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CARNITINE METABOLISM AND FUNCTION IN HUMANS

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INTRODUCTION

L-Carnitine [β-hydroxy-(γ-*N*-trimethylammonio)-butyrate] is a natural constituent of higher organisms and, in particular, cells of animal origin. Research on carnitine function and metabolism in humans has increased dramatically in the last 15 years, owing primarily to two important observations: Broquist and colleagues (71, 152) discovered that carnitine is ultimately derived from lysine, a limiting amino acid in diets of many third-world populations; and Engel and coworkers (43, 75) described human carnitine deficiency syndromes of apparent genetic origin. These observations provided impetus for extensive investigation into biosynthesis, metabolism, and functions of carnitine. These studies in turn led to identification of carnitine deficiency associated with a variety of genetic and acquired diseases and conditions, and to possible therapeutic uses of carnitine in human health and disease.

This review discusses recent research on carnitine metabolism and function in humans. Where appropriate, studies of experimental animals are described to provide clarification or substantiation of results obtained in human studies. This review is not intended to be exhaustive; the reader is directed to several recent reviews that discuss areas not covered here, or that provide greater detail (19, 22, 44, 57, 123, 147).

FUNCTION

The role of carnitine in transport of long-chain fatty acids into the mitochondrial matrix has been well established in experimental animals for many years (see 22 for review). The work of Engel & Angelini (43), utilizing isolated mitochondria from a patient with muscle carnitine deficiency, verified that carnitine was necessary for transport of long-chain fatty acids into human mitochondria. Long et al (87) examined the relationship between concentration of carnitine and oxidation of oleate in homogenates prepared from human skeletal muscle, as well as from rat liver, kidney, and heart, and from rat and dog skeletal muscle. Carnitine content of these tissues varied widely, as did the carnitine concentration required for half-maximal rate of fatty acid oxidation in vitro. However, they concluded that for any given tissue the normal carnitine content was set at a level necessary for optimal rate of long-chain fatty acid oxidation.

Carnitine also participates in modulation of the intramitochondrial acyl-coenzyme A/coenzyme A ratio (13). Several mitochondrial pathways produce coenzyme A esters of short- and medium-chain organic acids. Under normal conditions these esters are further metabolized to regenerate free coenzyme A. Under conditions of stress, when one or more of these metabolic pathways produces large amounts of these esters, the organic acid may be transesterified

to carnitine, freeing reduced coenzyme A to participate in other mitochondrial pathways, e.g. the tricarboxylic acid cycle. Under normal conditions the role of carnitine as a mitochondrial buffer for excess organic acids probably is minor. However, under abnormal conditions, such as diabetes, anoxia, or a defect of mitochondrial β-oxidation, this role may have major importance in maintaining mitochondrial function and viability of the cell. This process is discussed subsequently with regard to renal handling of carnitine, disorders of carnitine metabolism, and cardiac function.

BIOSYNTHESIS AND METABOLISM IN THE NORMAL ADULT

Biosynthesis

The pathway of carnitine biosynthesis has been studied most extensively in the rat. Virtually all available evidence indicates that the enzymatic pathways in rats and in humans are identical. The ultimate precursors of carnitine are lysine and methionine (115). S-Adenosylmethionine provides the methyl groups for enzymatic trimethylation of peptide-linked lysine (115, 116). Numerous proteins contain ε-*N*-trimethyllysine residues, including histones, cytochrome c, myosin and calmodulin (see 106 for a review). Attempts to demonstrate methylation of free lysine in human tissues or tissues of other mammalian species have been unsuccessful to date, and it is generally believed that this pathway does not exist in mammals. One caveat to this assumption follows from the study by Khan-Siddiqui & Bamji (78), in which they showed a significant rise in plasma carnitine concentration in human adults within six hours after oral administration of a bolus dose of lysine. The authors interpreted this result to indicate methylation of free lysine, because the process of protein synthesis, methylation of peptide-linked lysine residues, and turnover of these proteins would not be rapid enough to account for the observed rise in plasma carnitine.

ε-*N*-Trimethyllysine residues are released for carnitine biosynthesis by protein turnover (41, 80). ε-*N*-Trimethyllysine undergoes the following series of transformations: ε-*N*-trimethyllysine → β-hydroxy-ε-*N*-trimethyllysine → γ-trimethylaminobutyraldehyde → γ-butyrobetaine → L-carnitine. Regulation of this process in humans has not been studied. Henderson et al (68) have reviewed the enzymology of the pathway. The role of ascorbic acid in ε-*N*-trimethyllysine and γ-butyrobetaine hydroxylation is reviewed in this volume (47).

Enzymes for conversion of ε-*N*-trimethyllysine to γ-butyrobetaine were found in all human tissues studied (skeletal muscle, heart, liver, kidney, and brain) (120). However, γ-butyrobetaine hydroxylase activity was present in human liver, kidney, and brain, but not in skeletal muscle or heart.

Although all tissues studied contain ε-*N*-trimethyllysine hydroxylase activity, it is not known whether ε-*N*-trimethyllysine produced within a tissue is totally or partially metabolized within that tissue or whether it is released into the circulation for metabolism by other tissues. Normal circulating levels of ε-*N*-trimethyllysine are 0.3–0.5 μM (82). Renal clearance of this amino acid is similar to that of creatinine (82), i.e. it is poorly or not at all reabsorbed. Urinary output of ε-*N*-trimethyllysine in humans was estimated to be 30–92 μMol/g creatinine (73, 82, 88).

Exogenous ε-*N*-trimethyllysine administered intravenously is in large part (66–84%) excreted unchanged in urine within 48 hours of administration (121). Circulating ε-*N*-trimethyllysine destined for carnitine biosynthesis is primarily taken up by the kidney, where it is converted mostly to carnitine, although some γ-butyrobetaine is released for hydroxylation in other tissues (119).

