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Original Communications

Dicarboxylic Acids and Glucose Utilization in Humans: Effect of Sebacate

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ABSTRACT. Dicarboxylic acids have been proposed as an alternate lipid energetic substrate for total parenteral nutrition. No data are yet available on the possible effect of dicarboxylic acids on glucose metabolism in humans. Thus, we examined the effect of a continuous intravenous infusion of the sodium salt of the10-carbon atom alyphatic dicarboxylic acid, sebacate (Sb), on insulin-dependent glucose metabolism in four control subjects, four patients with insulin-dependent diabetes mellitus, and four obese subjects. All subjects received a constant 5-hour infusion of saline or sebacate (6.6 g/h), in a randomized order on two different days. After 3 hours of infusion, a 120-minute euglycemic, hyperinsulinemic clamp procedure was performed (insulin infusion rate = 40 mU/m^2 per minute). Glucose uptake, plasma sebacate, insulin, glucagon, C-peptide, and ketone bodies were measured. No significant differences in insulinemia were found among groups either during the saline infusion or the sebacate infusion. On the contrary, glucose uptake (molar) was significantly reduced during the sebacate *vs* the saline day in all three groups: 6.7 ± 0.04 *vs* 3.7 ± 1.3 in control subjects ($p < .001$), 4.6 ± 0.4 *vs* 2.5 ± 1.2 in patients with insulin-dependent diabetes mellitus ($p < .001$), and 4.8 ± 0.5 *vs* 2.7 ± 0.2 mg/kg per minute in obese subjects ($p < .001$). In conclusion, Sb administration was associated with a glucose-sparing effect as shown by the reduced glucose uptake in all patients studied. Sebacate did not stimulate insulin secretion, inasmuch as no modification of C-peptide plasma levels was observed after 3 hours of Sb infusion. In addition, no change in Sb steady-state levels was observed during hyperinsulinemia, suggesting that insulin does not influence Sb plasma clearance. (*Journal of Parenteral and Enteral Nutrition* **18**:9–13, 1994)

Recently we proposed the use of dicarboxylic acids (DAs) in the form of salts of inorganic cations in parenteral nutrition, as an alternate lipid substrate.[1–3] The major advantages of DAs are their water solubility and the fact that, because they do not require hydrolysis steps, contrary to both medium- and long-chain triglycerides (MCTs and LCTs), DAs are immediately available for cellular utilization as fuel substrate. Water solubility seems to be an important advantage of DAs over other lipid substrates from the point of view of preparation, because both LCTs and MCTs require emulsioning. Because DAs with an even number of carbon atoms can be completely oxidized in the cell to CO_2 and H_2O via succinyl-CoA formation, whereas the oxidation of odd-chain DAs stops at malonyl-CoA, which is, in turn, the starting point for fatty acid synthesis,[3] even-numbered DAs seem to be energetically more useful for nutritional purposes. Even-numbered DAs are also potentially antiketogenetic and gluconeogenetic.[4–5] In this study, sebacate (decanedioic acid) was used as a representative of even-chain diacids.

Conventional lipid substrates used in total parenteral nutrition (eg, LCTs), but also alternate lipid fuels such as MCTs, have been shown to exert an inhibitory effect on glucose uptake and oxidation. The first evidence of this inhibition was provided by Randle et al in isolated rat hearts and hemidiaphragms.[6] Felber and Vannotti[7] later demonstrated that fat infusion causes glucose intolerance in normal subjects. Thiébaud et al[8] reported that hyperlipidemia, caused by intravenous (IV) infusion of LCT (Intralipid 20%, 1 mL/min) in healthy volunteers, determines a significant reduction in total glucose uptake.

No data are available on the possible relationship between DAs and glucose metabolism. Thus in this study, we examine the effect of IV infusion of sebacate in men under normal and pathological conditions, such as obesity and diabetes mellitus.

MATERIALS AND METHODS

Subjects

The study groups consisted of male subjects: four nonobese healthy volunteers, four obese, and four insulin-dependent diabetes mellitus (IDDM) patients whose clinical and metabolic features are outlined in Table I. Body composition was calculated in all subjects. Hume and Weyers'[9] formula was used to determine total body water (TBW) as follows: TBW = (0.2968 × kg) + (0.1948 × cm) − 14.0129. Lean body mass (LBM) was then computed by dividing TBW by 0.73, because the body contains approximately 73% water. Fat body mass was calculated as the difference between body weight and LBM.

