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CARNITINE

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CONTENTS

INTRODUCTION

Carnitine is absolutely required for the transport of long chain fatty acids into the mitochondrial matrix. Since all the enzymes for β-oxidation are located within the mitochondrial matrix, tissues must contain adequate concentrations

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of carnitine or β-oxidation of long chain fatty acids will be stymied and cellular energy metabolism will be severely impaired. This critical metabolic function of carnitine was not recognized for more than 50 years after the discovery of carnitine in animal tissue. The first 50 years of carnitine investigations were discussed in a review published in 1957 (92). The proceedings of a symposium convened in 1964 to discuss research on carnitine and its relationship to lipid metabolism have been published (242).

Carnitine nutriture received little attention until 1973 (66 years after the discovery of carnitine), when the first carnitine deficient patient was described (79). Nutritionists had always assumed that an individual would either synthesize adequate amounts of carnitine, ingest adequate amounts of dietary carnitine, or meet carnitine needs from both sources. Carnitine was never considered a possible essential nutrient for any segment of the healthy population or for diseased individuals. Suddenly, individuals were described who required an exogenous source of carnitine to maintain normal energy metabolism. A series of three excellent papers by M. E. Mitchell reviewed the increased interest in carnitine metabolism in the early 1970s and identified many of the questions concerning carnitine metabolism that remained unanswered (161, 162, 163). Fraenkel noted that a computer search of the carnitine literature since 1970 yielded about 600 titles, none of which seemed to deal with nutritional requirements (91).

Human carnitine deficiency was at first thought to be a rare pathophysiological condition. Clinical investigations of the last decade have clearly demonstrated that carnitine deficiency occurs both in classical carnitine deficiencies and in a number of other commonly occurring disease entities. These clinical reports have been the impetus to the recent near-logarithmic growth of basic and clinical research investigations designed to answer questions concerning carnitine metabolism, carnitine nutriture, and anomalies of carnitine metabolism that result in clinical symptoms.

The introduction of the radioisotope method of Cederblad & Lindstedt (60) improved the accuracy and precision of the assay methods used in carnitine concentration determinations and provided another important impetus to carnitine investigations. Modifications and improvements of this method have been published (156, 176, 181), but the basic procedure remains the same. Older spectrophotometric methods (152) and a new gas chromatographic method (140) have been used, but the radioisotope methods are preferred for most investigations.

The transferase and translocase enzymes that use carnitine as a substrate are important components in energy metabolism. These topics have been reviewed (14, 93, 113, 114, 122, 177, 178, 187) and are not discussed extensively here.

The metabolic capacity to form acylcarnitine in response to appropriate stimuli is of great importance. However, the acylcarnitine:carnitine ratio in

hepatic tissue reflects the metabolic state of the liver rather than the carnitine pool causing changes in hepatic metabolism (36). A discussion of the metabolic regulatory processes controlling the acylcarnitine:carnitine ratio in any physiological state is beyond the scope of this review, which focuses on regulatory processes controlling total carnitine concentrations. The term carnitine deficiency should never be used to describe a decrease in free carnitine concentrations when there may be a corresponding increase in acylcarnitine concentrations [See Broquist & Borum, 41]. The term "carnitine deficiency" is applicable only when the number of carnitine molecules (as measured by total carnitine concentrations) is too low to maintain normal metabolism.

This review focuses on the metabolic and nutritional factors controlling the total carnitine concentrations, the functions of carnitine in metabolism, and the abnormalities of carnitine metabolism that result in clinical symptoms.

CARNITINE BIOSYNTHESIS AND TRANSPORT INTO TISSUES

Carnitine Biosynthetic Pathway

Carnitine is synthesized in the body from two essential amino acids, lysine and methionine. S-adenosylmethionine was recognized as the donor of the three methyl groups on the nitrogen of carnitine, but lysine was not recognized as the source of the nitrogen and carbon chain until the early 1970s (40, 41, 72, 73, 115, 217). The first step of carnitine biosynthesis in *Neurospora crassa* is the stepwise methylation of free lysine by S-adenosylmethionine: ε-N-L-lysine methyltransferase that has been purified to homogeneity (31, 191). However, this enzyme has not been found in mammalian systems. Protein-bound trimethyllysine appears to be an excellent precursor for carnitine in mammalian systems (137). Desialylated 6-N-[Me^{14}C]trimethyllysine glycoproteins were cleared from the blood by rat liver and rapidly hydrolyzed within hepatic lysosomes. Within 3 hr, 34.6% of the trimethyllysine in the administered protein was converted into carnitine. An isolated perfused rat liver converted 30% of the added peptide-bound trimethyllysine into carnitine in 90 min of perfusion. Partially methylated protein-bound lysines were not precursors for carnitine. No radioactive carnitine was detected in a rat carcass 22 hr after injection of 6-N-[Me^{14}C]-monomethyl and dimethyllysine labeled asialofetuin (137).

The biosynthetic steps between trimethyllysine and γ-butyrobetaine have been elucidated recently (34, 110, 117). The enzyme catalyzing the last step in the carnitine biosynthetic pathway was the first enzyme of the pathway to be identified and characterized (142, 143, 144). The enzyme, γ-butyrobetaine

hydroxylase, hydroxylates γ-butyrobetaine to form carnitine and plays an important role in regulation of the pathway (see below). A recently published review discusses the carnitine biosynthetic pathway in detail (41).

