoglycemia associated with glutaric aciduria type II in an adult. N Engl J Med 1979; 301: 1405–1409.
20. Gregersen N, Kolvraa S, Rasmussen K et al. Biochemical studies in a patient with defects in the metabolism of acyl-CoA and sarcosine: another possible case of glutaric aciduria type II. J Inher Metab Dis 1980; 3: 67–72.
21. Sweetman L, Nyhan W L, Tauner D A, Merritt T A, Singh M. Glutaric aciduria type II – Pediatr 1980; 96: 1020–1026.
22. Goodman S I, Mc Cabe E R B, Fennessey P V, Mace J W. Multiple acyl-CoA dehydrogenase deficiency (Glutaric aciduria type II) with transient hypersarcosinemia and sarcosinuria; possible inherited deficiency of an electron tranfer flavoprotein. Pediatr Res 1980; 14: 12–17.
23. Naylor E W, Mosovich L L, Guthrie R, Evans J E, Tieckelmann M. Intermittent non-ketotic dicarboxylic aciduria in two siblings with hypoglycemia: An apparent defect in β-oxidation of fatty acids. J Inher Metab Dis 1980; 3: 19–24.
24. Reye R O K, Morgan G, Baral J. Encephalopathy and fatty degeneration of the viscera: A disease entity in childhood. Lancet 1963; 2: 749–752.
25. Tonsgard J H, Getz G S. Effect of Reye's syndrome serum on isolated chinchilla liver mitochondria. J Clin Invest 1985; 76: 816–825.
26. Vamecq J, Draye J P. Peroxisomal and mitochondrial β-oxidation of monocarboxylyl-CoA, ω-hydroxymonocarboxylyl-CoA and dicarboxylyl-CoA esters in tissues from untreated and clofibrate-treated rats. J Biochem 1989; 106: 216–222.
27. Vamecq J, Draye J P. Comparison between the formation and the oxidation of dicarboxylylcarnitine esters in rat liver and skeletal muscle: possible implications for human inborn disorders of mitochondrial β-oxidation. J Inher Metab Dis 1989; 12: 59–63.
28. Borst P, Loos J A, Christ E J, Slater E C. Uncoupling activity of long-chain fatty acids. Biochim Biophys Acta 1962; 62: 509–518.
29. Mingrone G, Greco A V, Arcieri-Mastromattei E. Free fatty acids stimulate mucin hypersecretion by rabbit gallbladder epithelium in vitro. Clin Sci 1990; 78: 175–180.
30. Tonsgard J H, Mendelson S A, Meredith S C. Binding of straight-chain saturated dicarboxylic acids to albumin. J Clin Invest 1988; 82: 1567–1573.
31. Tonsgard J H, Meredith S C. Characterization of the binding sites for dicarboxylic acids on bovine serum albumin. Biochem J 1991; 276: 569–575.
32. Bertuzzi A, Finotti E, Mingrone G, Greco A V. Sebacic acid binding to human plasma albumin. Biochem Pharmacol 1993; 45: 697–702.
33. Greco A V, Mingrone G, Raguso C et al. Metabolic effects and disposition of sebacate, an alternate dicarboxylic fuel substrate. Ann Nutr Metab 1992; 36: 1–11.
34. Weissman C, Chiolero R, Askanazi J, Gil K M, Elwin D, Kinney J M. Intravenous infusion of medium-chain triglyceride-enriched lipid emulsion. Crit Care Med 1988; 16: 1183–1190.
35. Hill J O, Peters J C, Yang D et al. Thermogenesis in humans during overfeeding with medium-chain triglycerides. Metabolism 1989; 38: 641–648.
36. Kou Y, Tserng Y, Shiow-Jen J. Metabolic conversion of dicarboxylic acids to succinate in rat liver homogenates. J Biol Chem 1991; 266: 2924–2929.
37. Mingrone G, Greco A V, Nazzaro-Porro M, Passi S. Toxicity of azelaic acid. Drugs Exptl Clin Res 1983; 9: 447–455.
38. Passi S. Azelaic acid: biochemistry and metabolism. Acta Derm Veneorol Suppl-Stockh 1989; 143: 8–13.
39. Tacchino R M, Mingrone G, Marino F, Arcieri-Mastromattei E, Greco A V, Castagneto M. Short-term infusion of azelaic acid vs intralipid in healthy subjects evaluated by indirect calorimetry. JPEN 1990; 14: 169–172.
40. Bertuzzi A, Gandolfi A, Salinari S et al. Pharmacokinetic analysis of azelaic acid disodium salt: a proposed substrate for total parenteral nutrition. Clin Pharmacokin 1991; 20: 411–419.
41. Greco A V, Mingrone G, Arcieri-Mastromattei E, Finotti E. Toxicity of sebacic acid. Drugs Exptl Clin Res 1990; 16: 531–536.
42. Mingrone G, Greco A V, Bertuzzi A et al. Tissue uptake and oxidation of disodium sebacate in man. JPEN 1991; 15: 454–459.
43. Mingrone G, Tacchino R M, Castagneto M, Finotti E, Greco A V. Use of even-numbered carbon atom dicarboxylic salts in parenteral nutrition as fuel substrate. JPEN 1992; 16: 32–38.
44. Tataranni P A, Mingrone G, De Gaetano A, Raguso C, Greco A V. Tracer study of metabolism and tissue distribution of sebacic acid in rats. Ann Nutr Metab 1992; 36: 296–303.
45. Bertuzzi A, Gandolfi A, Greco A V, Mingrone G, Salinari S. A nonlinear model for the pharmacokinetics of sebacic acid. In: Eisenfeld J, Levine D S, Witten M, eds Biomedical modeling and simulation. Amsterdam: North Holland, 1992: 431–437.
46. Bertuzzi A, Gandolfi A, Salinari S, Mingrone G, Greco A V. Pharmacokinetics of dicarboxylic acids in man. Engng Med Biol 1994; 13: 472–478.
47. Mingrone G, Greco A V, Castagneto M, De Gaetano A, Tataranni P A, Raguso C. Kinetics and thermogenesis of medium chain monocarboxylic and dicarboxylic acids in man: sebacate and medium chain triglycerides. JPEN 1993; 17: 257–264.
48. Raguso C, Mingrone G, Greco A V, Tataranni P A, De Gaetano A, Castagneto M. Dicarboxylic acids and glucose utilization in humans: effect of sebacate. JPEN 1994; 18: 9–13.
49. Mingrone G, Greco A V, De Gaetano A, Tataranni P A, Raguso C, Castagneto M. Pharmacokinetic profile of dodecanedioic acid, a proposed alternative fuel substrate. JPEN 1994; 18: 225–230.
50. Royle G T, Wolfe R R, Burke J F. Glucose and fatty acid kinetics in fasted rats: effects of previous protein intake. Metabolism 1982; 31: 279–283.

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