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TABLE I
Clinical characteristics of the subjects

	Weight (kg)	Height (cm)	TBW (L)	LBM (kg)	FBM (kg)	BMI (kg/m^2)
Control	81.8 ± 5.7	177.8 ± 8.6	44.8 ± 3.3	60.4 ± 4.5	20.4 ± 1.8	25.9 ± 1.3
IDDM	61.3 ± 3.4	170.8 ± 7.1	37.4 ± 2.3	51.2 ± 3.1	10.0 ± 1.4	21.0 ± 1.1
Obese	88.3 ± 4.8	171.3 ± 1.0	45.5 ± 1.4	62.3 ± 1.9	26.0 ± 2.9	30.1 ± 1.7

Values are expressed as mean ± SD. IDDM, insulin-dependent diabetes mellitus; TBW, total body water; LBM, lean body mass; FBM, fat body mass; BMI, body mass index.

Subjects were clinically euthyroid; had no stigmata of renal, cardiac, or hepatic dysfunction; and were not treated with drugs that affect carbohydrate or insulin metabolism. The subjects were studied in the postabsorptive state after a 12- to 14-hour overnight fast. The glycemia level of diabetic patients was maintained below 100 mg/dL by small bolus doses of short-acting human insulin (Actrapid HM, Novo Nordisk, Denmark) until the beginning of the study. All subjects consumed a weight-maintaining diet consisting of at least 250 g of carbohydrate a day for 1 week before the study.

The protocol was approved by the Ethical Committee of the Institutional Review Board of the Catholic University Hospital and School of Medicine in Rome. After written informed consent was obtained, all subjects were admitted to the Department of Metabolic Diseases of the Catholic University.

Experimental Protocol

All subjects were admitted to the Department of Metabolic Diseases of Catholic University at 7 AM. The infusion catheter was inserted into an antecubital vein. The sampling catheter was introduced in the contralateral dorsal hand vein, and this hand was kept in a heated box (60°C) to obtain arterialized blood. At 8 AM, after a 12- to 14-hour overnight fast, an infusion of disodium Sb (infusion rate [IR] = 6.6 g/h) was started and maintained for 5 hours. Three hours after the infusion was started, the euglycemic hyperinsulinemic glucose clamp procedure was performed according to De Fronzo et al.[10] A priming dose of short-acting human insulin was given during the initial 10 minutes in a logarithmically decreasing way, to acutely raise the serum insulin to the desired concentration. Then, insulinemia was maintained constant with a continuous infusion of insulin (110 minutes) at an infusion rate of 40 μU/m^2 per minute for 110 minutes. During the clamp procedure, glucose level was monitored every 5 minutes and the infusion rate of a 20% glucose solution was adjusted following the algorithm detailed by De Fronzo.[10] Because serum potassium levels tend to fall during this procedure, potassium chloride was given during each study at a rate of 15 to 20 mEq/h to maintain the serum potassium between 3.5 and 4.5 mEq/L.

The subjects were examined with the same scheme on a different day when saline was infused (IR = 3 mL/min) instead of disodium sebacate. The order of saline and sebacate days was randomized (Fig. 1).

Arterialized blood samples were collected every 60 minutes during sebacate infusion and every 20 minutes during the clamp study to measure insulin, glucagon, C-peptide, ketone bodies, and sebacate concentrations.

The subjects voided before starting the study; subsequently, urine was collected for 24 hours to measure the urinary sebacate excretion for each subject.

Analytical Methods

Plasma sebacic acid was analyzed by high-performance liquid chromatography after ethylacetate extraction and derivatization with *p*-bromophenacyl bromide in CH_3CN in the presence of *N,N*-diisopropylethylamine as catalyst as previously described in detail.[1]

Serum glucose was measured by the glucose oxidase method using a Beckman Glucose Analyzer II (Beckman Instruments, Fullerton, CA). Plasma insulin, glucagon, and C-peptide were measured by radioimmunoassay (RADIM, Pomezia, Italy). β-Hydroxybutyrate and acetoacetate were assayed by a standard method[11]: reported data (ketone bodies) are the sum of the two concentrations.

