Effect of Long-Term Valproic Acid Administration on the Efficiency of Carnitine Reabsorption in Humans

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To elucidate the etiology of valproic acid–induced carnitine deficiency, we tested the hypothesis that long-term valproic acid administration decreases the rate of carnitine reabsorption. Thirteen healthy men participated in a 34-day protocol in which carnitine clearance was measured before and after 28 days of valproic acid administration. During valproic acid administration (days 6 to 33), plasma free and total carnitine concentrations decreased (18% and 12%, respectively, $P < .05$) by 16 days, but returned to pretreatment concentrations by 28 days. From day 14 to day 30, the rate of free carnitine excretion was 50% lower than at baseline (day 4, $P < .05$). Free and total carnitine clearance, indexed to the glomerular filtration rate, was lower after valproic acid administration ($P < .01$). Contrary to our hypothesis, after 28 days of valproic acid administration, the rate of carnitine reabsorption was enhanced independent of the glomerular filtration rate and filtered load. Changes in the plasma concentration, rate of excretion, and clearance were specific for carnitine and were not generalized in magnitude or direction to the other amino acids. We conclude that the kidney adapts to conserve carnitine during valproic acid administration and therefore does not cause valproic acid–induced carnitine depletion in adults.

VALPROIC ACID is a commonly prescribed medication for the treatment of simple and complex absence seizures and an adjunct in the treatment of other types of seizures. Long-term use of this anticonvulsant is sometimes associated with fatal hepatic necrosis resembling Reye's syndrome.[1] Decreased carnitine concentrations in plasma and skeletal muscle have been associated with valproic acid therapy in humans, particularly children.[2,3] In some patients, carnitine administration corrected the hyperammonemia associated with valproic acid therapy.[4] Thus, maintenance of normal or supranormal carnitine status in patients treated with valproic acid may be desirable.[2]

In humans, carnitine homeostasis is maintained by absorption of carnitine from dietary sources, endogenous synthesis of carnitine, primarily in the liver and kidney, and efficient reabsorption of carnitine.[5] Subnormal carnitine status may result from a valproic acid–induced alteration in any one or more of these processes. In this investigation, we examined the effect of valproic acid on the efficiency of carnitine reabsorption. The following hypothesis was tested: Long-term valproic acid administration specifically decreases the rate of carnitine reabsorption independent of the filtered load and glomerular filtration rate. If this hypothesis is correct, we reasoned that a decreased renal reabsorption of carnitine, and consequently, an increased rate of carnitine excretion, would lead to depletion of carnitine stores in patients treated long-term with valproic acid.

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SUBJECTS AND METHODS

Subjects

Fourteen men were recruited from the Iowa City community to participate in a longitudinal study of the effect of valproic acid on carnitine reabsorption. Subjects were judged to be healthy following a review of their medical history, physical examination, and liver function tests. Exclusion criteria used to screen potential participants included chronic use of medication, tobacco products or alcohol, and a history of renal and/or hepatic disease, pancreatitis, diabetes, abnormal blood pressure, or blood clotting problems including frequent bruising. Written informed consent was obtained prior to matriculation into the study. The research protocol was reviewed and approved by the University of Iowa Committee on Research Involving Human Subjects and the General Clinical Research Center (GCRC) Protocol Review Committee.

Materials

L-Carnitine (inner salt) for injection was provided by Sigma-tau Pharmaceuticals (Gaithersburg, MD) as a sterile solution (1 g/5 mL). This material was diluted with sterile 0.45% NaCl for infusion. Inulin for injection was obtained from Iso-Tex Diagnostics (Friendswood, TX). Divalproex sodium (Depakote; Abbott Laboratories, Chicago, IL; 125-, 250-, and 500-mg delayed-release tablets) was obtained from the University of Iowa Hospitals and Clinics Pharmacy. A kit for analysis of valproic acid in plasma was obtained from Syva (Palo Alto, CA). Reagents for automated quantification of ammonia and creatinine were obtained from Ciba-Corning (Oberlin, OH).