Regulation of Biosynthetic Pathway

Although a multitude of questions concerning the regulation of carnitine biosynthesis remain to be answered, we know that carnitine biosynthesis is regulated by the diet, age, and hormonal status of the animal. Two essential amino acids (lysine and methionine), three vitamins (ascorbate, niacin, and vitamin B_6), and a metal ion (reduced iron) are required for the biosynthesis of carnitine (41). A diet limited in lysine led to reduced carnitine concentrations in plasma, heart, skeletal muscle, cardiac muscle, and epididymis—presumably owing to impaired carnitine biosynthesis (30, 218). Scorbutic young male guinea pigs had 50% less carnitine in heart and skeletal muscle than control animals but the same liver, kidney, and plasma carnitine concentrations (170). In vivo hydroxylation of trimethyllysine was decreased in scorbutic animals, and the enzyme activity was restored by addition of ascorbic acid either in advance or at the time the labeled substrate was injected (170). When guinea pigs were fed a low ascorbic acid diet, muscle carnitine concentrations were reduced even before the emergence of the symptons customarily regarded as characteristic of hypovitaminosis C (116). Perhaps muscle carnitine deficiency could account for the lassitude and fatigue reported to precede the emergence of frank scurvy in man. Guinea pigs supplemented with dietary carnitine survived longer on an ascorbic acid–free regime than unsupplemented animals (126). This "sparing" effect of carnitine supports a role for ascorbic acid in the conversion of lysine and methionine to carnitine. In the presence of 1-amino-D-proline, a vitamin B_6 antagonist, the total production of γ-butyrobetaine, carnitine, and acetylcarnitine from protein-bound trimethyllysine was depressed by as much as 60–80% in perfused rat liver. The decreased synthesis of carnitine was accompanied by accumulation of an intermediate in the carnitine biosynthetic pathway (3-OH-6-N-trimethyllysine). The effects of 1-amino-D-proline were almost completely reversed by inclusion of pyridoxine in the perfusing medium (77).

Animals of all ages synthesize γ-butyrobetaine, but the activity of γ-butyrobetaine hydroxylase is age dependent. The ability of the rat liver to synthesize carnitine from γ-butyrobetaine increased from low levels in the fetus to adult values on the eighth day after birth (99). In three human infants, the γ-butyrobetaine hydroxylase activity was 12% of the normal adult mean. By 2.5 years, the activity was 30% of the adult mean, and by 15 years the level was within the standard deviation of the adult mean (189). Glucagon and insulin activity control intracellular protein catabolism that takes place within hepatic lysosomes. One important metabolic fate of these liposomal digestive products

is the conversion of released trimethyllysine to carnitine (2). L-thyroxine treatment (6 mg/kg body weight for 10 days) nearly doubled γ-butyrobetaine hydroxylase activity (179).

An important regulatory mechanism controlling carnitine biosynthesis is the tissue distribution of the carnitine biosynthetic enzymes. Trimethyllysine is converted to γ-butyrobetaine in rat liver, kidney, skeletal muscle, cardiac muscle, testis, and epididymis. However, only rat liver (and perhaps rat testis) can convert γ-butyrobetaine to carnitine (21, 53, 108, 219). In the rat the isolated small intestine absorbed trimethyllysine well but probably plays a minor role in metabolizing physiological quantities of this compound in the whole animal (246). The initial conversion in the rat of trimethyllysine to γ-butyrobetaine occurred predominantly in kidney (47, 192). Human liver, brain, kidney, heart, and skeletal muscle converted trimethyllysine to γ-butyrobetaine, but only human liver, kidney, and brain converted γ-butyrobetaine to carnitine (190, 193). Crude extracts from kidneys of cat, hamster, and rabbit had levels of γ-butyrobetaine hydroxylase activity equal to or exceeding that in liver. Crude extracts from kidneys of dog, guinea pig, and mouse exhibited little or no capacity to hydroxylate γ-butyrobetaine (81). There has been one report of γ-butyrobetaine hydroxlyase activity in ovine muscle (83), but two other laboratories have been unable to detect any activity in ovine muscle (57, 80). Thus the liver of the rat and the liver and kidney of the human are the major sites of carnitine production.

Transport of Carnitine into Tissues

Since tissues such as cardiac muscle and skeletal muscle depend upon fatty acid oxidation as a major source of energy but cannot synthesize carnitine, transport of carnitine from its site of synthesis to its site of action is of critical importance to cellular energy metabolism.

A series of elegant studies of carnitine transport into Giraidi human heart cells (an established cell line) have yielded much valuable information. The uptake of carnitine was saturable and was three- to tenfold higher in heart cells than in fibroblasts. γ-Butyrobetaine was taken up to the same extent as carnitine (23). Compounds structurally related to carnitine that contained the trimethylamino group and a carboxylic group reduced carnitine uptake. L-carnitine had a greater affinity for binding to the transport mechanism than D-carnitine (166). Increasing the concentration of L-carnitine from 2–100 μmol/liter in the growth medium of the heart cell line increased the rate of uptake by 50%. The increased rate of uptake was postulated to be the result of an increased number of carriers on the surface of the cell as judged by increased velocity of uptake but unchanged apparent K_D. This effect of L-carnitine could be inhibited by cycloheximide, indicating dependence on protein synthesis (167). Prednisolone (10^{-8}–10^{-5}mol/liter) in the growth medium also stimulated

carnitine uptake. The effects of prednisolone and carnitine were additive in increasing the number of carriers and in increasing carnitine uptake (164). Diphtheria toxin in the growth medium reduced the rate of uptake of carnitine. The decreased rate of uptake was postulated to be the result of inhibition of the synthesis of carnitine carriers as judged by a decreased velocity of uptake but unchanged apparent K_D (165). N-ethylmaleimide, 5,5-dithiobis-(2-nitrobenzoic acid), parachloromercuribenzoate, and cystamine all reduced uptake of L-carnitine, indicating the importance of sulfhydryl groups in the uptake process (132).

