Original Paper

Carnitine Increases Glucose Disposal in Humans

Andrea De Gaetano, MD, PhD (Math), Geltrude Mingrone, MD, PhD, FACN, Marco Castagneto, MD, FACS, and Menotti Calvani, MD, PhD

Consiglio Nazionale delle Ricerche, Centro Fisiopatologia Shock, Laboratorio di Biomatematica (A.D.G., M.C.), Istituto di Clinica Medica, Universita` Cattolica del Sacro Cuore (G.M., M.C.), Rome, ITALY

Key words: glucose kinetics, insulin kinetics, carnitine, minimal model, theoretical models, mathematics

Objective: The goal of this work is to assess the effect of L-carnitine on glucose disposal, particularly on insulin sensitivity, in healthy volunteers.

Methods: Fourteen healthy human volunteers were subjected to the intravenous glucose tolerance test (analyzed by means of the minimal model technique), together with indirect calorimetry and measurement of serum free fatty acids, after a bolus of glucose plus carnitine (C) or a bolus of glucose plus saline (P).

Results: The minimal model demonstrated a significant increase in glucose disposal from plasma with carnitine: Glucose effectiveness passed from 2.7%/min to 3.8%/min. No significant changes were observed in the Insulin Sensitivity Index or in Insulin/C-Peptide secretion. Calorimetry showed a significant increase in respiratory quotient, resulting from a significant increase in carbohydrate oxidation rate during carnitine administration by an average of 0.0176 ± 0.0118 g/min ($p = 0.015$). Energy expenditure was not modified by treatment. A smaller decrease in plasma fatty acid concentrations was noted with carnitine plus glucose than after glucose alone.

Conclusions: From these data it appears that carnitine stimulates glucose disposal and oxidation in the healthy volunteer. Therefore, carnitine might be useful as an adjunct in the therapy of diabetes mellitus.

INTRODUCTION

The central role of carnitine (3-hydroxy-4N-trimethylammonio-butanoate) as an intramitochondrial carrier of acyl groups is well known. Acquired or congenital carnitine deficiency results, in fact, in impaired fat oxidation [10]. Less well understood is the role that carnitine plays in carbohydrate metabolism, either directly, or indirectly through its action on fatty acids. A specific short-chain carrier system, carnitine-acetyl-transferase (CAT), present on mitochondrial membranes, catalyzes the reversible formation of the acetyl-carnitine complex. Thus carnitine acts as a carrier of acetyl groups from mitochondria to cytosol [5,17]. As shown in human skeletal muscle *in vitro* [17], carnitine traps acetyl-CoA by lowering the intramitochondrial acetyl-CoA/CoA-SH ratio. This stimulates the activity of pyruvate-dehydrogenase (PDH). However, the importance of this cellular mechanism on whole body glucose utilization in humans is unclear. Reports in the literature are conflicting. Some suggest no action at all of carnitine on glucose utilization [1,4,16], some maintain that carnitine administration increases glucose oxidation [5], and some claim that carnitine improves non-oxidative glucose disposal [6,13]. These studies have been based upon either simple substrate concentration [1,16,22,25], on indirect calorimetry [13,27], or on the euglycemic hyperinsulinemic clamp technique [6,13].

In the present work we study the effect of increased circulating carnitine levels on glucose metabolism in healthy subjects. Whole-body glucose uptake was measured by the Frequently Sampled I.V. Glucose Tolerance Test (IVGTT), in which plasma C-peptide, glucose and insulin concentrations were measured. Data were analyzed using the minimal model of glucose and insulin kinetics according to Bergman, Cobelli *et al.* [2,8,26]. This model incorporates parameters that characterize the cellular glucose uptake, the sensitivity of pancreatic β-cells to glucose and the kinetics of the delivered insulin. Substrate oxidation and energy expenditure before and during IVGTT were estimated by indirect calorimetry.

