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Carnitine improves peripheral glucose disposal in non-insulin-dependent diabetic patients

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Summary

To investigate the effects of carnitine on insulin sensitivity in non-insulin-dependent diabetes, insulin-mediated glucose disposal was measured in nine diabetic patients (age 54 ± 3 years, BMI 27 ± 1 kg/mq) during a primed (3 mmol) constant (1.7 μmol/min) intravenous infusion of carnitine. In control experiments, the same patients received saline instead of carnitine. Plasma glucose concentration was maintained constant at the level of 100 mg/dl during both studies while plasma insulin was raised to a plateau of 60 μU/ml. Despite similar insulin levels, whole-body glucose utilization was higher with carnitine (4.05 ± 0.37 mg/kg/min) than saline infusion (3.52 ± 0.36). Blood lactate concentrations were similar in the basal state and decreased significantly during carnitine infusion ($P < 0.05$–0.005), whereas it remained substantially unchanged during saline infusion. Plasma FFA decreased to a similar level (0.1 mmol/l) in both studies. We conclude that an acute carnitine administration is able to improve insulin sensitivity in NIDDM patients. The lactate data suggest that this effect may at least in part be mediated by carnitine activation of pyruvate dehydrogenase.

Key words: Carnitine; Insulin; NIDDM; Insulin-resistance

Introduction

The function of L-carnitine is related to the transport of activated long-chain fatty acids from the cytoplasmic compartment into the mitochondrial matrix where the B-oxidation enzyme system is located [1–3]. Based on this mechanism of action, carnitine is recognized as playing a key role in the regulation of free fatty acid oxidation [4,5]. Furthermore, by trapping acetyl groups, L-carnitine decreases the intramitochondrial acetyl CoA/CoA ratio, thus stimulating the activity of pyruvate dehydrogenase [6–8]. At the same time, the reduced levels of acetyl CoA in the cytosol contribute further to activate the glycolytic pathway [9]. In the light of the influence that carnitine exerts on pyruvate dehydrogenase, it has been postulated that carnitine may have some effects on glucose metabolism in vivo. Actually, recent

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studies in healthy subjects have documented that an acute carnitine administration is able to potentiate insulin action on glucose metabolism primarily by increasing non-oxidative glucose disposal [11]. This finding raises the question of whether carnitine is equally active in pathological states characterized by a defect in insulin-stimulated glucose uptake, such as non-insulin-dependent diabetes and obesity. Such data would be of particular importance given the limited availability of therapeutic interventions able to ameliorate insulin resistance [11]. Therefore, the present study was designed to investigate the effects of an acute administration of L-carnitine on insulin-mediated glucose disposal in patients with non-insulin-dependent diabetes mellitus.

Materials and Methods

Nine non-insulin-dependent diabetic patients ranging in age from 39 to 64 years participated in the study. Their clinical characteristics are shown in Table 1. Two patients were treated with insulin and seven patients with oral hypoglycemic agents. They were instructed to keep unchanged their therapeutic regimen and to consume an isocaloric diet containing 200 g of carbohydrate for the entire study period. All patients were in good glycemic control, as evidenced by fasting blood glucose and HbA_{1c} below 140 mg/dl and 8%, respectively. Informed consent was obtained from all participants. The experimental protocol was approved by the Ethical Committee of the University of Naples School of Medicine. The studies were performed in the morning after an overnight fast. Polyethylene cannulas were inserted into a large antecubital vein for administration of test substances and retrogradely into a hand vein for intermittent blood sampling. The hand was warmed in a heated box (60°C) to allow arterialization of venous blood. Each subject was studied twice, in random order, once with carnitine and once with saline. A minimum of 1 week was allowed between the two studies.

At the beginning of each study (−120 min), 3[^{3}H]glucose (Amersham Ltd, Buckinghamshire, U.K.) was infused as a bolus of 25 μCi followed by a continuous infusion for 4 hours. At −60 min, a priming dose of L-carnitine (3 mmol) (Carnitene, Sigma Tau, Rome) or saline was given, followed by a continuous infusion of 1.7 μmol/min for 3 hours. This dose was chosen based on a previous human study showing an effect of carnitine to increase glucose utilization [10]. At time zero, a euglycemic insulin clamp was performed to assess insulin sensitivity [12]. Peripheral plasma insulin concentrations were