A cardiac carnitine binding protein has been isolated from rat hearts that may serve as the carrier for the transport of carnitine across the heart cell membrane (44). The carriers identified on the surface of the heart cell line and the isolated cardiac carnitine binding protein have the following characteristics in common: *(a)* protein associated with the plasma membrane, *(b)* specific and saturable binding of carnitine, *(c)* less effective competition for binding by D-carnitine than L-carnitine, *(d)* competition of binding by structural analogs containing a trimethylamino group and a carboxyl group, and *(e)* involvement of a critical sulfhydryl group in the binding.

Carnitine transport has been demonstrated in working swine hearts and isolated adult rat heart myocytes (3, 141). L-carnitine was taken up by a carrier-mediated active transport system in rat extensor digitorum longus muscle (188). The transport mechanism of the soleus muscle had a greater affinity for L-carnitine than the extensor digitorum longus muscle, which may explain the difference in carnitine concentrations in red and white muscles in the intact animal (239). Carnitine binding protein for a skeletal muscle has been identified (unpublished results). Data from experiments with isolated rat liver cells indicated the existence of a common carrier in the plasma membrane that mediated uphill transport of both carnitine and γ-butyrobetaine. The liver carrier had a higher affinity for γ-butyrobetaine than for carnitine, which is consistent with the role of liver hydroxylating γ-butyrobetaine produced by other tissues (70). A liver carnitine binding protein has been identified (unpublished results). Glucagon slightly stimulated carnitine transport into the liver cells (69). Rat kidney cortex slices had a high-affinity component and a low-affinity component for carnitine transport. Uptake of L-carnitine in the kidney was inhibited by D-carnitine, γ-butyrobetaine, and acetylcarnitine (119, 120). At a low concentration, carnitine was absorbed by rat small intestine by a stereospecific sodium dependent active process. At higher carnitine concentrations such as those obtained after a large therapeutic dose, the small intestine absorbed carnitine by passive diffusion (203). Rat brain slices possessed a relatively low affinity and high capacity active transport system for carnitine. Unlike that in other tissues, carnitine transport in brain was strongly inhibited by γ-aminobutyric acid. The data indicated that carnitine and γ-aminobutyric acid interact at a common carrier site. The authors sug-

gested that carnitine may modulate γ-aminobutyric acid transport (118). Both spermatozoa and epididymal cells had a carnitine uptake mechanism. The epididymal system was especially active in the distal caput and corpus segment (125). At carnitine concentrations normally present in the plasma, the uptake of carnitine by epididymal cells from normal rats was ten times greater than that of cells from castrated rats. Uptake by epididymal cells from normal rats was a saturable process, whereas the uptake by cells from castrated rats was a nonsaturable process. The authors postulate that castration may result in a loss from the cell membrane of a carrier molecule specific for carnitine (124). An epididymal carnitine-binding protein has been identified (unpublished results).

Regulation of Tissue Carnitine Concentrations

The carnitine concentration of a tissue at one particular time is the summation of several metabolic processes. Dietary carnitine, synthesis of carnitine, transport of carnitine into the tissue, transport of carnitine out of the tissue, carnitine degradation, and carnitine excretion may all affect tissue carnitine concentrations.

A poor nutritional status often leads to a poor carnitine status. Malnourished children had lower plasma-carnitine concentrations than healthy controls and showed inprovement with dietary treatment for the malnutrition (130). Patients with schistosomiasis, who also showed signs of malnutrition and vitamin deficiency, had subnormal levels of serum carnitine. After nutritional repletion, a significant increase was observed in the carnitine levels of most patients (159). Plasma and urinary carnitine levels were higher in Thai adults living in Bangkok city than those living in Ubol villages. Nutritional status in Ubol adults was inadequate, as evidenced by decreased urinary creatinine excretion, serum albumin, and hematocrit levels. Rice, which is limiting in carnitine, was the main protein and energy source consumed by Ubol adults and may have contributed to their inadequate carnitine status (220). Dietary choline deficiency in rats caused a decrease in heart and liver carnitine concentrations that increased upon choline administration (46, 71). As discussed above, a lysine deficient diet reduced tissue carnitine concentrations. A lysine deficient diet increased the triglyceride content of liver, heart, and muscle and resulted in impaired oxidation of [1-^{14}C]palmitate by the 600 × g supernatant of rat heart homogenates. Supplementation of the lysine deficient diet with carnitine increased the tissue carnitine concentrations and restored fatty acid oxidation to normal (131, 221).

Since plasma and urine are readily accessible, they are frequently used for assessment of carnitine status even though plasma carnitine concentrations have not always correlated with carnitine concentrations of tissues such as muscle (62). The plasma, heart, and skeletal muscle carnitine concentrations

increased in normal rats during the first day of life (27). Weanling rats showed no differences in plasma, liver, heart, or skeletal muscle carnitine concentrations. Plasma, heart, and muscle concentrations were higher in adult male rats than in adult females. However, the liver carnitine concentration was higher in adult female than in adult male rats. Epididymal carnitine concentration of rats increased rapidly from 50–70 days of age, and the differences in carnitine concentrations between the sexes also became apparent during this time (27). Normal adult male rats had a plasma carnitine concentration of 54.5 ± 1.7 nmol/ml (±SEM) and normal adult female rats had a plasma carnitine concentration of 23.4 ± 0.8 nmol/ml (±SEM). Sham castration had no effect, but castration increased the female level to 37 nmol/ml and decreased the male level to 37 nmol/ml. Male and female rats injected with androgens had plasma carnitine concentrations similar to that of the normal male. Male and female rats injected with estrogens had plasma carnitine concentrations similar to that of the normal female (28). Newborn infants also had lower plasma, heart, and skeletal muscle carnitine concentrations than adults (9). Adult levels were reached by 6 months of age (10). The plasma carnitine concentration of normal adult males was higher than in normal adult females (54). Pregnant women had lower plasma carnitine concentrations than nonpregnant women (6, 201).