Hydroxylation of γ-butyrobetaine has been the most intensely studied reaction of the pathway in humans. Lindstedt and coworkers (85) showed that the kinetic properties of human renal γ-butyrobetaine hydroxylase are similar to those of the enzyme in other species. Further, they identified multiple isoenzymes of γ-butyrobetaine hydroxylase in human kidney and liver (86). The enzyme was present in three forms, which are separable by chromatofocusing (isoelectric points of 5.6, 5.7, and 5.8). The specific activities of each form were identical, as were their molecular weights (64 kDaltons) and cofactor requirements. The three isoenzymes appeared to be dimeric combinations of two subunits differing in charge but not size, as isoenzyme 2 (isoelectric point = 5.7) was resolved into two protein bands by isoelectric focusing in polyacrylamide gels containing urea. Isoenzyme 1 contained only one of these bands and isoenzyme 3 the other.

Human liver γ-butyrobetaine hydroxylase is developmentally regulated. Enzyme activity in three infants was approximately 12% and in a 2.5-year-old boy 30% of the adult mean (120). By 15 years of age, hepatic enzyme activity was within the range of adult values. No data are currently available on the relative rates of renal γ-butyrobetaine hydroxylase in infants, children, and adults.

Carnitine is not considered to be an essential nutrient in the diet of adult humans, primarily because some human tissues are able to synthesize this amino acid. However, surprisingly little evidence is available to indicate that humans can synthesize sufficient quantities of carnitine to meet requirements. Studies from India (77) and Thailand (153) have shown that individuals consuming cereal-based diets very low in carnitine maintained plasma carnitine concentrations at or near levels typical of adults in Western nations, where carnitine is abundant in most diets. Adult surgical patients supported by carnitine-free total parenteral nutrition maintained normal plasma carnitine levels for twenty days, but subsequently a gradual decline of plasma carnitine

concentration was observed (65). Although normal plasma carnitine levels are maintained in the human adult in the absence (or virtual absence) of dietary carnitine, the adequacy of plasma carnitine concentration as an indicator of carnitine status in humans has not been demonstrated. Thus, further investigation into the ability of endogenous carnitine biosynthesis to maintain body stores of carnitine in the absence of dietary sources of this amino acid is desirable. This question is particularly relevant for infants and children, in whom growth places extra demand for carnitine to supply newly synthesized tissue.

Absorption

L-Carnitine is found in a variety of food sources; however, foods of animal origin are much more abundant in this amino acid than plant-derived foods (125). Red meats and dairy products are particularly rich sources of carnitine.

Absorption of carnitine from dietary sources has not been studied directly. Hamilton et al (67) studied carnitine transport across the human proximal small intestinal mucosa in vitro. They concluded that movement across this membrane was via an active process that depended on Na^+ cotransport. K_T for the process was 974 μM and V_{max} was 27.4 nmol/ml intracellular water/min. A passive, diffusional process was also identified, which may be important for absorption of large doses of carnitine. These results are similar to those reported by Gross & Henderson (61) and Gudjonsson et al (62), using live rats and isolated vascularly perfused intestine. These studies demonstrated relatively rapid transport of carnitine into intestinal mucosa from the lumen, acetylation of up to 50% of the carnitine accumulated in the tissue, and slower release of the free and acetylcarnitine into the circulation.

L-Carnitine in amounts normally found in the human diet was thought to be virtually totally absorbed. The basis for this assumption was the very small amount of carnitine normally found in human feces, i.e. less than 1% of that excreted in urine (125). Studies in humans (125) as well as in dogs (124) and rats (24, 31) have suggested that a small but significant amount of dietary carnitine is degraded in the gastrointestinal tract. Conclusive demonstration of the role of indigenous flora of the rat gastrointestinal tract in this process was recently reported (129), but similar studies in humans have not been described.

Tissue Accretion and Turnover

Plasma total carnitine levels in normal adults 2–85 years old ranged from 30 to 89 μM (123). Mean values in males tended to be higher than in females: 59.3 ± 11.9 μM for males versus 51.5 ± 11.6 μM for females (mean ± S.D.; $N = 40$ for males, $N = 45$ for females). Skeletal muscle contains over 90% of total body carnitine in humans. Carnitine levels in skeletal muscle of normal humans ranged from 11 to 52 nmol/mg noncollagen protein (mean ± S.D.; 20.5 ± 8.4

for males, 20.1 ± 5.3 for females) (123). Thus the concentration of carnitine in skeletal muscle is approximately 70 times higher than in plasma. Similar but less steep carnitine concentration gradients are present between other tissues and extracellular fluid.

The steady-state rate of entry of carnitine into human muscle and heart, calculated by kinetic analysis, was 11.6 nmol/h/g tissue (125). This value is consistent with rates determined experimentally in isolated rat tissues (114, 159), and by kinetic analysis in dogs (124). Carnitine concentration in muscle is reduced by exercise, and the distribution of free and esterified carnitine is shifted toward increased esterification (83). Normal regulatory processes that maintain tissue carnitine gradients have not been identified, although hormonal interactions may be important (see the section on renal handling).

Using the technique of kinetic compartmental analysis, Rebouche & Engel (125) estimated turnover times for tissues, extracellular fluid, and whole-body carnitine. Turnover time for carnitine in skeletal muscle and heart was approximately 8 days, and for other tissues (thought to be primarily liver and kidney), 11.6 hours. Turnover time for carnitine in extracellular fluid was 1.13 hours and for the whole body, 66 days.