Experimental Design

The following protocol was used for each subject. For the duration of the study, subjects consumed a diet calculated to provide the individual's usual daily intake of carnitine[5] and energy and a constant macronutrient composition (35% fat and 50% carbohydrate as a percent of available energy). During days 1 through 4, participants consumed the study diet without any other intervention. On the morning of the fourth day, a fasting plasma sample was obtained, and also on day 4, a 24-hour urine collection was obtained to determine baseline concentrations and excretion rates of the measured solutes (carnitine, creatinine, and amino acids). On the morning of the fifth day, the glomerular filtration rate and clearance of solutes were measured. For the next 28 days (days 6 thru 33), valproic acid, in the form of divalproex sodium (a 1:1 mixture of valproic acid and sodium valproate), was administered (described later). Blood samples were collected every 7 days (morning fasting, before breakfast and first valproic acid administration) to

measure plasma concentrations of carnitine, creatinine, ammonia, and valproic acid. Twenty-four-hour urine collections were obtained on 3 consecutive days each week to measure the rate of carnitine and creatinine excretion. On day 34, the glomerular filtration rate and solute clearance measurements were repeated. Following completion of this test, each subject was released from the study.

The rates of carnitine reabsorption, indexed to the glomerular filtration rate and at discrete filtered loads, were compared before and after the 28-day treatment regimen with valproic acid. Longitudinal data for the plasma carnitine concentration and rate of carnitine excretion during the course of valproic acid administration were also compared.

Administration of Valproic Acid

Valproic acid (divalproex sodium) was administered in three equally divided doses with the meals, initially at a total dose of 1.73 mmol/d (250 mg/d) and increasing by 1.73 mmol/d every 2 days until a final dose of approximately 104 μmol/kg body weight/d (15 mg/kg body weight/d) was achieved (on day 12). Divalproex sodium was dispensed and compliance monitored by the GCRC staff.

Measurement of Glomerular Filtration Rate and Solute Clearance

On days 5 and 34, subjects were admitted as outpatients to the GCRC for measurement of the glomerular filtration rate and solute (carnitine and selected amino acids) clearance, as previously described.[5] Carnitine was infused during the procedure to obtain carnitine clearance rates over a range of plasma carnitine concentrations.

Analytical Procedures

Plasma and urine samples were analyzed for free and total (free plus esterified) carnitine by the radioenzymatic procedure of Cederblad and Lindstedt[6] with modifications.[5] Inulin levels were measured in plasma and urine by the method of Liedtke and Duarte.[7] Selected amino acids (alanine, arginine, glutamic acid, glutamine, glycine, hydroxyproline, leucine, lysine, methionine, phenylalanine, proline, serine, taurine, tryptophan, tyrosine, and valine) in plasma and urine were measured spectrophotometrically after derivatization with phenylisothiocyanate and separation by high-performance liquid chromatography.[8] The creatinine level was measured colorimetrically as previously described.[9] The plasma ammonia level was measured by the method of Mondzac et al.[10] The valproic acid concentration in plasma was quantified by homogeneous enzyme immunoassay.[11,12] Methods for measurement of creatinine, ammonia, and valproic acid levels were adapted for automated analysis using the SBA 300 Clinical Chemistry Analyzer (Gilford Systems, Oberlin, OH).

Duplicate meals for each subject were prepared, homogenized, and analyzed for total energy, nitrogen, fat, and carnitine.[13]

Calculations

The rates of carnitine excretion and reabsorption were indexed to the glomerular filtration rate (inulin clearance). The following equations were used to calculate the glomerular filtration rate (inulin clearance [C_I]), carnitine clearance (C_C), carnitine excretion (E_C), and carnitine reabsorption (Tr_C): $C_I = (U_I \times V)/P_I$, $C_C = (U_C \times V)/P_C$, $E_C = 100 \times (U_C \times V)/C_I$, and $Tr_C = [(P_C \times C_I) - (U_C \times V)] \times (100/C_I)$. U_I and P_I are the urine and plasma concentrations of inulin (grams per liter), respectively, and U_C and P_C are the urine carnitine concentration and average plasma carnitine concentration (micromoles per milliliter) at the start and end of each collection period, respectively. V is the rate of urine flow (milliliters per minute).