Daily urinary carnitine excretion increased with age from 3.5–18 years in normal children and adolescents (78). Adult men excreted more urinary carnitine than adult women (59, 147), but adult male rats excreted less carnitine than adult female rats (28, 48). It has been reported that carnitine excretion varied widely in women during the menstrual cycle but reached a maximum at the time of ovulation (147). Fasting increased urinary carnitine excretion (147, 213). Although there have been reports of carnitine being degraded to methylcholine (129, 202), other workers have found no evidence of carnitine being converted into other compounds (39, 61, 245).

The epididymis had the highest carnitine concentration found in any tissue in the adult animal (38, 49, 153). Examination of the effects of castration and testosterone replacement showed the accumulation of carnitine in the epididymis to be under androgen control (24, 38). When rats were injected intramuscularly with [^{3}H]γ-butyrobetaine, castration had no effect on conversion of γ-butyrobetaine to carnitine or on carnitine uptake by the heart. However, castration reduced carnitine accumulation in the cauda epididymis to 6% of control values, and unilateral orchiectomy reduced carnitine accumulation by the cauda epididymis to 40% of that occurring on the nonoperated side (24). The carnitine content of cells from tubules of rabbit proximal corpus epididymis cultured 24 hr with dehydrotestosterone was greater than that in cells from tubules cultured without androgen (51). Caput spermatozoa incubated in [methyl-^{14}C]carnitine took up radioactivity, but caudal cells did not (50). Carnitine was present in testicular fluid of rats in concentrations of less than 1

mM, but the concentrations increased in the luminal fluid to 53 mM in the cauda epididymis. A high concentration of carnitine was found in the luminal fluid from the distal caput epididymis at approximately the point where spermatozoa become motile (112). The function of carnitine in the epididymis is unclear, but it has been proposed to function in the maturation process of spermatozoa. An increase in motility of ejaculated human spermatozoa was observed after the addition of acetylcarnitine (216). The acetylation state of carnitine greatly increased in monkey and bovine spermatozoa incubated in vitro with natural substrates, indicating that acetylation of carnitine may play an important role in normal spermatozoan metabolism. It has been postulated that the carnitine:carnitine acetyltransferase system buffers against rapid changes in acetyl coenzyme A concentrations (43, 52). Patients with normal seminal vesicle and epididymal function had seminal fluid carnitine concentrations of 250 μg/ml or above. Patients with defective epididymis but functional seminal vesicle, or defective seminal vesicle but functional epididymis, had carnitine concentrations of 100–200 μg/ml. Extremely low carnitine concentrations (less than 100 μg/ml) were found in the seminal fluid of patients when both the epididymis and seminal vesicle were defective (139). Human seminal carnitine concentrations have been proposed to be of diagnostic value for epididymal function (96, 240).

Human carnitine concentrations vary with different disease states (25). During the first ten days after injury, the plasma carnitine concentrations of burn patients were slightly decreased, while the carnitine concentrations in liver and muscle were elevated. The carnitine concentrations of burn wound fluid were similar to that of plasma (109). Burn patients have an increased excretion of carnitine in the first eight days following injury (58). In contrast to results obtained in humans, the plasma carnitine concentration of rats increased at 6 hr following the administration of a 20% body surface full thickness burn (240). Plasma levels of total carnitine were lower in young obese mice (ob/ob) than in their lean litter mates (100). Soon after denervation in rats, a marked drop in muscle carnitine concentration was observed that was more pronounced in red than white muscles (128). Intravenous lipid administration decreased blood carnitine concentrations and urinary carnitine excretion (134).

Endocrine control of tissue carnitine concentrations appears to involve more hormonal factors than the steroids mentioned above. Implantation of MtT-F4 tumor—a pituitary tumor that secretes large quantities of prolactin, growth hormone, and ACTH—increased total liver carnitine concentrations ninefold and decreased the serum carnitine concentrations (180). Hypothyroid patients had markedly reduced urinary carnitine excretion, which was increased after substitution therapy with thyroid hormones (78, 145, 146). Hyperthyroid patients had markedly increased urinary carnitine excretion, which returned to normal upon treatment with antithyroid drugs (145). Mice given eight sub-

cutaneous injections of 20 μg L-thyroxine at 12 hr intervals had lower skeletal muscle carnitine concentrations than control mice (55).

CARNITINE IN NORMAL METABOLISM

Accepted Functions of Carnitine

The one universally accepted function of carnitine is the transport of long chain fatty acids into the mitochondrial matrix (see introduction). Two other related functions of carnitine have been recognized.

It is generally accepted that carnitine plays an important role in thermogenesis in brown adipose tissue. Brown adipose tissue of late fetal rats and suckling rats accumulated subcutaneously injected [^{14}C]-DL-carnitine more rapidly than did heart or muscle (105). Rat brown adipose tissue carnitine concentrations increased rapidly after birth, attaining a peak at about day ten, and then decreased (104). The body pool of carnitine was eight times greater in cold acclimated rats than in rats maintained at 25°C (222).