TABLE 1

Clinical characteristics of the subjects

Patients No.	Sex (M/F)	Age (years)	BMI (kg/m^2)	FPI (μU/ml)	Duration of diabetes (years)	Therapy
1	M	64	27	8	20	OHA
2	M	39	28	8	7	OHA
3	F	43	26	11	4	OHA
4	F	56	33	14	10	OHA
5	M	66	26	9	3	OHA
6	M	54	22	9	6	I
7	M	53	29	13	12	I
8	M	55	29	11	15	OHA
9	M	58	24	9	4	OHA
Mean ± SE		54 ± 3	27 ± 1	9 ± 2	10 ± 1	

FPI, fasting plasma insulin; I, insulin; OHA, oral hypoglycemic agents.

acutely raised and maintained at 60 μU/ml by means of a constant infusion (0.8 mU/kg/min) of regular insulin. Plasma glucose concentration was allowed to decline from the basal value of 140 mg/dl to 100 mg/dl, at which level it was clamped by means of a variable glucose infusion. The glucose infusion rate was adjusted by measuring plasma glucose at 5-min intervals by means of a Beckman glucose analyzer (Beckman Palo Alto, CA). Blood samples for hormone, substrate and glucose specific activity measurements were taken at 10–30 min intervals.

Analytical procedures

Plasma glucose was measured by the glucose oxidase method (Beckman Analyzer). Plasma insulin was measured by RIA [13]. Blood lactate was measured on perchloric extract of whole blood by an enzymatic procedure [14]. Plasma FFA were determined by an enzymatic method [15]. 3[^{3}H]glucose concentration in plasma samples was measured as previously described [16].

The amount of glucose metabolized by the whole body was calculated by adding the average glucose infusion rate during the last 30 min of the clamp (M value) to the rate of residual hepatic glucose production (HGO). HGO was determined by the isotopic dilution technique as previously described [17]. All data are given as mean $\pm$ SEM. Statistical analysis was performed by Student's paired t-test.

Results

In the post-absorptive state, plasma glucose concentration was similar in the control (142 $\pm$ 8 mg/dl) and carnitine (140 $\pm$ 7 mg/dl) study, and was clamped at the same level (100 mg/dl) in both groups with a coefficient of variation below 5%. The time required for blood glucose to fall from the basal value to the euglycemic level was 46 and 54 min in control and carnitine group, respectively. Plasma insulin levels were 11 $\pm$ 1 in control and 9 $\pm$ 1 μU/ml in

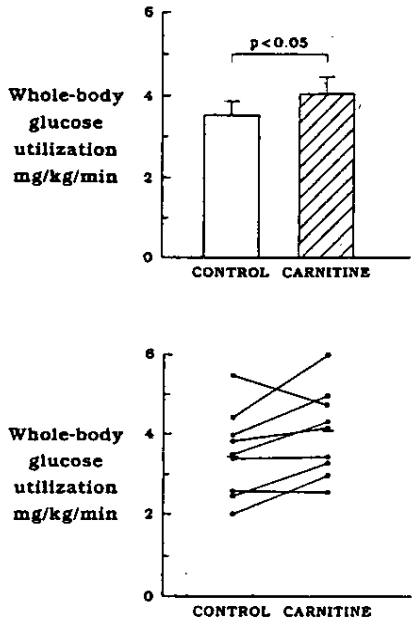

Fig. 1. Mean $\pm$ SE insulin-stimulated glucose disposal during carnitine (▨) and control (□) studies.

carnitine study and rose to a similar plateau of 60 μU/ml during insulin infusion. Despite similar plasma insulin levels, the amount of glucose metabolized by the whole body was higher during carnitine (4.05 $\pm$ 0.37 mg/kg/min) than saline infusion (3.52 $\pm$ 0.36, $P < 0.05$) (Fig. 1). In six out of nine subjects, the increase in total glucose disposal ranged from 10 to 50%; in two patients no increase in glucose disposal was observed, in one patient a slight decrease occurred. As shown in Fig. 2, lactate concentrations were similar in the two groups in the fasting state. In the control study, blood lactate remained substantially unchanged. In contrast, carnitine infusion caused a marked decrease in basal lactate concentration, which ranged 25–40% ($P < 0.05$–0.005). Plasma FFA levels were similar in the basal state in the two studies, averaging 0.48 $\pm$ 0.05 mmol/l (control) and 0.62 $\pm$ 0.12 (carnitine) and fell to a similar extent (0.1 mmol/l) during insulin infusion (Fig. 3). Endogenous glucose production was similar in the basal state in the two groups (2.0 $\pm$ 0.2 and 2.1 $\pm$ 0.3 mg/kg/min) and was