Statistical Analyses

Differences in the rates of carnitine excretion and reabsorption at discrete filtered loads before and after valproic acid therapy were analyzed by the paired *t* test procedure.[14] Longitudinal data for plasma concentrations of carnitine, ammonia, valproic acid, and amino acid and rates of carnitine and amino acid excretion before and during valproic acid administration were compared by repeated-measures ANOVA.[14] Differences were detected by single degree of freedom contrasts with the corresponding values on day 4 (before the start of valproic acid administration). Because there were missing data for plasma ammonia and valproic acid concentrations between days 16 and 30, data for each solute were condensed (days 16, 23, and 30) for repeated-measures ANOVA (day 9 or days 16, 23, and 30 *v* day 4). For valproic acid and ammonia, respectively, repeated-measures data for 12 and nine subjects were compared. Likewise, for longitudinal measures of amino acid excretion, the rates on 3 consecutive days (7 to 9, 14 to 16, 21 to 23, or 28 to 30) were averaged and compared with the rates on day 4. For all analyses, differences were considered significant at a P level less than .05.

RESULTS

Data are reported for 13 subjects who completed the study protocol. The age range of participants was 19 to 40 years. One subject withdrew from the study on day 17 because of gastrointestinal distress thought to be associated with valproic acid administration. All participants were within 25% of their ideal body weight for height as determined from the midpoints of ranges provided in the 1983 Metropolitan Height and Weight Tables.[15] There were no differences in the body weight, glomerular filtration rate, or creatinine clearance before and after valproic acid administration (Table 1).

Trough valproic acid concentrations in plasma reached a plateau by day 16 of the study (Fig 1). The mean ammonia concentration in plasma increased modestly from baseline (day 4) by day 16 and remained higher than baseline through day 30 (Fig 2). Plasma carnitine concentrations decreased from baseline by day 16 (total carnitine) and day 9 (free carnitine; Fig 3). Both free and total carnitine concentrations in plasma returned to baseline by days 30 and 23, respectively, despite continued administration of valproic acid at the maximal dosage.

The rate of urinary free carnitine excretion was significantly lower by day 14 of the study compared with the baseline (day 4; Fig 4). Free carnitine excretion remained significantly lower versus baseline until the end of the study, and by day 30, the rate was approximately half the baseline rate. These results were the same whether carnitine excretion was indexed to body weight or to creatinine excretion. The rate of total carnitine excretion declined by about 16% during the course of valproic acid administration, but differences (compared with baseline) were significant only on day 28 (rate indexed to body weight) or days 21, 22, and 23 (rate indexed to creatinine excretion).

On days 5 and 34, carnitine clearance was measured over a

Table 1. Subject Characteristics

Parameter	Day	Mean ± SD
Weight (kg)	5	81.3 ± 11.6
	34	82.0 ± 11.9
Glomerular filtration rate (mL · min^{-1}) (body surface area/1.73)$^{-1}$	5	98.0 ± 8.40
	34	102 ± 11.1
Creatinine clearance (mL · min^{-1})	5	103 ± 11.5
	34	111 ± 15.0
Valproic acid dose (μmol · kg body weight^{-1} · d^{-1})	12-33	101 ± 2.91