Renal Handling

Carnitine is highly conserved in humans. At normal physiological concentrations in plasma, more than 90% of filtered carnitine is reabsorbed by the kidney (128). Several parameters have been used to describe the efficiency of the reabsorption process in humans (46, 126). In nine subjects ages 13 to 37, tubular maximum for carnitine reabsorption was 7.4 ± 0.44 μmol/dl glomerular filtrate (mean ± S.D.; range, 5.5–7.8 μmol/dl glomerular filtrate). Fractional reabsorption for a plasma total carnitine concentration of 65 μM was 90 ± 3.9% (mean ± S.D.; range, 84–95%). Even at very low plasma carnitine concentrations seen in some premature infants (see below) or patients with systemic carnitine deficiency, small amounts of carnitine are excreted in the urine. Thus a true renal plasma threshold for carnitine excretion cannot be determined. However, Engel et al (46) calculated an "apparent" renal plasma threshold for carnitine excretion. This value was estimated by plotting observed carnitine excretion versus plasma carnitine concentration and then extrapolating the curve to the abscissa for subjects infused over 3 hours with L-carnitine (0.25 μmol/min/kg body weight) (see Fig. 1 of Ref. 46). In six normal humans the apparent renal plasma threshold for carnitine excretion was 51 ± 7.4 μM (mean ± S.D.; range 45–59 μM) (46). In most individual subjects these values closely paralleled the plasma carnitine concentration (mean ± S.D., 53 ± 5.3 μM; range 46–59 μM). These results suggest that under normal conditions, plasma carnitine concentration is regulated, at least in part, by the kinetics of carnitine reabsorption by the kidney.

L-Carnitine formed intracellularly in the kidney may be partially secreted into

the tubular lumen, either in free form (119) or as short-chain acylcarnitine esters (46). The significance of renal secretion of carnitine and carnitine esters is unclear. However, several investigators (32, 40, 148) have suggested that excretion of carnitine esters may be a mechanism for removing excess short- or medium-chain organic acids, particularly as they occur in excessive amounts in genetic diseases such as propionic acidemia and methylmalonic acidemia (see the section on disorders of carnitine metabolism). In this regard, it is noteworthy that the zenobiotic compound pivalic acid (2,2-dimethyl propionic acid), when administered orally as pivaloyl-1'-oxyethyl-(S)-3-(3,4-dihydroxyphenyl)-2-methylalaninate, was excreted almost entirely as pivaloylcarnitine in humans, but as the glucuronate conjugate in other species (160). Moreover, valproylcarnitine was identified in urine from two children undergoing chronic valproic acid therapy (94). Bieber & Kerner (14) demonstrated the presence of Δ6-octenoylcarnitine, Δ6-2-methyloctenoylcarnitine and 2-methyloctanoylcarnitine in human urine. The authors suggested that the acyl moieties were ingested from dietary dairy products and not synthesized de novo in humans. To date it is not known if these organic acids are conjugated with carnitine in the kidney or elsewhere in the body.

Several factors have been identified that affect carnitine excretion in human subjects, including serum thyroxine concentration (89). Hyperthyroidism markedly increased urinary carnitine excretion whereas hypothyroidism depressed urinary loss of carnitine. Because plasma carnitine levels were not reported in the study cited, it is not known if thyroxine induced release of carnitine from tissues, raising the plasma carnitine concentration, or if this hormone lowered the apparent plasma threshold for carnitine excretion. In another study (90) administration of β^{1-24}ACTH-Z to healthy subjects resulted in a six-fold increase in urinary carnitine excretion, and this increase was paralleled by a rise in plasma carnitine concentration.

Fasting for 36 hours in normal subjects decreased renal clearance of free carnitine but increased clearance of acylcarnitine esters (54). Total carnitine excretion was increased. Fasting decreased serum free carnitine (54, 70) but increased serum acylcarnitine ester and total carnitine concentrations (70). Urinary excretion of acylcarnitine esters increased parallel to rising plasma carnitine concentration (70). Ketoacidotic diabetics showed a similar increase in plasma acylcarnitine esters (55). This rise, both in fasting subjects and in diabetic ketoacidosis, was postulated to result from insulin deficiency (56).

THE ROLE OF CARNITINE IN PERINATAL ENERGY METABOLISM

Glucose is the major metabolic fuel for the fetus (162). At parturition the infant must adapt to lipid as a major source of calories. Immediately at birth rapid elevation of blood free fatty acid and β-hydroxybutyrate levels occurs due to

release of free fatty acids from adipose tissue (102). Later, high levels of free fatty acids in blood reflect intestinal absorption of fatty acids and triglycerides supplied by the diet (102). Human milk and many formula diets contain more than 40% of total calories as lipid. Fatty acids derived from these sources become the preferred fuel for heart and skeletal muscle (166). Thus, carnitine becomes an important cofactor for energy production in the neonate.

Human milk contains 28–95 nmol of total carnitine per ml (131, 162). Most milk-based formulas contain comparable or slightly higher levels of carnitine (20). However, formulas manufactured from soybean protein or casein and casein hydrolysate contain little or no carnitine (20, 162)[1]. Infants fed soy protein–based formula diets develop lower plasma carnitine concentrations than breast-fed infants or infants fed milk-based formula diets (102). Novak et al (99) studied a group of normal term infants, five of whom were fed an unsupplemented soy protein–based formula and seven of whom were fed the same formula, except supplemented with 50 μM of L-carnitine, from birth to five months. Plasma free carnitine was significantly increased at one, two, and three months of age, and plasma acylcarnitine esters were increased at two and three months in carnitine-supplemented infants. Plasma triglycerides at two and three months of age were significantly lower in infants given L-carnitine. Plasma free fatty acids were decreased significantly at three months of age in infants receiving L-carnitine. No difference in plasma β-hydroxybutyrate was found at one, two, or three months.