Address reprint requests to: Andrea De Gaetano, MD, PhD(Math), Laboratorio di Biomatematica, CNR—Centro Fisiopatologia Shock, UCSC—L.go Gemelli, 8—00168 Roma—ITALY.

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MATERIALS AND METHODS

Experimental Subjects

Fourteen healthy volunteers (seven males and seven females, aged 33.8±10.9 years, weighing 65.1±11.2 kg with a Body Mass Index of 23.6±2.7, data expressed as mean±SD) participated in the study. All subjects had negative family and personal histories for diabetes mellitus and other endocrine diseases, were on no medications, had no current illness and had maintained a constant body weight for the six months preceding the study. For the three days preceding the study and until conclusion of the study each subject followed a standard composition diet (55% carbohydrate, 30% fat, 15% protein) *ad libitum* with at least 250 g of carbohydrates per day.

Written informed consent was obtained in all cases; the study protocol was conducted according to the Declaration of Helsinki and along the guidelines of the institutional review board of the Catholic University School of Medicine, Rome, Italy.

Procedure

Each subject was studied twice: under carnitine (C) and under placebo (P), in randomized order, with an interval of about one week. Each study was performed at 8:00 AM, after an overnight fast, with the subject supine in a quiet room with a constant temperature of 22 to 24°C.

Bilateral polyethylene IV cannulas were inserted into antecubital veins. Indirect calorimetry was started using a portable Deltatrac (Datex Instrumentarium, Helsinki, Finland) metabolic cart and continued for 40′ (T-40 to T0) to establish a baseline. Calorimetric monitoring was then continued for two and one-half more hours (T0 through T150).

The standard IVGTT was performed, without the addition of Tolbutamide in order to be able to use the recorded data for pancreatic secretion evaluation: at T0 a 33% glucose solution (0.33 g Glucose/kg Body Weight) additioned with L-Carnitine (Sigma Tau, Rome, Italy; 80 mg carnitine/g Glucose administered; C study) or with an equal amount of saline (P study) was rapidly injected (less than 3 minutes) through one arm line. Blood samples (three mL each, in lithium heparin) were obtained at T-30, T-15, T0, T2, T4, T6, T8, T10, T12, T15, T20, T25, T30, T35, T40, T50, T60, T80, T100, T120, T140, T160 and T180 through the contra lateral arm vein. Each sample was immediately centrifuged and plasma was separated. Plasma glucose was measured by the glucose oxidase method (Beckman Glucose Analyzer II, Beckman Instruments, Fullerton, CA, USA). Plasma insulin and C-peptide were assayed by standard radio immunoassay technique. Plasma free fatty acids (NEFA) were measured by enzymatic spectrophotometric method (Boehringer-Mannheim Yamanouchi K.K., Tokyo, Japan) on plasma samples at 0, 6, 12, 25, 50, 100, 180 minutes. Urine was collected for each subject and urinary nitrogen measured by the Kejedahl method.

Data Analysis

Plasma glucose, insulin and C-peptide curves were fitted to the three appropriate minimal models [2,8,26] by non-linear least squares, using a Variable Metric minimization algorithm and a Runge-Kutta technique to reconstruct the predicted curve from the unsolved system of differential equations [9,23]. For C-peptide, the more robust one-compartment model was used for all subjects. For each model, the effect of carnitine on each parameter was evaluated using a backward stepwise approach as follows: The full model was specified, including both the four structural parameters G_0 through b_3 and the relative difference parameters G_{0d} through b_{3d}, the difference parameters expressing the difference between the carnitine and the placebo treatments. With the stepwise procedure, the model was fitted iteratively, and after each iteration the difference parameter with the highest relative standard error was removed until all remaining difference parameters were simultaneously significant by one-sample *t* test (testing the departure of the difference parameter from zero). Table 1 shows the model equations. Notice that the parameter b_1 (K_1 with the carnitine effect added in) is also referred to as S_G (Glucose Effectiveness) and expresses the tendency of glucose *per se* to increase its own