Data Analysis

All glucose turnover data were averaged over the last 60 minutes of the study, when a steady state was reached. Data were expressed as mean ± SD. Analysis of variance and Bonferroni-corrected *t* tests were used for the detection of overall and intergroup differences. Paired-data *t* tests were used to compare calories from glucose and from sebacate within each treatment group.

RESULTS

No significant difference in Sb urinary loss (which corresponded to about 29% of the given dose) was found among the three groups examined (10.43 ± 3.23

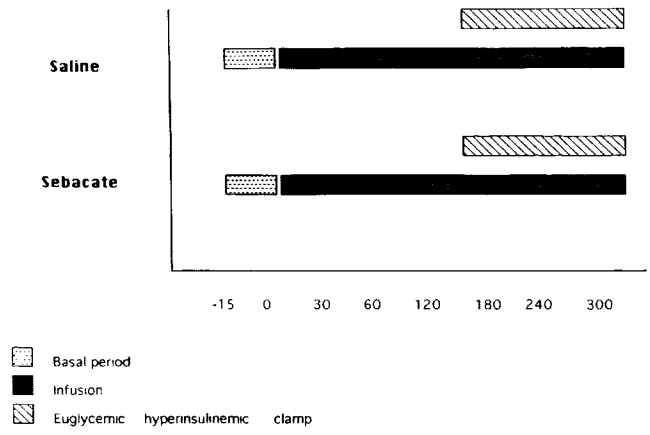

FIG. 1. Experimental protocol. Saline or sebacate was infused for 5 hours; after the first 3 hours the euglycemic hyperinsulinemic clamp was used.

g/24 h in control subjects, 8.83 ± 2.02 g/24 h in IDDM patients, and 9.63 ± 3.70 g/24 h in obese patients).

Mean plasma Sb concentrations over time are shown in Figure 2*A* through 2*C* for the three experimental groups (control, IDDM, and obese patients).

Plasma clearance rates of sebacate were estimated for each subject by dividing the infusion rate by the plasma concentration and then normalizing for LBM. Sb plasma clearance was 2.5 ± 0.09 mL/kg_{LBM} per minute in control subjects, 4.1 ± 0.4 mL/kg_{LBM} per minute in IDDM patients, and 4.1 ± 0.3 mL/kg_{LBM} per minute in obese patients. When compared with control subjects, both IDDM and obese patients showed a significantly ($p < .05$) higher Sb plasma clearance. No significant difference in Sb plasma clearance was found between IDDM and obese patients.

Table II reports the values of serum glucose, plasma insulin, C-peptide, glucagon, and ketone bodies at time 0 and at 180 minutes for both saline and substrate infusion days. The obese group showed a basal value of plasma insulin three times higher than that of control subjects; this finding is not surprising because obese subjects are generally hyperinsulinemic. However, the highest levels of plasma insulin were found in IDDM patients who received small boli of insulin to keep glycemia levels lower than 100 mg/dL. The basal glycemia, plasma insulin, C-peptide, glucagon, and ketone body levels were not significantly different between saline and substrate infusion days; these parameters were also not significantly modified by the infusion (paired *t* test between time 0 and time 180, not significant for both saline and substrate).

The clamp technique was effective in keeping glycemia levels close to the target levels (those at time 0); the coefficient of variation for each patient was lower than 4%.

TABLE II
Effects on metabolic parameters of 3-hour sebacate infusion

	Serum glucose (mg/dl)	Plasma insulin (μU/ml)	Plasma C-peptide (ng/ml)	Plasma glucagon (pg/ml)	Plasma ketones (μmol/L)
Min 0					
Control					
Saline	84.2 ± 7.8	5.3 ± 3.9	1.2 ± 0.3	167.2 ± 12.1	190 ± 25
Sebacate	85.3 ± 5.9	5.1 ± 2.9	1.2 ± 0.5	165.3 ± 9.1	330 ± 23
IDDM					
Saline	87.3 ± 5.1	29.5 ± 8.1	<0.1	174.8 ± 18.2	220 ± 19
Sebacate	85.2 ± 8.1	27.3 ± 6.5	<0.1	152.7 ± 20.2	230 ± 10
Obese					
Saline	87.6 ± 4.7	13.9 ± 6.7	1.1 ± 0.9	193.2 ± 10.1	340 ± 26
Sebacate	88.2 ± 5.7	14.6 ± 2.5	1.2 ± 0.6	195.6 ± 15.2	370 ± 10
Min 180					
Control					
Saline	83.3 ± 9.3	5.0 ± 4.2	1.3 ± 0.7	165.7 ± 14.0	200 ± 17
Sebacate	86.4 ± 8.5	4.6 ± 3.0	1.5 ± 0.4	164.8 ± 8.5	290 ± 26
IDDM					
Saline	86.8 ± 4.2	24.6 ± 7.3	<0.1	165.7 ± 24.6	230 ± 18
Sebacate	86.5 ± 7.3	25.8 ± 7.9	<0.1	144.5 ± 10.7	240 ± 9
Obese					
Saline	88.3 ± 5.3	14.6 ± 2.5	0.9± 0.6	194.0 ± 14.4	400 ± 30
Sebacate	88.6 ± 6.9	15.9 ± 6.1	1.3± 0.4	197.5 ± 13.5	380 ± 18