Clinical symptoms of carnitine deficiency in infants fed soy protein–based formulas are rare. However, subclinical consequences of mild to moderate carnitine deficiency, particularly relating to growth and development of the child, are unknown. The study by Novak et al (99) suggests differences in lipid metabolism in infants fed soy protein–based formulas with or without supplemental carnitine, but whether these differences have any short- or long-term clinical significance is at present a matter for speculation.

Plasma carnitine levels in preterm infants (less than 36 weeks gestational age) at birth are borderline normal or lower than normal (mean ± S.E., 29.0 ± 1.8 μM; $N = 53$; Ref. 139) with respect to levels in children and adults. These levels are maintained or increased by enteral feeding of milk-based formulas or human milk (110, 133). However, upon initiation of intravenous feeding with parenteral nutrition solutions (which to date are not routinely supplemented with carnitine), carnitine levels in blood fall to as low as 13 μM (110, 133). Further, Penn et al (109) reported that acid-soluble carnitine levels in heart and liver, but not in skeletal muscle, were significantly lower in premature infants fed intravenously for more than 15 days compared to premature or term infants

[1]At this writing, soy protein–based formula supplemented with L-carnitine is available from at least one commercial manufacturer.

fed intravenously for fewer than 36 hours. In a separate study, Shenai & Borum (138) demonstrated a positive correlation between gestational age and muscle carnitine concentration. Some infants of less than 30 weeks gestation had muscle carnitine levels considered borderline or deficient by criteria used to diagnose systemic carnitine deficiency (123).

Because exogenous carnitine is not provided by parenteral feeding solutions, it is reasonable to assume that, in the absence of excessive urinary carnitine excretion, the reduced carnitine levels result from the inability of endogenous biosynthesis to proceed at a rate sufficient to maintain "normal" concentrations in plasma and some tissues. Several investigators (64, 100, 138) have suggested that low (relative to adult levels) hepatic γ-butyrobetaine hydroxylase activity limits the rate of carnitine biosynthesis in infants. Rebouche & Lehman (127) demonstrated that carnitine biosynthesis in growing rats could be stimulated 100-fold by dietary ε-*N*-trimethyllysine. In another study Rebouche (117) showed that in growing rats urinary output of carnitine was increased 65-fold (with concomitant increases in tissue carnitine levels) by addition of γ-butyrobetaine to a carnitine-free diet (as 0.1% of diet). Thus, because levels of hepatic γ-butyrobetaine hydroxylase activity in the rat and human are comparable, it is unlikely that even with a 10-fold reduction in activity of this enzyme (as occurs in human infants relative to adults) would the rate of this reaction be limiting for carnitine biosynthesis.

The question arises: Do reduced plasma and tissue carnitine levels in these infants hinder the utilization of lipid for energy production? It is well known that premature infants can tolerate only limited amounts of parenterally infused triglyceride (140). Infusion of the commercial lipid emulsion Intralipid® is generally considered safe at a rate of 150 mg/kg body weight/h or less. Lipid supplementation of parenteral feedings at 150 mg/kg body weight/h is considered adequate for lipid-derived caloric needs of the infant. However, it is not known if increased caloric intake, if tolerated, would improve growth performance and rate of development in parenterally fed premature infants.

To determine if low plasma and tissue levels of carnitine impair lipid utilization by premature infants, several investigators (104, 105, 134, 135, 165) have employed a lipid tolerance test (infusion of Intralipid at 1 g/kg body weight over 4–8 hours) with or without carnitine supplementation. Some studies were initiated shortly after birth (presumably before carnitine stores were depleted) or after 7 or more days of parenteral alimentation. In some studies normal feeding was continued during the course of the study, in others the infants received only the lipid emulsion. Various parameters were measured, including plasma free, acyl, and total carnitine; plasma free fatty acids, triglycerides, β-hydroxybutyrate, acetoacetate, and glycerol; and the plasma free fatty acid/β-hydroxybutyrate ratio.

Results of studies by Orzali et al (104, 105) suggest that glucose is the

preferred substrate for energy production in the premature infant. Lipid is utilized only to the extent that glucose cannot meet the caloric needs of the individual. Under certain conditions, the effect of exogenous carnitine on the metabolism of bolus doses of triglycerides appeared to be an increase in the rate of oxidation of fatty acids either derived from the lipid infusion itself or from mobilization of adipose tissue (104, 135). In this regard, Novak et al (101) showed that carnitine enhances glycerol release from newborn subcutaneous adipose tissue in vitro. The positive correlation between plasma β-hydroxybutyrate and plasma total carnitine (134) suggests a carnitine-related enhancement of mitochondrial fatty acid oxidation.

Although some of these short-term studies with relatively high doses of lipid indicate a positive relationship between lipid utilization and carnitine concentration in plasma, they do not foretell the adequacy or extent of lipid utilization to provide energy for the parenterally alimented premature infant in a normal clinical setting. A recent study by Curran et al (38) bears directly on this issue. Premature, parenterally alimented infants of birth-weight between 800 and 1500 g (appropriate for gestational age) were divided into four groups: (*a*) infants given fat-free nutrition with carnitine (13 μmol/kg/day) or (*b*) without carnitine, and (*c*) infants given intravenous nutrition including Intralipid 20% (maximum 3 g/kg/day) with carnitine or (*d*) without carnitine. Amino acids and glucose were provided at 2.5 and 15 g/kg/day, respectively. Infants were maintained on this regimen for at least 5 days. The authors found no statistically significant differences in levels of plasma β-hydroxybutyrate (no evidence of increased ketogenesis) in any of the groups. There was a significant increase in free fatty acids in group (*c*) compared to group (*a*) after 12 days of the study, but no significant decrease in plasma free fatty acids when carnitine was provided to infants receiving Intralipid. Significant hypertriglyceridemia was not observed in infants receiving Intralipid. This study provides no evidence that carnitine supplementation alters the substrate preference for energy production in premature infants receiving total parenteral nutrition in a normal clinical situation. However, the parameters used in this study to detect alterations in substrate utilization are not unequivocal. Thus further study of this question is warranted.