Table 1. Minimal Models

MM1: INSULIN SENSITIVITY

$dG(t)/dt = -[K_1 + X(t)]G(t) + K_1\, G_b$, $G(0) = K_{G0}$

$dX(t)/dt = -K_2\, X(t) + K_3[I(t) - I_b]$, $X(0) = 0$

where C=0 for basal, 1 for carnitine,

$K_{G0} = G_0 + C\, G_{0d}$

$K_1 = b_1 + C\, b_{1d}$

$K_2 = b_2 + C\, b_{2d}$

$K_3 = b_3 + C\, b_{3d}$

Insulin Sensitivity Index, $S_i = K_3/K_2$

MM2: POST-HEPATIC INSULIN APPEARANCE

$dI(t)/dt = K_4\, [G(t) - K_5]^+\, t - K_6\, [I(t) - I_b]$, $I(0) = K_{I0} + I_b$

where C=0 for basal, 1 for carnitine,

$K_{I0} = I_0 + C\, I_{0d}$

$K_4 = b_4 + C\, b_{4d}$

$K_5 = b_5 + C\, b_{5d}$

$K_6 = b_6 + C\, b_{6d}$

$$AUC_1 = K_{I0} + \int_0^{180} [b_4[G(t) - b_5]^+ t + I_b b_6]dt$$

MM3: C-PEPTIDE PANCREATIC SECRETION

$dP(t)/dt = K_7\, [G(t) - K_8]^+ t - K_9\, [P(t) - P_b]$, $P(0) = K_{P0} + P_b$

where C=0 for basal, 1 for carnitine,

$K_{P0} = P_0 + C\, C_{0d}$

$K_7 = b_7 + C\, b_{7d}$

$K_8 = b_8 + C\, b_{8d}$

$K_9 = b_9 + C\, b_{9d}$

$$AUC_1 = K_{P0} + \int_0^{180} [b_7[G(t) - b_8]^+ t + P_b b_9]dt$$

disposal or decrease liver glucose output, while the insulin sensitivity index S_i, expressing the effect of insulin in increasing tissue glucose disposal, is computed as b_3/b_2 (or K_3/K_2). Similarly, while for notational convenience in the present work the parameters of the pancreatic secretion model referring to Insulin have been given names different from those referring to C-peptide, these parameters are often referred to in the literature as γ (b_4, b_7), h (b_5, b_8) and n (b_6, b_9). The areas under the insulin ($AUC_{Insulin}$) and C-peptide ($AUC_{Cpeptide}$) time-secretion curves were computed and subtracted in order to determine the overall percentage of hepatic insulin extraction during the time T0 to T180. While fitting the C-peptide model, the b_8 (K_8) parameter (target glycemia) was kept fixed to the corresponding b_5 (K_5) parameter of the Insulin model, previously fitted on the same subject.

Calorimetric data (oxygen consumption, VO_2; carbon dioxide production, VCO_2) were automatically acquired every minute over an RS232 interface from the Deltatrac and averaged over the first 40 minutes (T-40 through T0) and over each subsequent half-hour. Energy expenditure (EE) and respiratory quotient (RQ) were computed from the period averages of VO_2, VCO_2 and urinary N_2 loss according to standard formulas [12]. RQ and EE were compared, for each time interval, between the P and C study using a Bonferroni-corrected paired-data Student *t* test. The average P and C rates of minute carbohydrate oxidation were compared by a paired-data Student *t* test. Since baseline free fatty acid levels varied significantly among subjects, percent variations from the baseline were compared between the P and C groups at each time point using a Bonferroni-corrected paired-data Student *t* test.

RESULTS

Glucose Disposal

Table 2 (MM1) reports the estimates of the parameters of the tissue glucose disposal part of the Minimal Model, together with their standard errors. One positive difference parameter (b_{1d}), expressing the increase of glucose effectiveness ($S_G=b_1$) associated with carnitine administration, was shown to be significant ($p=0.0401$) and is reported in the table. The other difference parameters were set to zero, following the backward stepwise procedure. Fitting was good to excellent for all subjects examined, as shown by the high R-squared values.