A careful investigation of the control of the initiation of ketogenesis has demonstrated that carnitine plays an important role in this process (155, 157). Treatment of fed rats with anti-insulin serum or glucagon, or a 24 hr fast, or alloxan diabetes enhanced long chain fatty acid oxidation and ketogenesis in perfused rat liver and increased liver carnitine concentrations two- to fourfold. Carnitine added to a medium that was perfusing liver from fed rats stimulated ketogenesis from oleic acid (158). Enhanced hepatic carnitine concentration alone was not sufficient to initiate ketogenesis. In the fed state, perfused livers from nursing mother rats synthesized ketone bodies from oleic acid at low rates compared with those seen after a 24 hr fast, despite the fact that hepatic carnitine concentrations were equally elevated in both groups (194). Reduced malonyl CoA concentrations in addition to increased carnitine concentrations appear to be the combination that maximally stimulates ketogenesis (157).

Suspected Functions of Carnitine

Catabolism of branched chain amino acids is important in energy metabolism in many normal physiological and pathophysiological conditions. Carnitine serves a facilitative role if not an obligatory role in branched chain amino acids catabolism (17). L-carnitine increased the oxidation of branched chain 2-oxoacids derived from leucine and valine (225). Incubation of isolated mitochondria with [Me^{3}H]L-carnitine and the branched chain 2-oxoacids resulted in the acylcarnitines corresponding to valine, leucine, and isoleucine (208). The amount of isobutyrylcarnitine and isovalerylcarnitine increased significantly in muscle from fasted animals, which is consistent with the hypothesis that carnitine functions in branched chain amino acid catabolism (68). Branched chain oxoacid dehydrogenase is probably localized on the inner surface of the inner mitochondrial membrane and is regulated as follows. The

reaction produces CO_2 and an acylCoA ester that inhibits the branched chain oxoacid dehydrogenase. Carnitine and the acylCoA react through the mediation of the carnitine acyltransferase II to produce an acylcarnitine ester. The acylcarnitine ester is transported out of the mitochondrial matrix, and intramitochondrial coenzyme A is liberated for further oxidation (154, 226).

Although not all laboratories agree (85, 86, 185), many laboratories have concluded that fatty acid oxidation plays an important physiological role in vivo in the regulation of gluconeogenesis. Oleic acid produced a two- to threefold stimulation of glucose production from lactate in perfused livers from fasted rats. The effect was completely blocked by (+) decanoylcarnitine, a known inhibitor of carnitine palmitoyl transferase. The effect of fatty acids on gluconeogenesis is determined by their rate of oxidation and not by their concentration in the perfusion medium (235, 236). Metabolic interactions between fatty acid oxidation and gluconeogenesis were investigated in vivo in 16 hr old newborn rats. The authors concluded that in the newborn rat in vivo hepatic fatty acid oxidation can increase the gluconeogenic flux by providing the acetylCoA necessary for the reaction catalyzed by pyruvate carboxylase and the reducing equivalents (NADH) to displace the reversible reaction catalyzed by glyceraldehyde-3-phosphate dehydrogenase in the direction of gluconeogenesis (87, 88, 237). Long chain L-acylcarnitine derivatives have been shown to increase glucose production by pigeon liver homogenates when the substrate was either lactate or alanine. In contrast D-fatty acylcarnitine derivatives inhibited incorporation of ^{14}C-labeled substrates into glucose and also decreased net glucose formation measured chemically. L-carnitine or acylcarnitine derivatives released this inhibition whereas D-carnitine did not (75). The rate of gluconeogenesis from propionate in rat kidney cortex slices was stimulated up to 3.5-fold by DL-carnitine and by bicarbonate (233). Addition of carnitine during the incubation of slices of rabbit liver with alanine-U-^{14}C increased radioactivity of the glucose that was recovered in suspending medium and tissue glycogen. Carnitine also promoted the incorporation of alanine carbons into glucose by slices of kidney cortex from fasted rabbits and the labeling of glucose by liver slices incubated in the presence of $NaH^{14}CO_3$ (13). Although the mechanism remains to be fully elucidated, the hypothesis that carnitine plays a role in gluconeogenesis is supported by the finding that many patients with genetic carnitine deficiency have severe bouts of hypoglycemia (41, 205).

Evidence is accumulating that carnitine and the short and medium chain carnitine acyltransferases in peroxisomes are involved in the shuttling of acetyl and medium chain acyl residues (which are the products of the chain shortening processes in the peroxisome) out of peroxisomes (17, 18).

Two hundred fifty-five children aged 3–6 years were treated at an institute for the prevention of tuberculosis. For 2–5 months, 122 children received oral carnitine (600 mg/day) and 133 children received a placebo. The mean increase

in weight of the treated group was significantly higher than that of the untreated group (1). Thirty-four infants (aged 1.5 months to 6 years) suffering from malnutrition and infections were treated with a 20% carnitine solution. The children experienced recovery of appetite and excellent tolerance of the supplementation. Their growth rates increased to rates approaching or equal to normal rates (26). These early reports have not been confirmed, but there have been isolated statements in case reports of children with genetic carnitine deficiency where carnitine supplementation increased appetite and growth rates [cited in (41)].

CARNITINE IN ABNORMAL METABOLISM

Carnitine in Muscle Disease

The genetic human carnitine deficiency discussed briefly in the introduction is actually a family of syndromes. Investigations of these patients have increased our knowledge of carnitine metabolism greatly, but space will not permit a detailed description of the 50 some patients that have been identified. A review of the first 28 patients identified has been published [Table IV in (41)].