DISORDERS OF CARNITINE METABOLISM

Primary Genetic Carnitine Deficiency

Primary carnitine deficiency syndromes are classified into two types, systemic and myopathic (123). The clinical features of these syndromes have been reviewed (123). Primary muscle carnitine deficiency, which has as its major clinical features mild to severe muscle weakness and variable excess of lipids in skeletal muscle fibers, was thought to arise from defective transport of carnitine

into muscle (43). Direct evidence for this hypothesis has not been reported. However, Rebouche & Engel (125) showed, by kinetic compartmental analysis, that the rate of uptake of L-carnitine by a compartment identified as skeletal muscle was in one patient 43% of the mean of six normal subjects, and 40% lower than the lowest control. These results support the above hypothesis, but kinetic studies of this type and/or more direct measurements of carnitine transport in additional patients are required to substantiate the conclusion that carnitine transport is impaired in primary muscle carnitine deficiency.

Primary systemic carnitine deficiency is often associated with multiple episodes of metabolic encephalopathy, hypoglycemia, hypoprothrombinemia, hyperammonemia, and lipid excess in hepatocytes during acute attacks (123). In these respects it resembles Reye's syndrome. Theoretically, primary systemic carnitine deficiency could arise from one or more of the following: (*a*) a defect in carnitine biosynthesis; (*b*) abnormal renal handling of carnitine; (*c*) alterations in cellular mechanisms for carnitine transport, affecting uptake and/or release of carnitine from tissues; (*d*) excessive degradation of carnitine; or (*e*) defective intestinal absorption of carnitine (123).

No evidence for a defect in carnitine biosynthesis was found in three patients with primary systemic carnitine deficiency (118, 121). Indirect evidence from balance studies indicated that defective absorption or excessive degradation of carnitine did not contribute to the pathogenesis of this syndrome in four patients studied (125). Efficiency of reabsorption of carnitine by the renal tubule was reduced in five cases of systemic carnitine deficiency (46, 161)[2]. For four of these subjects fractional reabsorption of total carnitine at a plasma carnitine concentration of 65 μM was 60 ± 2.9% (mean ± S.D.; range 57–64%) compared to 90 ± 3.9% (range 84–95%) for nine normal subjects (126). However, fractional reabsorption of carnitine for one control subject with normal skeletal muscle carnitine concentration and no clinical symptoms of carnitine deficiency was 43 and 59% in two separate measurements (46). Thus it was concluded that decreased efficiency of carnitine reabsorption in the patients studied could not entirely account for the clinical presentation of systemic carnitine deficiency, but this abnormality may have contributed to the pathogenesis of the syndrome.

Kinetic measurements of carnitine transport into cultured skeletal muscle cells and skin fibroblasts of patients with systemic carnitine deficiency did not differ from those of normal subjects (122). Kinetic compartmental analysis of carnitine metabolism revealed a reduced rate of carnitine transport into muscle in each of four subjects with systemic carnitine deficiency[2], but the decreased rate was directly attributed to the reduced plasma carnitine concentration in

[2]Three of these cases subsequently were shown to be associated with medium-chain acyl-CoA dehydrogenase deficiency in skin fibroblasts or leukocytes (36).

these individuals (125). In the same study, markedly variable day-to-day plasma carnitine concentrations in these four subjects were reported. Mean coefficient of variation for consecutive daily measurements over 27–28 days was 0.35 (range 0.29–0.42) compared to 0.09 (range 0.05–0.11) for six normal subjects. These fluctuations suggested an abnormality in regulation of the muscle/plasma carnitine concentration gradient. To date, factors that regulate the flow of carnitine into and out of muscle have not been clearly defined.

Clinically, systemic carnitine deficiency is a heterogeneous syndrome. For example, age of onset (or recognition) has varied considerably. Some patients present with cardiomyopathy (see discussion below) whereas others do not (123). The response to treatment with supplemental carnitine has been variable (123). These observations suggest that heterogeneity in the etiology of different cases of this syndrome may also exist.

Two cases of clinically diagnosed dietary-dependent carnitine deficiency have been reported (48, 143). One child developed systemic carnitine deficiency after switching from a milk-based formula diet to a soy protein–based formula (143). Classical symptoms were observed: recurrent episodes of hypoglycemia and liver dysfunction, with very low plasma and urine carnitine levels. The child also developed marked dicarboxylic aciduria. After returning to a carnitine-enriched diet (beef and beef broth and milk-based formula) carnitine levels in plasma and urine increased, dicarboxylic aciduria subsided, and clinical evidence of systemic carnitine deficiency was absent. A similar case of diet-induced carnitine deficiency was reported in a 12-year-old child on a strict vegetarian diet (48). Supplementation of the child's diet with carnitine restored plasma carnitine levels to normal, improved muscle strength, and prevented further attacks of metabolic encephalopathy. The dramatic response of these patients to dietary carnitine suggests a possible error in carnitine biosynthesis. To date, no genetic defect in this process has been demonstrated.

Deficiency Syndromes Secondary to Other Genetic or Acquired Disorders

Carnitine deficiency has also been recognized secondary to a variety of genetic defects of intermediary metabolism or other disorders and conditions (for reviews, see 45, 123).