Insulin Secretion

As reported in Table 2 (MM2, MM3), no parameters resulted in being significantly different for either the Insulin or the C-Peptide time courses as analyzed by Minimal Modelling. Fitting was typically good with only two subjects exhibiting R-squared values around 40% in the C-peptide fittings.

Fig. 1, Fig. 2 and Fig. 3 show the sampled time courses and the model-derived curves for glucose, insulin and C-peptide respectively in a typical experimental subject.

Table 2. Minimal Model Parameter Values

Parameter	Estimated Value	Standard Error	Units of Measurement
MM1			
G_0	246.6	±8.21	mg/100mL
b_1	0.0274	±0.0043	min^{-1}
b_2	0.0202	±0.0028	min^{-1}
b_3	$1.886* 10^{-6}$	$\pm 0.289* 10^{-6}$	$min^{-2}pM^{-1}$
b_{1d}	0.011	±0.0049	min^{-1}
S_i	0.004186	±0.00409	$min^{-1}pM^{-1}$
R^2 from 0.971 to 0.998			
MM2			
I_0	665.0	±96.8	pM
b_4	0.010	±0.0034	$min^{-2}pM(mg/100mL)^{-1}$
b_5	92.1	±9.06	mg/100mL
b_6	0.0844	±0.0103	min^{-1}
R^2 from 0.700 to 0.960			
MM3			
P_0	1460.6	±145.5	pM
b_7	0.0393	±0.0105	$min^{-2}pM(mg/100mL)^{-1}$
b_8*	92.1	±9.06	mg/100mL
b_9	0.0515	±0.0149	min^{-1}
R^2 from 0.392 to 0.972			

* parameter values fixed to the corresponding b_5 values estimated from the Insulin data.
Average hepatic insulin extraction=61.4±9.5%
$hie=100*(AUC_{Cpeptide}-AUC_{Insulin})/AUC_{Cpeptide}$

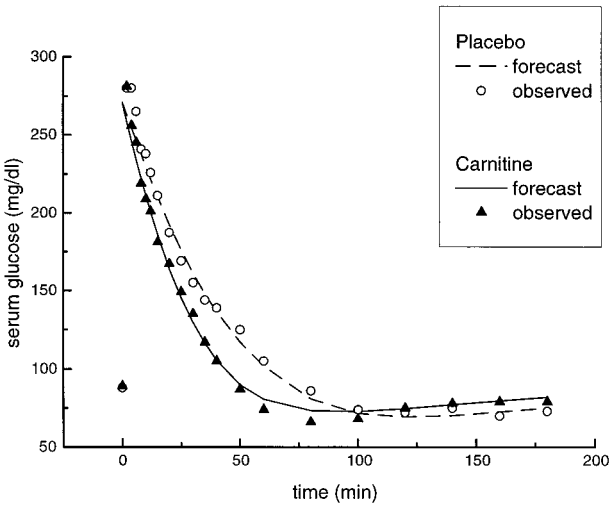

Fig. 1. Time/concentration data points and fitted model curves for blood glucose in experimental subject #9. Lines are predicted concentrations; points are observed values.

Indirect Calorimetry

Fig. 4 and Fig. 5 report the observed RQ and EE averages and standard errors, over half-hour periods. No significant

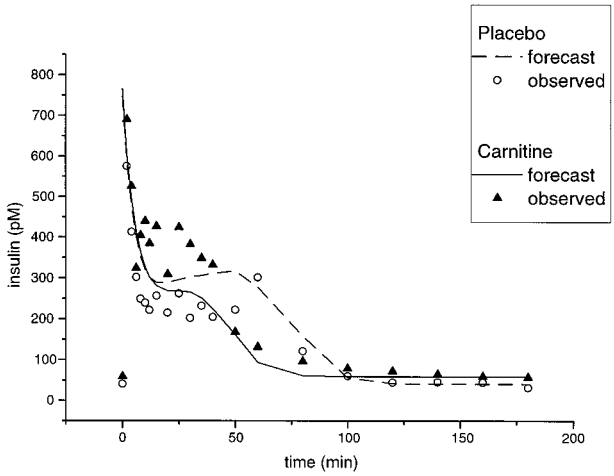

Fig. 2. Time/concentration data points and fitted model curves for blood insulin in experimental subject #9.