Values are expressed as mean ± SD. IDDM, insulin-dependent diabetes mellitus.

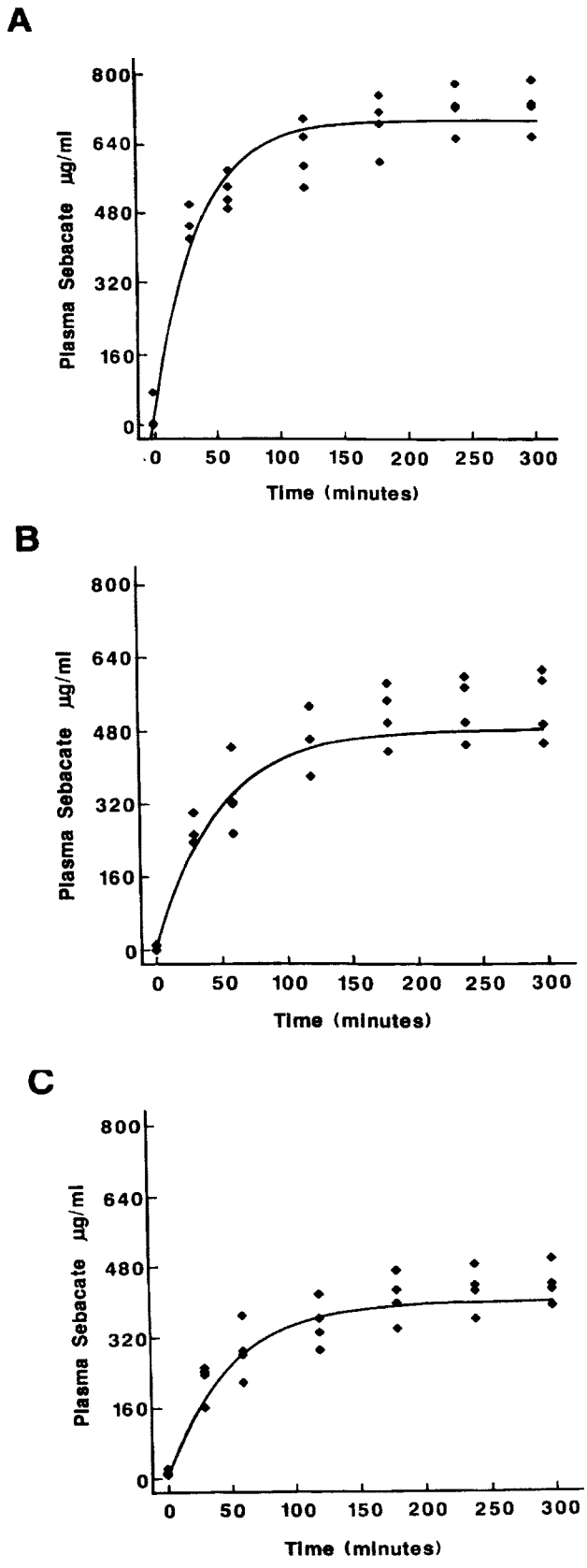

FIG. 2. Plasma sebacate time/concentration average curves: control subjects (*A*), patients with insulin-dependent diabetes mellitus (*B*), obese subjects (*C*).

Steady-state (last 60 minutes of clamp) values of glycemia, insulin, C-peptide, glucagon, and ketone bodies were not significantly different between sebacate or saline infusion.