ORGANIC ACIDURIA Of this heterogeneous group of disorders and conditions, the organic acidurias are of particular interest, because they suggest a new physiological role for carnitine in intermediary metabolism. Carnitine deficiency has been recognized in long- (66) and medium-chain acyl-CoA dehydrogenase deficiency (36, 145), isovaleric acidemia, glutaric aciduria, propionic and methylmalonic acidemia (32), and short-chain acyl-CoA dehydrogenase deficiency (157). Chalmers et al (32) have shown that total

carnitine excretion in 23 of 35 patients with various organic acidurias was higher than the range of controls (greater than 255 nmol/mg creatinine). For all patients studied except one, urinary acylcarnitine ester concentration was more than twice that of free carnitine (the mean ratio was 1.45 in normal subjects) and for 25 of 35 patients the ratio was greater than 10. Oral supplementation with L-carnitine in three of the patients led to even greater levels of acylcarnitine esters in urine.

The results suggested that carnitine was being utilized as a means of removing excess organic acids, and they support the hypothesis of Bieber et al (13) that carnitine acts as an intramitochondrial buffer to remove excess acyl moieties, allowing regeneration of free CoA to be used to maintain normal metabolic functions of the mitochondrion. Presumably excess acylcarnitine esters are released from cells and preferentially excreted (i.e. they are reabsorbed less efficiently than free carnitine). Alternatively, in some patients plasma acylcarnitine concentration is not abnormally high; therefore, increased urinary acylcarnitine esters may arise from renal carnitine metabolism via secretion or passive diffusion into the urinary tract. In normal individuals carnitine lost as acylcarnitine esters is readily replaced by endogenous carnitine synthesis and from dietary sources. However, loss of extraordinarily large amounts of acylcarnitine esters in genetic disorders characterized by organic aciduria may lead to the observed secondary carnitine deficiency.

RENAL DISEASE Carnitine deficiency has been described in Fanconi syndrome, a condition characterized by excessive excretion of numerous substances that normally are efficiently reabsorbed (11, 13). Mean fractional excretion of free carnitine was 33% and of acylcarnitine esters 26% in 21 subjects with Fanconi syndrome, compared to 3 and 5%, respectively, in normal individuals (11). Total free carnitine excretion in Fanconi syndrome patients correlated with total amino acid excretion ($r = 0.76$). Plasma free carnitine levels in 19 affected children were very low (11.7 ± 4.0 μM; mean ± S.D.) compared to normal values (42.0 ± 9.0 μM). Muscle free and total carnitine levels in two patients were marginally low and biopsies revealed, in one case, a mild increase in lipid droplets, and in the other case, evidence of myopathy. In one patient a five-hour fast resulted in a normal increase in plasma β-hydroxybutyrate, which suggested that hepatic fatty acid oxidation was intact.

Hypercarnitinemia has been demonstrated in uremia (35). However, in 1974 Bohmer et al (18) first demonstrated that hemodialysis therapy for this condition reduced serum carnitine by 25% of the value occurring before dialysis. Later, the same group (17) showed that intermittent hemodialysis caused a dramatic loss of carnitine from skeletal muscle and plasma into the dialysate fluid. A number of studies have confirmed these results and it is now well

established that chronic hemodialysis can induce muscle and possibly myocardial carnitine deficiency (15, 16, 108, 132). Usually plasma carnitine levels are restored within 8 hours after dialysis, presumably from increased hepatic synthesis (16, 108). This loss of carnitine has been related to the complications often accompanying intermittent hemodialysis, i.e. hyperlipidemia, cardiomyopathy, and skeletal muscle asthenia and cramps (post-dialysis syndrome). Treatment with oral carnitine has been shown to attenuate the loss of carnitine from plasma and skeletal muscle and improve some of the above symptoms (5, 7, 10, 12, 25, 28, 49, 50, 63, 79, 81, 151, 158).

Several studies have demonstrated a lipid-lowering effect of carnitine treatment in chronically uremic patients supported by maintenance hemodialysis. Administration of intravenous (12) or oral (28, 63, 81) DL-carnitine decreased mean serum triglyceride concentration and increased high-density lipoproteins (HDL). However, in some patients DL-carnitine evoked a myasthenia-like syndrome, with alterations in the electromyogram and decreased muscle action potentials (8). Administration of only the physiologically active L-isomer did not elicit this syndrome and was effective in reducing serum triglyceride and increasing HDL (7).

Three studies did not confirm the lipid-lowering effect of DL-carnitine (4, 33, 50), which suggests that some dialysis patients are not responsive to carnitine. This apparent discrepancy may be attributed to differences in the effective dose of carnitine required to produce a significant lipid-lowering effect. Vacha et al (158) demonstrated a lipid-lowering effect of carnitine (i.v. 20 mg/kg) in hemodialysis patients with hypertriglyceridemia and low HDL-cholesterol values; but in patients with hypertriglyceridemia and normal HDL-cholesterol levels a much higher dose of L-carnitine (60 mg/kg) was required to produce a significant lipid-lowering effect.

Only two studies have investigated the effects of carnitine supplementation on hemodialysis-induced muscle alterations (10, 50). In the study by Fagher et al (50), three patients on regular hemodialysis were supplemented with DL-carnitine (900 mg/day) for four weeks. Carnitine treatment was associated with improved heat production by skeletal muscle. Hepatic function was assessed using an intravenous galactose load test and was normalized by carnitine treatment. In a double-blind cross-over study, Bellinghieri et al (10) treated 14 uremic patients with L-carnitine (2 g/day) for 60 days and found a significant decrease in asthenia and cramps during and after dialysis. These improvements were associated with parallel increases in serum and muscle L-carnitine concentration. Except for one patient, alterations in muscle histology were not corrected with carnitine therapy.