Patients with Duchenne muscular dystrophy (15, 32, 45, 200) or with Becker dystrophy (32) had a skeletal muscle carnitine deficiency that was less severe than the deficiency in the classical carnitine deficiency syndrome but that may have contributed to the muscle weakness experienced by the patients. There are conflicting reports concerning urinary carnitine excretion in patients with Duchenne dystrophy (76,133,148), but all available data indicate that patients with Duchenne dystrophy have abnormal carnitine metabolism.

Carnitine in Cardiac Disease

Fatty acid oxidation is a major source of energy for cardiac tissue, and any disturbance of fatty acid oxidation leads to severe metabolic consequences for cardiac tissue (169, 174, 175, 228). Occlusion of the left anterior descending coronary artery for 30 min led to significant increase in acylCoA levels in mitochondria of the ischemic heart cells. Preinfusion of 1 ml/kg of lipid further increased the acylCoA accumulation. Administration of carnitine prior to reperfusion not only suppressed accumulation of acylCoA in reperfused mitochondria but also preserved mitochondrial function despite preinfusion of lipid (136, 212). Long chain acylCoA esters inhibited adenine nucleotide translocation in heart mitochondria, but this inhibition could be reversed by carnitine (204). Infusion of carnitine may benefit ischemic myocardium by maintaining tissue levels of free carnitine and reversing the inhibition of adenine nucleotide translocase by acylCoA (89). The percent of total cellular carnitine associated with mitochondria increased from 8–9% in control hearts

to 25% in ischemic hearts, indicating a net transfer of carnitine from the cytosol to the mitochondrial matrix (123).

Twenty-one patients with coronary artery disease were subjected to two rapid sinus pacing studies 15 min apart. Eleven patients received DL-carnitine (20 or 40 mg/kg) before the second pacing study. The treated group had a significantly increased mean heart rate, pressure rate product, and pacing endurance after the administration of carnitine (223). Eight patients suffering from stable angina pectoris had a significantly increased work threshold of appearance of angina on effort when given carnitine intravenously at a dose of 40 mg/kg body weight (67). Eighteen patients with coronary artery disease were subjected to two exercise sessions separated by two weeks. DL-carnitine (40 mg/kg body weight) or placebo was given intravenously 3 min prior to exercise. Carnitine administration resulted in lower exercise heart rate, lower pressure rate product, and prolongation of exercise time prior to onset of angina (135). Two groups of patients with stable angina pectoris recorded their number of angina attacks and nitroglycerin consumption per week. At the end of the 21 day washout period the two groups did not differ. The two groups were given oral carnitine every 6 hr for 60 days. One group received DL-carnitine (100 mg/kg daily) and the other group received L-carnitine (50 mg/kg daily). During the first 30 days of carnitine, both groups had a reduction in the number of angina attacks and in nitroglycerin consumption. From day 30 to day 60 there was a further reduction in angina attacks and nitroglycerin consumption in the group treated with L-carnitine but not in the group treated with DL-carnitine. The group treated with L-carnitine had a significantly lower number of angina attacks and lower nitroglycerin consumption at day 45 and day 60 than the group treated with DL-carnitine (95).

Pretreatment of dog hearts with ligated coronary arteries with L-carnitine reduced the grade of ventricular arrhythmia induced both by acute myocardial ischemia and by supplementation of excess free fatty acids (214). Free fatty acid induced arrhythmias appeared to be related to the disturbance of mitochondrial calcium binding activity induced by accumulation of acylCoA. Carnitine, especially propionylcarnitine, was effective in preserving the mitochondrial calcium binding activity despite subsequent infusion of lipid (211). Diphtheria toxin induced fatty degeneration of myocardium and decreased the rate of oxidation of long chain fatty acids, with a markedly decreased concentration of carnitine and an excessive accumulation of triglyceride. Exogenous carnitine restored the rate of palmitate oxidation in vitro in myocardial homogenates and in isolated perfused diphtheritic guinea-pig hearts (37, 64, 241). Adriamycin is an important antineoplastic drug, but it can induce a cardiomyopathy that may be fatal. Carnitine has been shown to protect against the adriamycin cardiomyopathy in some animal models (210) but not in others (97). Myocardial carnitine concentrations are markedly reduced in both

chronically and acutely uremic rats (234). Hamsters suffering from a genetic cardiomyopathy have reduced cardiac carnitine concentrations that probably result from impaired transport of carnitine into the myocyte due to an altered cardiac carnitine binding protein (33, 244).

Carnitine in Liver Disease

Patients hospitalized for advanced cirrhosis frequently have subnormal plasma carnitine concentrations. Post mortem concentrations of carnitine in liver, muscle, heart, kidney, and brain of these patients averaged 25–33% of those in corresponding tissues of normally nourished nonhepatic patients. The investigators postulate that the carnitine depletion results from three factors: substandard intake of dietary carnitine; substandard intake of lysine and methionine; and the loss of capacity to synthesize carnitine from lysine and methionine (196).