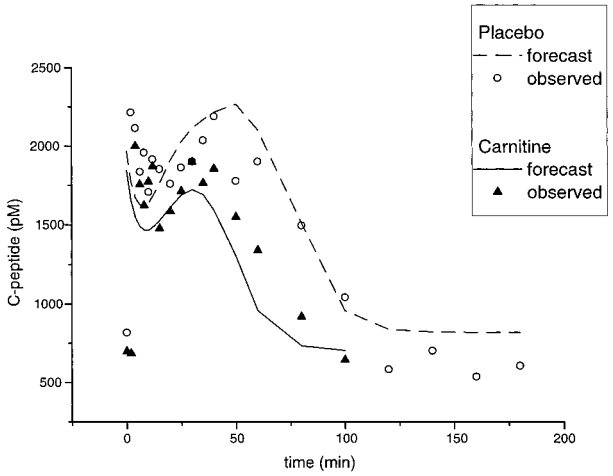

Fig. 3. Time/concentration data points and fitted model curves for blood C-peptide in experimental subject #9.

difference was observed in EE during the experiment. RQ is significantly higher in C than in P studies during the first hour after glucose bolus (0–30′, C *vs.* p: 0.858±0.026 *vs.* 0.826±0.019, p=0.023; 30–60′, C *vs.* p: 0.894±0.021 *vs.* 0.863±0.021, p=0.018; data expressed as mean±SE). Carbohydrate oxidation rates during carnitine administration were higher than the corresponding placebo by an average of 0.0176±0.0118 g/min (p=0.015).

Free Fatty Acid Levels

Fig. 6 shows the variations of NEFA levels as percent of baseline in C and P studies. There are marginally significant differences at 6′ (C *vs.* P: −11.6±3.1% *vs.* −2.3±4.7%, p=0.047), and at 25′ (C *vs.* P: −32.0±4.1% *vs.* −40.5±3.8%, *p*=0.049), and a clear-cut difference at 100′ (C *vs.* P: −15.8±8.1% *vs.* −43.0±7.7%, p=0.0062).

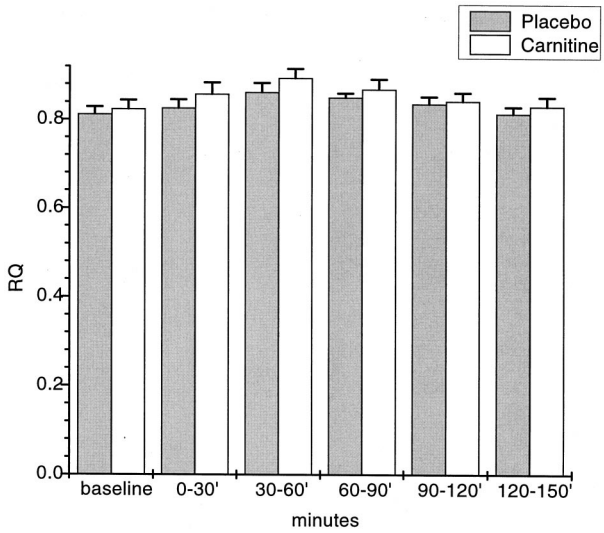

Fig. 4. Group averages and standard errors (I-bars) for RQ during successive time periods. Shaded: placebo; hollow: carnitine. Significant differences between placebo and carnitine at (0–30′) and at (30–60′).