Heart failure is a major cause of death in hemodialysis patients (25). Since myocardial carnitine deficiency has been associated with cardiomyopathy in other patients (123, 161), it is conceivable that the cardiomegaly in hemodialy-

sis patients may be due to loss of carnitine from the heart into the dialysate. The effects of dialysis on myocardial carnitine content have not been investigated extensively. Only one study on the peritoneally dialyzed uremic rat demonstrated a significant reduction of carnitine in the heart (5). Another study in patients showed an inverse correlation between plasma carnitine and cardiomyopathy as assessed by the cardiothoracic ratio (79). Carnitine treatment of dialysis patients has been shown to enhance cardiac performance as evaluated by echocardiography (50) and to reduce arrhythmias significantly (151). However, a more recent study demonstrated that, in 28 randomly selected hemodialysis patients, L-carnitine administration did not improve left ventricular function, as monitored by echocardiography, electrocardiogram, phonocardiogram, and carotid pulse tracing (49).

The effect of peritoneal dialysis on plasma and muscle carnitine content appears to be different from that of intermittent hemodialysis (95, 96). As discussed above, a number of studies have shown that hemodialysis will decrease both plasma and skeletal muscle carnitine levels. In contrast, Moorthy et al (95) found that in patients receiving long-term peritoneal dialysis (either intermittent or continuous ambulatory peritoneal dialysis) normal plasma and muscle carnitine levels were maintained despite significant loss of carnitine into the dialysate. It was suggested that hemodialysis causes a rapid lowering of plasma carnitine, which triggers the release of carnitine from muscle stores, but in patients on peritoneal dialysis a much slower loss of carnitine into the dialysis fluid occurs and plasma and muscle carnitine levels are maintained, primarily by increased hepatic synthesis and/or dietary ingestion of carnitine. These results were recently confirmed in another 27 patients by the same group (96).

However, Bartel et al (5, 6) and Buoncristiani et al (26) reported that, in uremic rats or human subjects subjected to peritoneal dialysis, serum and muscle carnitine content declined sharply. These conflicting findings may be partially related to differences in the volume of dialysis fluid used during peritoneal dialysis and whether the kidneys of the patient were removed, but this information was not provided in the studies cited. Further investigation into the effects of peritoneal dialysis versus intermittent hemodialysis and the efficacy of carnitine therapy for dialysis patients is needed.

THE ROLE OF CARNITINE IN OTHER ABNORMAL METABOLIC CONDITIONS

Myopathic Heart Disease

In normal heart muscle approximately 60% of total energy metabolism comes from oxidation of fatty acids (103). Carnitine plays an essential role in transporting long-chain fatty acids into mitochondria (22); therefore adequate levels are required for normal fatty acid and energy metabolism in heart muscle.

Carnitine may also be of metabolic importance because of its role in buffering fluctuations in mitochondrial acetyl-CoA levels. Through the enzyme carnitine acetyltransferase, carnitine can provide an alternative metabolic pathway for excess acetyl units generated via β-oxidation or glycolysis.

Carnitine acetyltransferase is found in relatively large amounts in cardiac tissue and facilitates formation of acetylcarnitine from acetyl-CoA and carnitine (13). The acetylcarnitine formed in the mitochondrial matrix can rapidly exchange with free or acylcarnitine across the mitochondrial inner membrane. By this mechanism excess acetyl units produced in the mitochondrial matrix may be stored in the cytosol as acetylcarnitine. Under conditions of increased energy demand, the cytosolic acetylcarnitine can be transferred rapidly back into the mitochondrial matrix, providing an additional and readily available source of acetyl units for the citric acid cycle. This function of acetylcarnitine may be of particular importance to the heart, because a single heart beat consumes more than the intramitochondrial acetyl-CoA content existing at any given instant (97).

The carnitine acetyltransferase reaction may also indirectly regulate the rate of free fatty acid activation to long-chain acyl-CoA by controlling the amount of free coenzyme A available to the cytoplasmic thiokinase enzyme. An increase in cytoplasmic acetylcarnitine will also increase formation of cytoplasmic acetyl-CoA and free carnitine by the action of microsomal carnitine acetyltransferase. Consequently the amount of cytoplasmic free coenzyme A available for thiokinase-catalyzed activation of free fatty acids would be decreased. By equilibrating both the mitochrondrial and cytoplasmic ratios of acetyl-CoA/coenzyme A and acetylcarnitine/carnitine, activation of long-chain fatty acids is coupled to the rate of β-oxidation. In addition, by controlling the acetyl-CoA/coenzyme A ratio, carnitine may be involved in regulation of glucose utilization, since this ratio is an important regulator of pyruvate dehydrogenase activity (76). It has been proposed that carnitine, through other carnitine acyltransferase enzymes, may also be involved in metabolism of branched-chain amino acids and elimination of excess acyl units from the heart (13).

The importance of carnitine in cardiac metabolism and function is emphasized by the growing number of studies demonstrating a close association between systemic and myopathic carnitine deficiency and both hypertrophic and congestive cardiomyopathies (27, 29, 34, 37, 42, 59, 107, 123, 155, 156, 161). In most cases, oral carnitine treatment improved cardiac contractile function and morphology (29, 34, 39, 42, 107, 155, 156). The lack of a beneficial response to carnitine therapy in some patients may be due to a carnitine transport defect in the heart. This possibility is supported by the fact that only a few studies have demonstrated any significant increase in muscle carnitine after replacement therapy with carnitine in myopathic carnitine deficiency (156, 161). Cases of secondary carnitine deficiency induced by genetic

defects of intermediary metabolism also have been associated with cardiomyopathy (3, 66, 146).

Myocardial carnitine deficiency is also found in a number of states and diseases such as aging (1), diabetes (93), diphtheria (23), and chronic heart failure (150). The correlation between carnitine deficiency and cardiomyopathy suggests that carnitine therapy may ameliorate alterations in cardiac contractile function associated with these conditions. A study in humans showed that carnitine administration to diphtheritic patients resulted in decreased incidence of heart failure, pacemaker implants, and lethality indices due to myocarditis (113). A few studies in experimental animals have indicated such an effect of carnitine in these diseases. At present no definite conclusion can be drawn concerning the efficacy of carnitine therapy for treatment of these conditions.