Jamaican vomiting sickness has many clinical characteristics in common with Reye's syndrome and is caused by the compound hypoglycin found in unripe ackee fruit. Intravenous administration of hypoglycin to mice caused severe hypoglycemia which was preceded by a decrease in palmitate oxidation by myocardial homogenates. Addition of carnitine to the myocardial homogenates of treated mice restored palmitate oxidation to normal levels. Administration of carnitine to hypoglycin-treated mice prevented the decrease in myocardial palmitate oxidation and prevented the hypoglycemia (82). During studies on the mechanism of inhibition of fatty acid oxidation by 4-pentenoic acid (a metabolite of hypoglycin), fatty acid oxidation was inhibited in rat liver mitochondria by CoA depletion resulting from incorporation of free CoA into a product of 4-pentenoic acid metabolism (94). There has been one report of the apparent failure of carnitine to prevent the effects of hypoglycin (151). The clinical symptoms of Reye's syndrome are also similar to the encephopathic symptoms of children with classical carnitine deficiency, and several children with carnitine deficiency have been diagnosed initially as having Reye's syndrome (41). However, patients with true Reye's syndrome have elevated serum carnitine concentrations during the acute phase. The levels return to normal in the convalescent phase of survivors (111). Reye's syndrome patients have normal liver and skeletal muscle carnitine concentrations (238).

Studies of patients with various lipid diseases indicate that carnitine affects lipoprotein metabolism in the liver. Perfused rat liver supplied with oleic acid was treated with 2-tetradecylglycidate, which inhibited fatty acid oxidation. This direct and specific inhibition of long chain fatty acid oxidation diverted exogenous fatty acids to the esterification pathway and enhanced the secretion of triglyceride in the form of VLDL. The rate of fatty acid oxidation in liver was therefore a major determinant in the producton of triglyceride-rich plasma lipoproteins (121). Fatty acids, whether supplied in the medium or synthesized

de novo, induced the formation of membrane-rimmed, triglyceride-rich vesicles in the cytoplasm of chick liver cells in culture. Vesicle triglyceride was rapidly mobilized in the presence of dibutyryl-cAMP, and the process was further accelerated by L-carnitine (168).

Two otherwise normal males were selected for normal serum cholesterol and triglycerides but low serum HDL-cholesterol. Oral L-carnitine treatment for 10–15 weeks (1 g/day) substantially increased the HDL-cholesterol and decreased the triglyceride (195). Twenty-six patients with type II or type IV hyperlipoproteinemia were treated with 3 g of oral carnitine per day with a marked reduction in serum cholesterol and serum triglyceride. The risk index—total cholesterol divided by HDL-cholesterol—was also reduced (186). Another study of patients with type IV hyperlipoproteinemia demonstrated a reduction in serum triglyceride concentrations with oral or intravenous carnitine but demonstrated no effect on serum cholesterol concentration (149). Clofibrate is frequently used to lower blood lipids in patients. Clofibrate treatment of rats increased liver, plasma, and total body carnitine (127, 150).

Carnitine in Kidney Disease

Serum carnitine concentrations were frequently above normal in patients with renal insufficiency (66). During hemodialysis there was a sharp decline in the serum carnitine concentrations. This decline could be accounted for almost quantitatively by the accumulation of carnitine in dialysate fluid (7). Plasma free carnitine concentrations in 6 patients fell 73% during dialysis and returned to normal within 6 hr. If the patients were given 3 g of oral DL-carnitine at the end of dialysis, plasma carnitine concentrations recovered within 2 hr (20). Using prolonged longitudinal plasma carnitine measurements, patients can be divided into a group in which there is a return to normal plasma carnitine concentrations after dialysis and another group in which chronic plasma carnitine deficiency was established by dialysis (8). Addition of L-carnitine to the dialysate (65 μmol/liter) completely prevented the decrease in plasma carnitine during dialysis (19). Administration of L-carnitine (2 g orally) 2 hr before dialysis of 17 renal patients maintained plasma carnitine concentrations within normal levels throughout dialysis and suppressed the increase in plasma free fatty acids that was seen without carnitine treatment (215). Two laboratories have reported a reduction in skeletal muscle carnitine concentrations in dialysis patients (16, 22) and one laboratory has found normal carnitine concentrations in the skeletal muscle of dialysis patients (160). In one study, intravenous administration of DL-carnitine (50 mg/kg body weight) after each dialysis significantly increased muscle carnitine concentrations at the end of two months of treatment (16). Blood carnitine concentrations of patients on continuous ambulatory peritoneal dialysis were maintained in the normal range during the first year of treatment but then declined slowly and progessively

until they were below normal limits by the end of the second year of treatment (42).

Fifty-one chronic hemodialysis patients receiving oral DL-carnitine for 3 days (2.4 g/day) showed decreased serum triglyceride concentrations and return of HDL cholesterol to normal levels (138). Dialysis patients receiving carnitine at 0.5 g/day for 8 weeks and 1.0 g/day for six additional weeks showed decreased serum triglycerides while patients receiving placebo showed no change (98). Ten hypertriglyceridemic hemodialysis patients were given DL-carnitine at a dose of 600 mg/day for eight weeks and then 1.2 g/day for 12 weeks. Some of these patients responded with a decrease in plasma triglyceride concentrations by as much as 50% and other patients showed an actual increase. The observation remains unexplained (65).

Carnitine in Diabetes

Diabetic rats have higher hepatic carnitine concentrations than normal rats (158) and higher skeletal muscle (soleus) carnitine concentrations (209). Diabetic sheep also have higher hepatic carnitine concentrations than normal animals (207). In a recent study myocardial carnitine concentrations and serum carnitine concentrations were reduced after 48 hr of severe diabetes or several weeks of mild diabetes. Carnitine transport into cardiac tissue was not altered in diabetic animals, but the serum carnitine concentration was decreased to a value near the Km for carnitine transport. The authors concluded that a decreased rate of transport of carnitine into heart due to lower serum carnitine could be responsible for the reduced carnitine concentrations seen in diabetic hearts (227). Patients with diabetes are reported to have reduced plasma carnitine concentrations but normal skeletal muscle carnitine concentrations (56, 63).