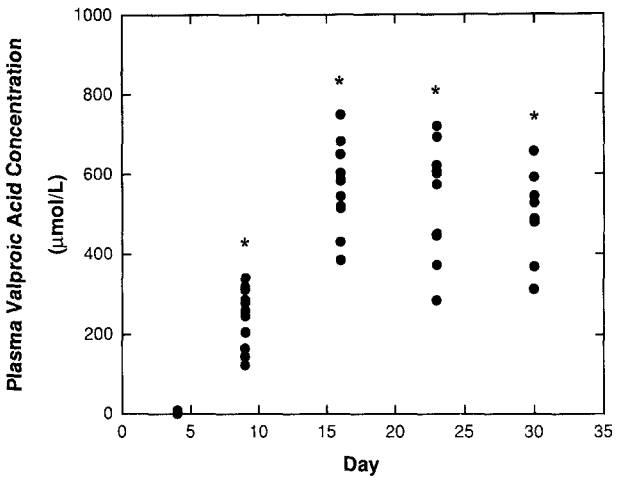

Fig 1. Total (free + protein-bound) trough valproic acid concentration on days 4 (baseline), 9, 16, 23, and 30. Blood samples were drawn into heparinized tubes without the use of a tourniquet, after an overnight fast. Each sample was placed on ice immediately. Plasma was obtained by centrifugation, harvested without disrupting the buffy coat layer of cells, and refrigerated. Analysis was performed within 2 hours of collection. *Significant difference *v* day 4 ($P < .05$).

range of plasma carnitine concentrations and indexed to the glomerular filtration rate (inulin clearance) by intravenous infusion of carnitine and inulin. Normalized (to glomerular filtration rate) rates of free and total carnitine excretion and reabsorption were calculated, providing pairs of curves (one each before and after valproic acid administration) for free and total carnitine excretion and reabsorption (representative data for one subject are shown in Fig 5). These curves were interpolated to provide the rates of free and total carnitine excretion (Fig 6) and reabsorption (Fig 7) at discrete plasma carnitine concentrations (5-μmol/L intervals). At each interval

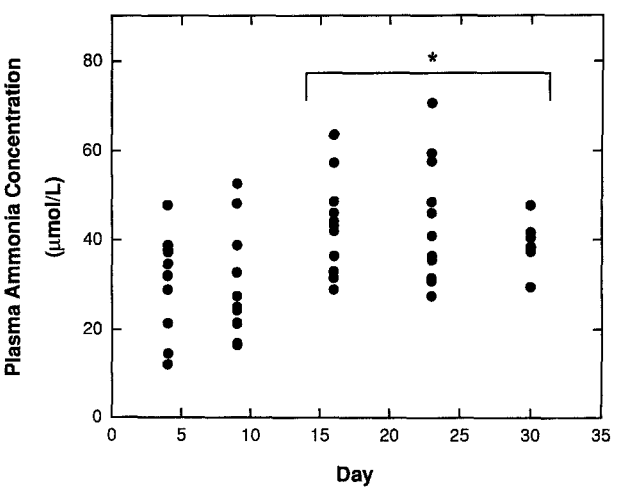

Fig 2. Plasma ammonia concentration on days 4 (baseline), 9, 16, 23, and 30. Blood samples were obtained and processed as described in Fig 1. Because there were missing data for plasma ammonia concentrations between days 16 and 30, data obtained for days 16, 23, and 30 were condensed for repeated-measures ANOVA. Repeated-measures data for 9 subjects were compared. *Significant difference *v* day 4 ($P < .05$).