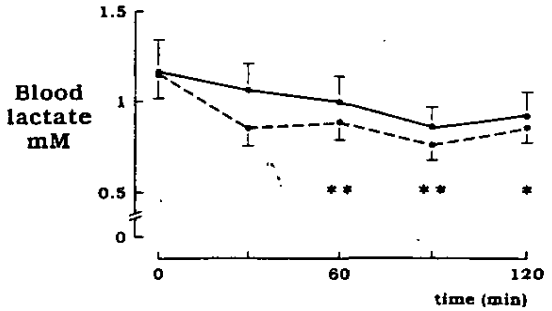

Fig. 2. Mean ± SE blood lactate concentration during euglycemic insulin clamp in carnitine (----) and saline (——) studies.

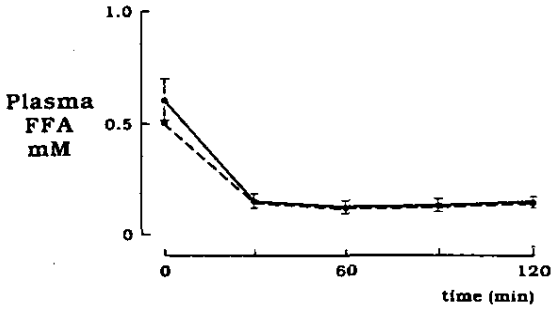

Fig. 3. Mean ± SE plasma FFA concentration during euglycemic insulin clamp in carnitine (----) and control (——) studies.

totally suppressed during insulin infusion on both occasions.

Discussion

The present study shows that an acute administration of L-carnitine is able to potentiate the stimulatory effect of insulin on glucose uptake by peripheral tissues in NIDDM patients. The improvement in glucose utilization achieved in these patients was quantitatively similar to that previously documented in normal subjects (17%) [10]. The magnitude of the effect varied among subjects, with some patients having a quite marked increase (30–50%) and others having marginal changes in peripheral glucose utilization. However, the effect of carnitine seems to be independent of body weight and/or the degree of insulin resistance. Nor was a relation to the previous hypoglycemic treatment demonstrable. It remains to be established whether raising the carnitine infusion rate would have produced a more marked improvement in glucose disposal. It should be also noted that, since the major part of glucose uptake during euglycemic hyperinsulinemia occurs in peripheral tissues, mainly skeletal muscle, it is very likely that the beneficial effect of carnitine on glucose metabolism also involves muscle tissue. On the other hand, it is known that this is a primary site of carnitine action from both a metabolic and energetic standpoint [7].

The mechanism underlying the improvement in glucose disposal induced by carnitine remains largely to be determined. Based on the more pronounced decline in lactate concentration during carnitine infusion, it is reasonable to suggest that the majority of glucose taken up by peripheral tissues is directed toward glycogen synthesis or complete oxidation. The latter hypothesis seems more realistic in view of the documented ability of carnitine to stimulate the activity of pyruvate dehydrogenase and, consequently, the oxidative utilization of glucose [6–8].

In the current study we also determined plasma FFA levels in order to make sure that between the two groups there was no difference in this substrate, given its known ability to compete with glucose disposal. The results show that FFA concentration was nearly identical during control and carnitine studies. This also indicates that carnitine did not affect the antilipolytic activity of insulin.

The current data showing that acute carnitine administration increases glucose disposal in NIDDM patients, opens the possibility that carnitine may be of clinical benefit in the treatment of NIDDM. Although the effect here demonstrated is not quantitatively impressive, we believe that the present finding is equally worthy of consideration for the following reasons. Firstly, there is paucity of therapeutic interventions capable of improving insulin sensitivity in patients with NIDDM [11], and each of them exerts an effect which is of comparable magnitude to that observed with carnitine. Secondly, L-carnitine

has the advantage of being a substance naturally produced in the body and, therefore, free of side effects. Nor, on the other hand, is there evidence of any disturbance caused by supraphysiological carnitine concentrations in the range of those achieved with exogenous administration [18]. Whether a long-term administration of L-carnitine may further enhance insulin effect on glucose uptake in NIDDM patients remains to be investigated.

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