In rats, plasma total carnitine decreased during the first 24 hr of a fast and then increased, reaching levels higher than the control. Hepatic and cardiac carnitine concentrations increase during fasting, but this increase may arise indirectly from changes in tissue mass (35). Total carnitine concentration in the blood of obese mice was lower than in lean mice at the start of the starvation period. It increased significantly and considerably during starvation in the obese mice, whereas it decreased in their lean litter mates (106).

CARNITINE THE NUTRIENT

Carnitine in the Infant Diet

Fatty acid oxidation in the developing animal or infant has been studied extensively (4, 5, 90, 101, 103, 229, 231, 232, 243). These investigators have demonstrated that oxidation of long chain fatty acids, which requires carnitine, is critical to survival and normal development of the newborn. Blood carnitine concentrations in the fetus and in cord blood are higher than in maternal blood

(6, 107). The initial carnitine concentration in the newborn depended upon the maternal carnitine concentration (172). Full term newborns have plasma carnitine concentrations similar to that of preterm infants of 33–36 weeks gestation but significantly lower than that of preterm infants of 30–33 weeks gestation. The plasma carnitine concentrations of full term infants increased during the first two weeks of life and reached adult levels by six months of age (10). All types of milk tested contain carnitine (84, 197, 206), and milk may be the source of the carnitine that accumulates in mammalian tissues during early development. Nursing mother rats were injected with [^{14}C-butyrobetaine], and the radioactivity was found as carnitine first in the maternal liver, then maternal plasma, then milk, and finally in neonatal tissues (194). Commercial infant formulas based on soy protein contain no detectable carnitine (34). Plasma concentrations of carnitine rapidly decreased in preterm newborns during the first three days after birth if no exogenous carnitine was given (172). Plasma carnitine concentrations of infants fed soy based formulas were lower than those found in infants fed breast milk, a milk based formula, or a soy based formula supplemented with carnitine (171, 173). The bioavailability of carnitine in breast milk was found to be greater than that in milk based formula (230). Several lines of evidence indicate that carnitine may be an essential nutrient for the newborn (29).

Carnitine in the Typical American Diet

Our knowledge of the carnitine content of foodstuffs has been limited (161). Recent analysis of several hundred foodstuffs in ready to eat form indicate that meat and dairy products are the major sources of carnitine in the United States diet. In general, the redder the meat the higher the carnitine content. When dairy products were fractionated, the water soluble carnitine remained in the whey portion of the product. Fourteen different diets used by hospitals in the United States were evaluated for their carnitine content, and carnitine intake was calculated for a large number of patients consuming the diets. The daily intake was usually between 2 and 100 mg but was 300 mg in some cases (unpublished results).

Carnitine in the Vegetarian Diet

Cereals, fruits, and vegetables contain little or no carnitine. The major source of carnitine in a vegetarian diet was the fermented soybean product tempeh. The mold used in the fermentation process synthesizes carnitine, increasing the carnitine content of tempeh (unpublished results).

Carnitine in Defined Enteral Diets

An increasing number of people are being maintained for long periods on defined enteral diets. Formulas whose main protein source is soy protein

isolate, casein, or egg white protein contain 4 nmol/ml carnitine or less, with most containing undetectable amounts of carnitine. Formulas made with milk contain 50 nmol/ml or more carnitine (34).

Carnitine in Total Parenteral Nutrition

All solutions used in total parenteral nutrition contain no carnitine. Plasma levels of total carnitine remained unaltered in adult surgical patients fed intravenously for up to about 20 days of feeding and then gradually declined (102). Infants maintained on total parenteral nutrition have lower plasma carnitine concentrations than those fed orally with expressed human milk or proprietary formula (198). Infusions containing lipid did not alter plasma carnitine concentrations (199). Total parenteral nutrition for more than 15 days resulted in significantly lower liver and heart carnitine concentrations in infants (183). One group of preterm infants was maintained on total parenteral nutrition and a second group of preterm infants was maintained on a carnitine-containing milk formula. Serum and urinary carnitine fell after five days on total parenteral nutrition while there was no change in the formula fed infants. Infants on total parenteral nutrition had lower serum carnitine concentrations on the fifth day of life than formula fed infants (184). Carnitine supplementation may be required for some patients receiving total parenteral nutrition.

CARNITINE IN THE FUTURE

Carnitine in Nutrition of the Normal Individual

The normal newborn, the normal pregnant woman, the normal lactating woman, and the normal adult with a diet low in lysine and methionine may require exogenous carnitine.

Carnitine in Treatment of Patients

Many disease states in addition to the classical carnitine deficiency may benefit from carnitine therapy. Recent clinical experience indicates that the L isomer and not the DL racemic mixture should be used in carnitine therapy. Myasthenia-like symptoms have been found in hemodialysis patients treated with DL-carnitine for 45 days (12, 74). The symptoms disappeared upon cessation of DL-carnitine supplementation. After a washout period, the same dosage of L-carnitine administered to the same patients did not cause any of the symptoms previously noticed with DL-carnitine treatment (11). Intraperitoneal injection of D-carnitine (750 mg/day) for four days produced an L-carnitine deficiency in cardiac and skeletal muscle (182).

SUMMARY

Carnitine has a critical role in energy metabolism. Many of the functions of carnitine are not clearly elucidated and many of the regulatory mechanisms

governing carnitine metabolism are ill-defined. Carnitine deficiency can be life threatening but may be resolved with carnitine supplementation. Various groups of individuals in addition to those with the classical carnitine deficiency syndrome may require exogenous carnitine. Carnitine nutriture can no longer be ignored.

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