Total body glucose uptake (molar; milligrams per kilogram per minute approximated by the glucose infusion rate required to maintain euglycemia) was very much reduced under sebacate infusion with respect to saline infusion, proportionally in all patient groups (control: 55.2%, $p < .001$; IDDM: 54.3%, $p < .001$; and obese: 57.1%, $p < .001$) (Table III). Figure 3 shows the changes in glucose uptake (molar) during sebacate infusion in the three classes of subjects examined.

The values of ΔM (milligrams per kilogram of lean body mass per minute), which corresponds to the difference between the glucose taken up by tissues during infusion of sebacate and that during saline infusion, was calculated for each subject and multiplied by 3.7 (caloric equivalent of glucose). In this way the reduction in the amount of glucose calories was computed, under the assumption that glucose was totally oxidized.

The amount of sebacate effectively available to tissues was individually calculated by subtracting Sb urinary loss to the infused quantity of Sb (33 g). If, to simplify calculations, we hypothesize that all sebacate present in the body was extracted from tissues and then oxidized, we find that 8.20 ± 1.32 cal/kg_{LMB} per minute are furnished by Sb in control subjects, 10.48 ± 1.05 in IDDM patients, and 8.9 ± 2.41 in obese patients. The reduction in calories from glucose, calculated on the basis of ΔM, was 8.20 ± 2.60 cal/kg_{LBM} per minute in control subjects, 6.67 ± 2.6 in IDDM patients, and 5.49 ± 0.89 in obese patients. Thus, in control subjects, the added calories supplied by Sb are not significantly different from those subtracted from the glucose quota. On the contrary, IDDM and obese patients seem to use more calories from sebacate than would be expected from the reduction in glucose utilization.

DISCUSSION

The present study showed that sebacate, when infused at a rate that was sufficient to reach an average plasma concentration of approximately 500 μg/mL was able to inhibit insulin-stimulated glucose utilization. It is well known that IV glucose is mostly captured by peripheral tissues (skeletal muscle) in humans.[12] It is therefore likely that the effect of sebacate prevalently occurs at the muscle level.

This effect of sebacate was observed in all three groups of subjects examined, although the degree of inhibition on glucose uptake was different in size. No significant difference in Sb urinary excretion was found among the three groups examined, but Sb plasma clearance, even when normalized by body weight, seemed to be significantly higher in obese and IDDM patients than in control subjects.

Individual-patient caloric balance computations showed that glucose in healthy volunteers was replaced by an equicaloric amount of sebacate in the energy-production pathway, but in IDDM and obese patients the amount of energy derived from sebacate was significantly higher than the amount spared from glucose metabolism.

With regard to IDDM patients, it has been hypothesized that in diabetes mellitus there is a shift in substrate utilization from carbohydrates to lipids.[13] An impaired activity of pyruvate dehydrogenase[14] and an increased activity of β-oxidation enzymes have been described in these patients.[15] Because sebacic acid is β-oxidized via the same enzymatic pathway as free fatty acid (FFA)[16], an increased utilization of Sb other than that of FFA might represent an explanation of its higher metabolic clearance. Unfortunately, we do not have information regarding substrate oxidation. Additional studies and different investigation techniques might contribute to a better understanding of this aspect of Sb metabolism in IDDM patients.

As for obese patients, it is possible that their relative insulin resistance contributes to a defect of glucose utilization and to the preferential use of other substrates like dicarboxylic acids. This hypothesis is supported by the observation that metabolism of sebacate seems to be unaffected by large modifications in plasma insulin levels.

Sebacate seems to exert an effect very similar to that of FFA on glucose uptake. Our data on the reduction

TABLE III
Metabolic parameters during use of euglycemic hyperinsulinemic clamp

	Glucose uptake (mg/kg/min)	Serum glucose (mg/dL)	Plasma insulin (μU/ml)	Plasma glucagon (pg/ml)	Plasma ketones (μmol/L)
Control					
Saline	6.7 ± 0.04*	87.0 ± 2.8	82.8 ± 10.7	189.0 ± 19.5	240 ± 4.2
Sebacate	3.7 ± 1.3	86.2 ± 13.5	93.0 ± 9.5	187.0 ± 6.9	350 ± 9.1
IDDM					
Saline	4.6 ± 0.4*	84.8 ± 14.9	91.0 ± 9.2	181.0 ± 4.6	250 ± 5.0†
Sebacate	2.5 ± 1.2	87.4 ± 14.3	94.0 ± 5.7	161.3 ± 15.0	130 ± 6.3
Obese					
Saline	4.8 ± 0.5*	87.4 ± 4.3	106.2 ± 6.9	192.4 ± 5.4	370 ± 36
Sebacate	2.7 ± 0.2	90.0 ± 2.0	98.5 ± 12.6	195.5 ± 5.2	270 ± 13

*$p < .01$, saline *vs* sebacate.
†$p < .05$
Values are expressed as mean ± SD. IDDM, insulin-dependent diabetes mellitus.