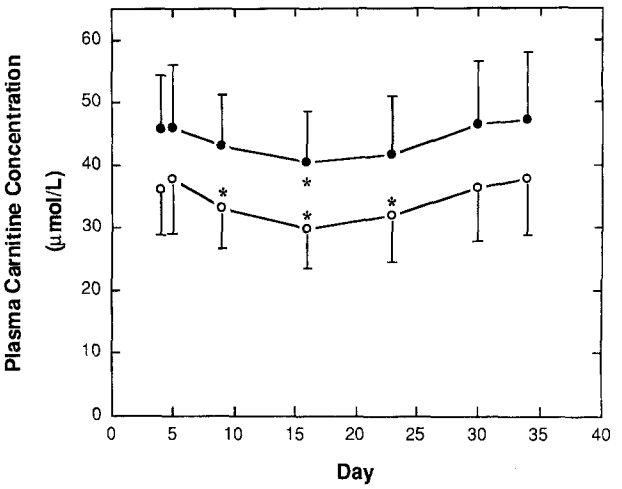

Fig 3. Mean plasma free (○) and total (●) carnitine concentration at baseline (days 4 and 5) and on days 9, 16, 23, 30, and 34. Values for days 5 and 34 were from the first (P_0) blood samples obtained during measurement of the glomerular filtration rate and solute clearance. *Significant difference *v* day 4 ($P < .05$). Vertical bars indicate the SD.

of plasma carnitine, data obtained before and after valproic acid administration were compared.

The rates of free carnitine excretion were significantly lower and rates of free carnitine reabsorption significantly higher after valproic acid administration (day 34) versus before (day 5) for plasma free carnitine concentrations between 40 and 85 μmol/L. Likewise, the rates of total carnitine excretion were significantly lower and rates of total carnitine reabsorption significantly higher after valproic acid administration versus baseline for plasma total carnitine concentrations between 50 and 95 μmol/L. Pairs of data for plasma free carnitine concentrations of 30 and 35 μmol/L and total carnitine concentrations of 35, 40, and 45 μmol/L were obtained, but the number of observations (three or less) was not sufficient to demonstrate statistically

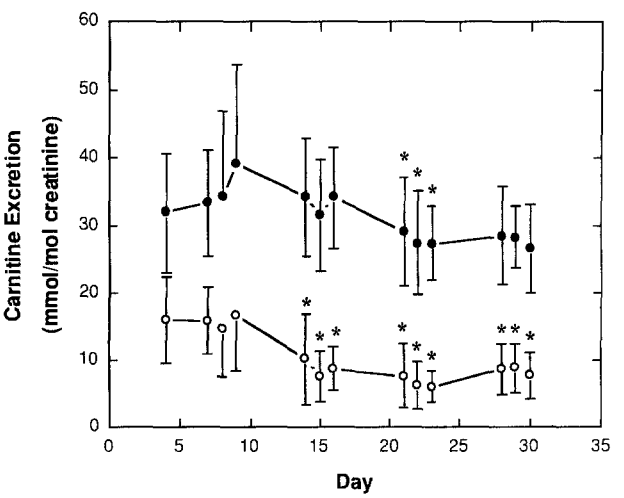

Fig 4. Mean rate of free (○) and total (●) carnitine excretion at baseline (day 4 and throughout the course of valproic acid administration. *Significant difference *v* day 4 ($P < .05$). Vertical bars indicate the SD.