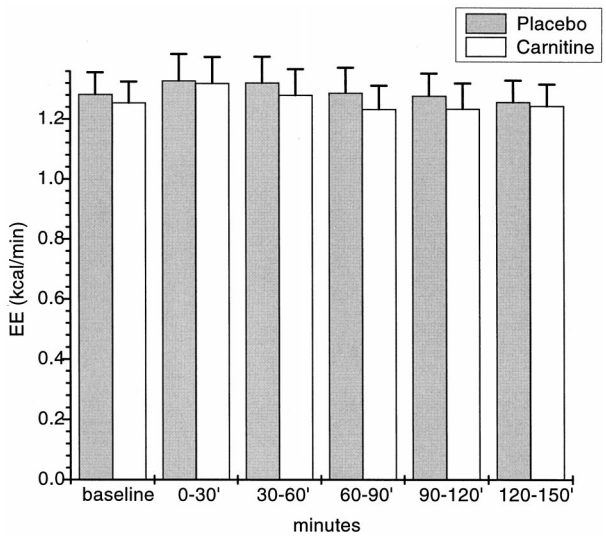

Fig. 5. Group averages and standard errors (I-bars) for EE during successive time periods. Shaded: placebo; hollow: carnitine. No significant differences between placebo and carnitine.

DISCUSSION

In our series, the minimal model has been used to evaluate the effect of an intravenous bolus of carnitine on glucose disappearance and insulin secretion. The average hepatic insulin extraction was also measured utilizing plasma C-peptide concentration data. Minimal modelling of glucose kinetics is an alternative to the clamp technique over which it has the advantage of a simpler experimental procedure. The model's result (a significant increase of the glucose effectiveness parameter S_G, reflecting either increased tissue glucose uptake or decreased

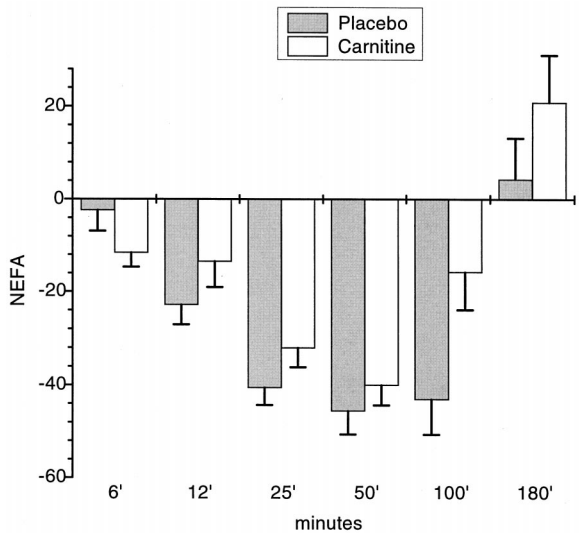

Fig. 6. Group averages and standard errors (I-bars) for NEFA (as % of baseline level) during successive time periods. Shaded: placebo; hollow: carnitine. Significant differences between placebo and carnitine at 6′, 25′ and 100′.

liver glucose output, at basal insulin levels) supports the existence of an insulin-independent action of carnitine, while not excluding the possibility of an associated insulin-dependent action as well. While the present data are sufficient to suggest that carnitine increases glucose mass action, a larger series of patients or different techniques could show its effect on insulin sensitivity as well. On the other hand, no effect of carnitine is apparent on the pancreatic insulin-release dynamics or on liver first-pass insulin extraction.

Glucose oxidation rate, calculated through indirect calorimetry, was significantly increased after carnitine intravenous bolus. This is consistent with the hypothesis that carnitine-induced glucose oxidation, therefore, increased glucose disposal is at least partially responsible for the glucose mass action, even though the results obtained from the calorimetric analysis of a transient response have to be interpreted with caution.

Finally, from the NEFA data it appears that the decrease of plasma NEFA levels after glucose administration is possibly quicker but clearly smaller after carnitine than after saline; this suggests a higher amount of glucose utilization for oxidation in place of NEFA. This is in accord with Randle's classical glucose-fatty acid cycle hypothesis [18,24], which maintains that the rates of glucose oxidation and free fatty acid oxidation vary in opposite directions compensating for the cellular choice of metabolic substrates. This has been shown to happen in humans [11,15] and is likely due to the fact that both substrates converge for final utilization into the Krebs cycle.