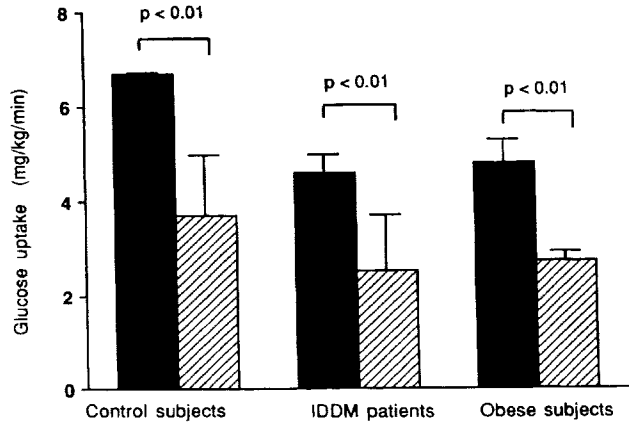

FIG. 3. Changes in glucose uptake (molar; milligrams per kilogram per minute) during sebacate infusion in the three classes (control subjects, patients with insulin-dependent diabetes mellitus (IDDM), and obese patients). ■, saline; ▨, sebacate.

of glucose uptake induced by sebacate, in fact, agree with the results of Thiebaud et al after administration of LCT.[8] These authors found that the increase in plasma FFA (on the order of 50% to 100% with respect to the basal level) induced a significant reduction (24% and 51%, respectively) of total glucose uptake. This decrease of glucose uptake was the result of a combined reduction of both glucose storage and glucose oxidation, in as much as concomitant calorimetric monitoring revealed a decrease in carbohydrate and an increase in the lipid oxidation rate.[8]

C-peptide plasma levels in both control and obese patients during the 3 hours of Sb infusion preceding euglycemic clamp remained unmodified with respect to baseline values. This seems to indicate that sebacate is not an insulin segretagogue. Moreover, Sb concentrations during clamp were not affected by increased insulin concentrations. Thus it is likely that the inhibition exerted by sebacate on the degree of glucose disposal is due to a peripheral effect on cellular metabolism rather than to an action mediated by insulin.

Although no apparent modification in glycemia or insulinemia was observed during Sb infusion before beginning the clamp, more pronounced changes became evident with the increased glucose uptake induced by hyperinsulinemia. This observation is in agreement with the conclusion of Ferrannini et al[17] about the effect of fatty acids on glucose production and utilization in humans. These authors hypothesized that a high grade of cellular glucose metabolism in insulin-dependent tissues is necessary to allow the inhibitory effect of FFAs on glucose uptake. In other words, high FFA levels are able to interfere with glucose utilization in insulin-sensitive tissues, only when an adequate level of insulin is available.

An inhibition of glucose disposal has also been observed during MCT infusion.[18] Because ketone bodies have been shown to inhibit glycolysis, pyruvate oxidation, and glucose transport both in heart and skeletal muscle,[18] it is very likely that the action of MCTs on glucose metabolism is exerted at least partially through the large increase they induce in ketone body concentration.

During the infusion of Sb alone, ketone bodies remained in a normal range, suggesting that the mechanism of Sb-induced inhibition of glucose uptake is not mediated by ketone bodies but is rather direct.

Another possible interaction between Sb and glucose metabolism may be the stimulation of hepatic glucose production. In fact, succinate, the end product of sebacate oxidation, can be directly converted to glucose.[2, 3] However, many studies[10, 17, 19] have shown that endogenous glucose production is completely suppressed under euglycemic hyperinsulinemic conditions. To further support this interpretation, a direct determination of endogenous glucose production should be made by primed-constant infusion of 3-^{3}H-glucose.