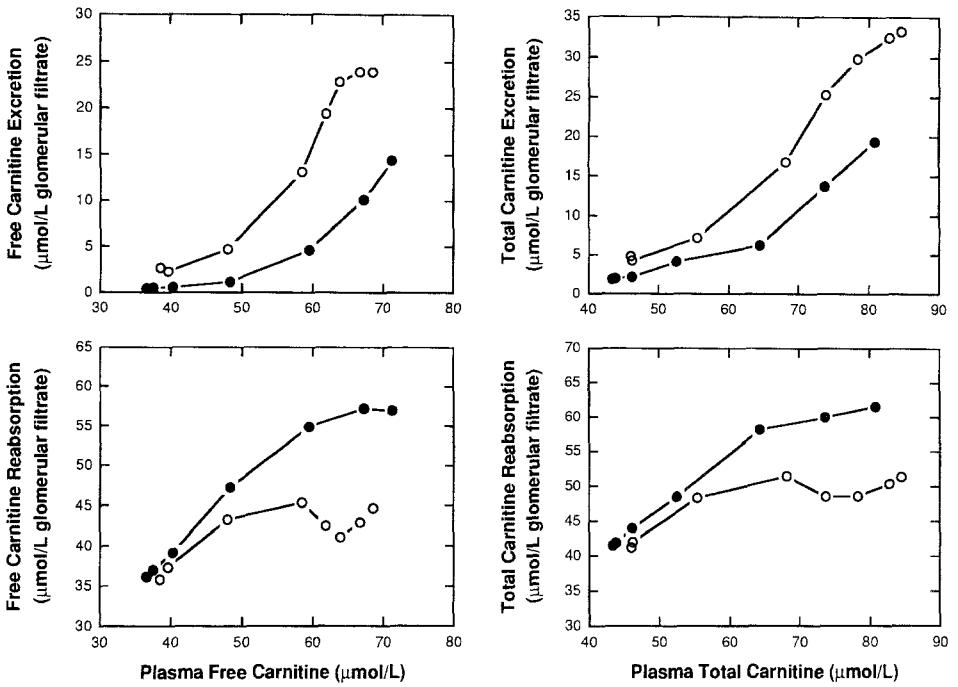

Fig 5. Free and total carnitine excretion and reabsorption (indexed to the glomerular filtration rate) before (○) and after (●) valproic acid administration. Data are for subject no. 10.

significant differences. For all other comparisons, the number of paired observations was three to 12.

Unlike carnitine, at no time during valproic acid administration was the plasma concentration of any measured amino acid significantly lower than at baseline. Plasma concentrations of methionine, glycine, proline, hydroxyproline, tyrosine, taurine, alanine, and valine were increased. Like carnitine, the rates of glutamine, hydroxyproline, tryptophan, and tyrosine excretion in urine were significantly decreased at least on some occasions during the course of valproic acid administration. But the rates for six other α-amino acids and taurine were unchanged or higher versus baseline during the treatment period. Also like carnitine, the urinary clearance of glutamine was reduced (by 71%) following valproic acid administration. But the urinary clearance of eight other α-amino acids and taurine was unchanged, and glycine clearance was increased (by 80%).

DISCUSSION

The etiology of valproic acid–induced carnitine deficiency is unknown. In healthy individuals, valproic acid administration may affect carnitine homeostasis by altering the absorption of carnitine from dietary sources, decreasing the rate of endogenous synthesis of carnitine, or decreasing the efficiency of reabsorption of carnitine. In individuals with chronic disease or compromised health status, the effect of valproic acid therapy on carnitine homeostasis may be exacerbated by underlying metabolic disease, insufficient intake of carnitine, drug-nutrient interactions, and simultaneous use of more than one medication (polypharmacy). To better understand the relationship between valproic acid therapy and carnitine homeostasis, we tested the hypothesis that long-term valproic acid administration decreases the rate of carnitine reabsorption independent of the glomerular filtration rate and filtered load.

Experimental evidence to support our hypothesis is found in several reports. Children treated with valproic acid were