Few studies are available in the literature on the action of carnitine on glucose disposition, and these few trace a rather controversial picture of it.

In two series of surgical patients [1,16], no statistically significant difference was found between carnitine and placebo on the post-traumatic glycemic response, even if one of the authors [16] suggested a likely reduction of insulin resistance after carnitine administration. During strenuous exercise in humans, both with normal oxygenation and under hypoxic conditions, the administration of carnitine was observed to be associated with a reduction of the respiratory quotient [27], from which the author inferred lower rates of carbohydrate oxidation. This observation seems to be in contrast with other experiments [5,6,13,28] where carnitine was observed to induce a significant increase in glucose disposition, even under hypoxic conditions (although with a very different experimental setting: myocardial homogenates) [28]. Furthermore, it has been observed that carnitine administration has a hypoglycemic effect on diabetic rats [21,25].

There are differences in interpretation, however, on how carnitine would produce an increase in glucose disposal. Using the euglycemic hyperinsulinemic clamp technique in humans Ferrannini [13] arrived at the conclusion that while glucose oxidation is unaffected by carnitine, nonoxidative glucose disposal increases by as much as 50 percent. It is possible that, in these experimental conditions, the effect of carnitine on glucose oxidation was more difficult to observe, due to the insulinization which, by itself, substantially stimulates glucose uptake. The clamp technique was also used by Capaldo *et al.* [6], who showed a carnitine-induced increase in whole-body glucose utilization in NIDDM patients and ascribed it to improved insulin sensitivity. It is difficult, however, to discriminate between enhanced insulin sensitivity and insulin-independent glucose disposal during a clamp at fixed insulinization levels. Moreover, these authors did not use indirect calorimetry and were therefore unable to discriminate between non-oxidative glucose disposal and glucose oxidation. Data of Broderick *et al.* [5], in an isolated perfused rat heart preparation, showed that increased myocardial carnitine levels induced an increase in glucose oxidation and a corresponding decrease in FFA oxidation, resulting in no changes in the overall ATP production.

Our data in healthy humans agree with the *in vitro* data of Broderick *et al.*, both as regards increased carbohydrate oxidation and decreased FFA utilization. The cellular mechanisms whereby carnitine effects its action on carbohydrate metabolism are still to be clarified. In particular, carnitine could act at the insulin receptor level, it could act by increasing transmembrane glucose transport (either insulin-dependent or insulin-independent), or it could act at a post-receptor level.

Insulin resistance is a common finding in Type 1 as well as in Type 2 diabetes. In some of these individuals, insulin resistance appears to be correlated with a functional deficiency of the receptors and can be corrected by increasing plasma insulin levels [7,14]. In most other individuals, although they show a relatively low number of receptors, increasing the insulin level does not correct the resistance, suggesting that insulin resistance is often due to a post-receptor defect: in fact, increasing

insulin levels in these patients may well increase insulin resistance through receptor down-regulation [19,20]. An additional support to the post-receptor defect theory in causing insulin resistance has been furnished by the recent study of Berliner *et al.* [3]. These authors show that increasing the cholesterol content in cellular membranes of cultured bovine aortic endothelial cells, results in resistance to the action of insulin. This resistance is not due to a decrease in the number of insulin receptors, nor to a decrease in receptor affinity for insulin, but rather to a post-receptor defect either at the membrane level or intracellularly. Since we have evidenced its insulin-independent effect, carnitine might play a role in the therapy of diabetes mellitus by improving insulin resistance with a post-receptor mechanism.

CONCLUSION

Carnitine seems to increase overall glucose elimination from plasma and glucose oxidation. Carnitine could thus play a role as a regulator of glucose oxidation in addition to its well-known action in fatty acid oxidation. As already indicated by animal experiments, this molecule could therefore have a role in the therapy of diabetes.

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