In conclusion, under euglycemic hyperinsulinemia, sebacate infusion (6.6 g/h) caused a very significant inhibition of total glucose uptake, not only in healthy subjects but also in obese and IDDM patients. This finding suggests that Sb effectively substitutes glucose in tissue uptake and utilization. This substitution was even more apparent in obese and IDDM patients. This effect appeared to be independent of insulin. The possibility of intervening directly at the level of the intracellular oxidative pathways with a glucose-sparing substrate has important implications in those states (diabetes mellitus, sepsis) in which the organism uses alternate neoglucogenetic substrates such as amino acids, with potentially damaging effects such as reduction of LBM.

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REFERENCES

1. Mingrone G, Greco AV, Bertuzzi A: Tissue uptake and oxidation of disodium sebacate in man. JPEN 15:454–459, 1991
2. Greco AV, Mingrone G, Raguso C, et al: Metabolic effects and disposition of sebacate, an alternate dicarboxylic fuel substrate. Ann Nutr Metab 36:1–11, 1992
3. Mingrone G, Tacchino RM, Castagneto M, et al: Use of even-numbered carbon atom dicarboxylic salts in parenteral nutrition as fuel substrate. JPEN 16:32–38, 1992
4. Wada F, Usami M: Studies on fatty acid ω-oxidation. Antiketogenic effect and gluconeogenecity of dicarboxylic acids. Biochim Biophys Acta 487:261–268, 1977
5. Tserng KY, Jin SJ: Metabolic conversion of dicarboxylic acids to succinate liver homogenates. A stable isotope tracer study. J Biol Chem 266:2924–2929, 1991
6. Randle PJ, Newsholme EA, Garland PB: Regulation of glucose uptake by muscle. Effects of fatty acids, ketone bodies and pyruvate and of alloxan diabetes and starvation, on the uptake and metabolic fate of glucose in rat heart and diaphragm muscles. Biochem J 93:652–665, 1964
7. Felber JP, Vanotti A: Effect of fat infusion on glucose tolerance and insulin plasma levels. Med Exp 10:153–156, 1964
8. Thiebaud D, De Fronzo RA, Jacot E, et al: Effect of long chain triglyceride infusion on glucose metabolism in man. Metabolism 31:1136–1142, 1982
9. Hume R, Weyers E: Relationship between total body water and surface area in normal and obese subjects. J Clin Path 24:234–238, 1971
10. De Fronzo RA, Tobin JD, Andres R: Glucose clamp technique: A method for quantifying insulin secretion and resistance. Am J Physiol 273:E214–E223, 1979
11. Williamson DH, Mellanby J, Krebs HA: Enzymatic determination of D(−)-βhydroxybutyric acid and acetoacetic acid in blood. Biochem J 82:90–96, 1962
12. De Fronzo RA, Jacot E, Jequier E, et al: The effect of insulin on the disposal of intravenous glucose results from indirect calorimetry and hepatic and femoral venous catheterization. Diabetes 30:1000–1007, 1981
13. Vranic M, Wasserman D: Exercise, fitness and diabetes. IN Exercise, Fitness, and Health: A Consensus of Current Knowledge, Bouchard C, McPherson B, Shepard RJ, et al (eds). Human Kinetic Publishers, Inc, Champaign, IL, 1990, pp 467–490
14. Krzentowsky G, Pirnay F, Pallikarakis N, et al: Glucose utilization in normal and diabetic subjects: The role of insulin. Diabetes 30:983–989, 1981
15. Norum KR: Activation of palmityl CoA: Carnitine palmityltransferase in livers from fasted, fat fed, or diabetic rats. Biochim Biophys Acta 98:654–660, 1965
16. Mortensen PB, Kolvraa S, Gregersen N, et al: Cyanide insensitive and clofibrate enhanced B-oxidation of dodecanedioic acid: Evidence of peroxisomal B-oxidation of dicarboxylic acids. Biochim Biophys Acta 713:393–397, 1982
17. Ferrannini E, Barrett E, Bevilacqua S, et al: Effect of fatty acids on glucose production and utilization in man. J Clin Invest 72:1737–1747, 1983
18. Yeh Y, Zee P: Relation of ketosis to metabolic changes induced by acute medium-chain triglyceride feeding in rats. J Nutr 106:58–67, 1976
19. Del Prato S, Enzi G, Vigili de Kreutzenberg S, et al: Insulin regulation of glucose and lipid metabolism in massive obesity. Diabetologia 33:228–236, 1990