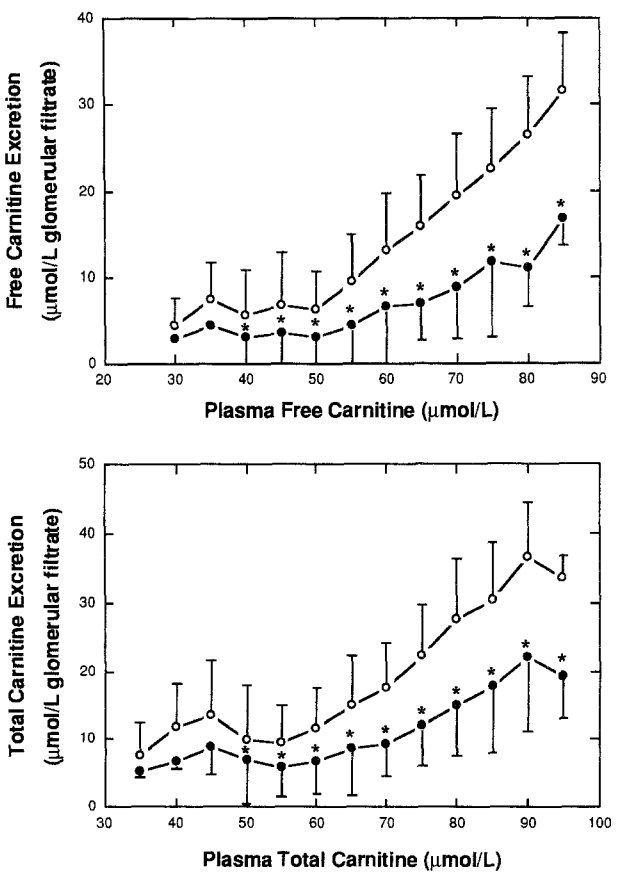

Fig 6. Mean free and total carnitine excretion. Data for each subject, as shown in Fig 5, were interpolated to provide the mean rate of carnitine excretion at 5-μmol/L intervals of the plasma carnitine concentration. *Significant difference before (○) and after (●) valproic acid administration at the indicated plasma carnitine concentration ($P < .05$). Vertical lines indicate the SD.

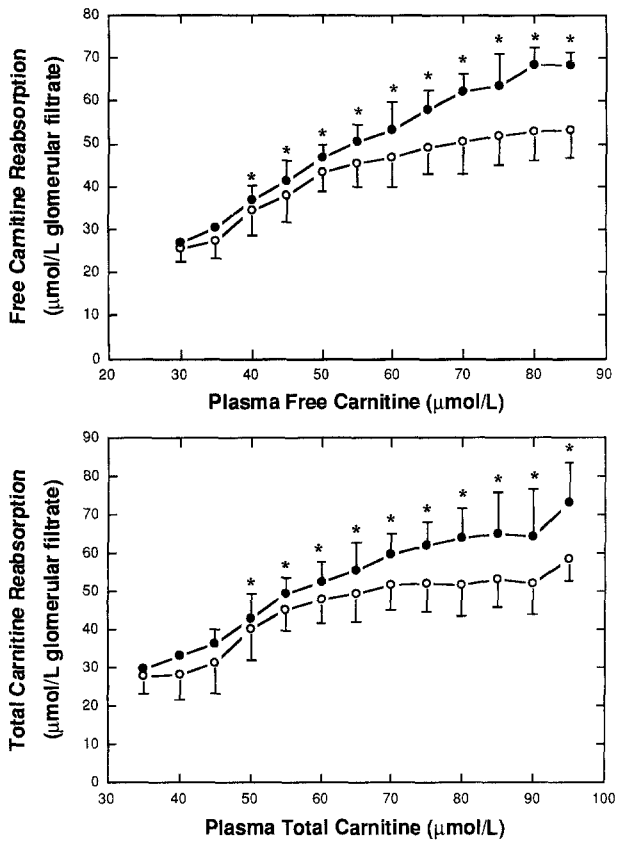

Fig 7. Mean free and total carnitine reabsorption. Data for each subject, as shown in Fig 5, were interpolated to provide the mean rate of carnitine reabsorption at 5-μmol/L intervals of the plasma carnitine concentration. *Significant difference before (○) and after (●) valproic acid administration at the indicated plasma carnitine concentration ($P < .05$). Vertical lines indicate the SD.

carnitine-deficient (mean concentration of free carnitine in plasma, 19.4 ± 4.6 nmol/L) and excreted eight times the amount of free carnitine and four times the amount of acylcarnitine esters compared with untreated healthy controls.[16] The investigators speculated that a higher concentration of acylcarnitine esters in the glomerular filtrate decreases the efficiency of free carnitine reabsorption and contributes to valproic acid–induced carnitine deficiency. In another study, valproylcarnitine was identified as a novel urinary metabolite among the spectrum of acylcarnitine esters excreted by patients on valproic acid therapy.[17] Although acylcarnitine ester excretion was two to five times greater among patients treated with valproic acid versus untreated controls, valproylcarnitine comprised less than 10% of the acylcarnitine esters excreted, and therefore could not account in full for the development of carnitine deficiency. These studies suggest that valproic acid–induced carnitine deficiency may be due, in part, to a decreased efficiency of carnitine reabsorption leading to an increased renal loss of free carnitine and acylcarnitine esters.