Cardiomyopathy may also be associated with elevated levels of carnitine in plasma and heart (156). The relationship between elevated plasma and tissue carnitine and cardiomyopathy is unclear.

Ischemic Heart Disease

Although controversial, carnitine has been suggested as an agent for protecting the ischemic myocardium. The rationale for this is that myocardial ischemia causes a loss of total intracellular carnitine (84, 142) but an increase in intracellular long-chain acylcarnitine and coenzyme A esters (142, 163). It was suggested that carnitine therapy would prevent the loss of carnitine and would decrease the accumulation of lipid intermediates (particularly long-chain acylcarnitine esters), which are believed to be toxic to the heart (2, 141). Studies in humans have shown that carnitine improves exercise tolerance (74) and atrial pacing tolerance in patients with angina pectoris (51, 52, 154). However, studies in experimental animals have produced conflicting results with respect to the protective effect of L-carnitine in ischemia (53, 58, 84, 98, 149). Because of these conflicting findings, the efficacy of carnitine for treatment of ischemic heart disease in man is questionable and requires further study.

Hyperlipidemia

Because of its essential role in fatty acid oxidation, carnitine may be an effective lipid-lowering agent. As discussed above, the effects of carnitine on lipid metabolism during hemodialysis and in newborn infants have been investigated (4, 12, 28, 33, 50, 63, 81, 99, 104, 105, 134, 135, 158, 162). A number of other studies have found a hypolipidemic effect of carnitine in other types of patients as well. Oral administration of carnitine to patients with Type IV hyperlipoproteinemia was shown to cause a pronounced reduction of serum triglycerides and free fatty acids without significantly changing total serum cholesterol (91, 111). Blood glucose levels were increased during carnitine

administration (900 mg/day, 8 weeks), which suggests a shift from glucose to fatty acid oxidation in these patients. In Type II hyperlipoproteinemia patients, supplementation with oral carnitine (3 g/day, 40 days) resulted in a marked reduction of serum triglycerides and cholesterol and a normalized lipoprotein electrophoresis pattern (111). Another study revealed that oral carnitine administration (330 mg, 3 times per day for 8 to 250 days) to Type II and IV hyperlipoproteinemia patients significantly reduced plasma cholesterol and triglycerides (112). Similar results were found in hyperlipidemic diabetic patients given oral DL-carnitine (750 mg/day, 4–6 weeks) (9). Administration of L-carnitine (1 g/day, 10–15 weeks) to patients with normal serum triglycerides but low HDL caused a substantial decrease in serum triglycerides and an increase in HDL (130). Since high levels of HDL are associated with reduced risk of arteriosclerotic cardiovascular disease, the effect of carnitine on HDL levels may be of particular importance. However, the mechanism for this increase in HDL is unknown. In contrast, other studies have failed to demonstrate a significant lipid-lowering effect of carnitine in fasted (54), fat-loaded (30), or normal individuals (30), or in patients with jejunoileal bypass (136).

Ketosis

Ketotic states are accompanied by an increase in carnitine content of liver (92) and an increased plasma-acylcarnitine-to-free-carnitine ratio (21, 54, 137). Carnitine stimulates ketogenesis in isolated perfused rat liver (92) and enhances the oxidation of acetoacetate by muscle and kidney mitochondria (72). These findings have led to speculation that carnitine has a regulatory role in both ketone body synthesis and utilization.

The effects of exogenous carnitine on blood ketone body levels vary considerably depending upon the metabolic state of the patient (60, 69, 161). Carnitine supplements were effective in lowering the β-hydroxybutyrate concentration of blood in fasted children (60) and in a patient with muscle carnitine deficiency (161). In contrast, other studies have shown that carnitine treatment stimulates ketosis. A recent study involving muscular dystrophy patients revealed that carnitine administration increased blood β-hydroxybutyrate concentration after an overnight fast (69). This effect was not observed in normal subjects under the same conditions. In some cases continuous carnitine treatment led to lethargy, irritability and caused personality changes that cleared after cessation of therapy (69). Another study reported that the beneficial effect of L-carnitine in a patient with medium-chain acyl-CoA dehydrogenase deficiency, secondary carnitine deficiency, and hypoglycemia was associated with increased ketone body levels (66).

The differential effect of carnitine may be explained partially in a study by Yeh (164). He found that in rats carnitine suppressed hyperketonemia induced by fasting, suckling, and fat feeding, but it did not alter production of $^{14}CO_2$

from [^{14}C]β-hydroxybutyrate. These findings provide presumptive evidence that carnitine does not affect ketone body utilization by peripheral tissues and strongly suggest that under some conditions carnitine can inhibit ketogenesis in the liver. This hypothesis is also supported by studies with isolated hepatocytes (164). In these cells high concentrations of carnitine inhibited ketone body production but at low concentrations ketone body production was stimulated. These results suggest that carnitine can be either ketogenic or antiketogenic depending on its concentration and the metabolic state of the subject. Thus, in patients receiving carnitine therapy it is advisable to monitor blood ketone body levels.

SUMMARY AND CONCLUSIONS

It is apparent from the foregoing discussion that carnitine plays an essential role in human intermediary metabolism. The question of a dietary requirement for carnitine, particularly for the human infant, is of significant theoretical and practical interest. Aberrant carnitine metabolism resulting from abnormal genetic or acquired conditions may have serious consequences for the affected individual. At present many of the treatment modalities for carnitine deficiency are empirical. Further clarification of the mechanisms by which carnitine depletion is manifest in these conditions is essential for designing treatment programs. Moreover, therapeutic use of carnitine in several human diseases not involving carnitine deficiency per se has been indicated. Before such treatment becomes generally accepted, we must determine precisely the role of this amino acid in the biochemical and physiological events that participate in the pathogenesis of each disease.

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