In the present study, we assessed the effect of long-term valproic acid administration on the efficiency of carnitine reabsorption in healthy men, thus eliminating the confounding effects of underlying disease, compromised health status, inadequate carnitine intake, and polypharmacy present in previous studies. The maximal dose of valproic acid (101 ± 2.91 μmol/kg/d), which is at the low end of the standard treatment range, was administered for 22 days following a gradual 6-day titration to this dose. Valproic acid administration did not affect the glomerular filtration rate, which, if altered, could significantly affect the rate of carnitine excretion. Plasma free and total carnitine concentrations decreased initially but returned to baseline by days 30 and 23, respectively, despite continued valproic acid administration. Our findings confirm a previous report in which no differences in plasma total, free, or acylcarnitine ester concentrations were observed before and after 1 month of valproic acid therapy.[18] However, in two other studies with a longitudinal design, lower plasma free and total carnitine concentrations were observed after initiating valproic acid therapy.[19,20] Case studies and case-control studies have repeatedly described decreased plasma carnitine concentrations among patients treated with valproic acid.[3,4,16,21-26] In all but one of these reports, the patients were children with underlying metabolic disease or compromised health status (severe malnutrition) or who required more than one medication for seizure control. These confounding factors were not accounted for in the study designs.

We noted that changes in plasma carnitine concentrations were followed, with a 1-week delay, by parallel changes in the rate of free and total carnitine excretion. Free carnitine excretion was lower than baseline levels from day 14 to the end of the study. Total carnitine excretion was lower than baseline levels on days 21 through 23 only. These results are considerably different from those of the prior studies already mentioned that described increased carnitine excretion during valproic acid therapy.

The return of plasma free and total carnitine to baseline concentrations may occur as a result of an internal signal that ultimately increases intestinal absorption of carnitine, stimulates endogenous synthesis of carnitine, releases carnitine from internal stores (muscle), increases the efficiency of carnitine reabsorption, or any combination thereof. Our findings suggest that an increased efficiency of carnitine reabsorption leads to a decreased rate of carnitine excretion and accounts, at least in part, for the rebound of plasma carnitine to baseline concentrations.

The results of this study do not support the hypothesis that valproic acid administration decreases the rate of carnitine reabsorption. Rather, the data show that in normal adults, the body adapts to conserve carnitine during valproic acid administration via increased efficiency of carnitine reabsorption. We conclude that the effects of valproic acid administration on renal carnitine metabolism were specific to carnitine, and were not generalized for solutes that are normally highly conserved. Thus, carnitine depletion or carnitine deficiency observed clinically with valproic acid treatment may be attributed to other mechanisms. These could include direct effects of valproic acid administration on carnitine biosynthesis or absorption or confounding effects of other factors (eg, polypharmacy, underlying chronic disease, or otherwise compromised health status) on any of these processes, including reabsorption of carnitine.

Interpretation of the results of this study must be made with the following precaution. Whereas in normal adults, the kidney adapts to valproic acid administration to restore normal carnitine homeostasis by increasing the efficiency of carnitine reabsorption, long-term administration of higher doses of valproic acid than used in this study might have a sufficiently greater impact on carnitine homeostasis such that the kidneys could not fully compensate, leading to a chronic state of carnitine depletion. Moreover, in children, the population most at risk for the hepatotoxic effects of valproic acid, the ability of the kidney to increase the efficiency of carnitine reabsorption may not be as great as in adults. Although there is currently no experimental evidence to support this hypothesis, it nevertheless cannot be excluded at this time.

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