ORIGINALARBEITEN

Z. Ernährungswiss. **21**, 257–265 (1982)

ISSN 0044-264 X

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Carnitine in human nutrition

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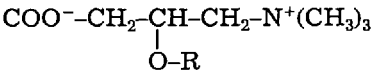
(Received March 5, 1982)

When an animal cell gets part of the energy it needs from the oxidation of long-chain fatty acids (those with more than 12 carbon atoms), it must transport them from the cytoplasm to the mitochondria, which contain the enzymatic mechanisms that catalyse beta-oxidation. Carnitine (beta-hydroxy-gamma-trimethylaminobutyrate) is indispensable for this transport.



if R = H, this is carnitine (mol. wt. 161.2)

if R = $CO-(CH_2)_n-CH_3$, this is acyl-carnitine

Indeed, long-chain fatty acids can cross the internal membrane of the mitochondrion only in the form of acyl-carnitines (1). A deficiency of carnitine in the tissues has been linked with an incapacity to oxidize fatty acids and their accumulation in the form of triacylglycerols in the cellular cytoplasm (2). Obviously, then, carnitine is of fundamental importance in the regulation of tissue oxidation of fatty acids (3) and in hepatic ketogenesis (4).

A sufficient concentration of carnitine is therefore essential for normal lipid metabolism. To meet the need for carnitine, animals make use of both endogenous synthesis and exogenous supplies. Certainly in mammals in general and in humans in particular, an essential need for exogenous carnitine has never been demonstrated (5). But newborn babies given a carnitine-free diet have lower serum carnitine concentrations than do babies given milk (6). The carnitine supplied in mother's milk not only raises the serum carnitine concentration in the nursing infant but also permits a larger energy contribution from fatty acids. In addition, in recently described cases of tissue carnitine deficiency (see ref. 7), a low level of endogenous synthesis of this substance is often considered partially responsible for certain disorders (muscular weakness, myopathy,

accumulation of lipids in the muscles, myoglobinuria) which sometimes regress when carnitine is administered.

These observations suggest that a review of current information about carnitine in nutrition would be useful, in dietetics (must a balanced diet include carnitine?), in therapeutics (when can a carnitine supplement remedy a carnitine deficiency?), and, finally, in research (for, as we shall see, many aspects of carnitine metabolism are worth studying).

Dietary content of carnitine

Only the L optical isomer of carnitine is found in nature; the D form is biologically inactive. Carnitine is found either free, or in an acylated form, bound to long-chain fatty acids (long-chain acyl-carnitines), to short-chain fatty acids (short-chain acyl-carnitines), or to acetate (acetyl-carnitine).

Carnitine is widely distributed in nature. Foods of plant origin (5, 8, 9) and microorganisms contain only small amounts; the former are not only poor in carnitine but are often also poor in lysine (as in certain cereals) and in methionine (as in some vegetables), which are precursors required for the endogenous synthesis of carnitine (10). Carnitine is more abundant in foods of animal origin (vertebrates or invertebrates), particularly in muscle (11, 12), from which is was first extracted at the beginning of the century.

Table 1. Total carnitine content (mg/100 g fresh consumable material) of various foods (data from references 14–18).

Beef	Fillet steak	59.80–88.66	Avocado (mesocarp)	1.25
	Shoulder, raw	67.40	Carrots	0
	Rump-steak, raw	61.60	Green beans	0.81
	Heart, raw	19.30	Peas	1.16
	Liver, raw	2.60	Spinach	0
	Kidney, raw	1.80	Tomatoes	2.93
Pork	Liver	4.92	Sauce (ketchup)	1.61
Lamb	Skeletal muscle	77.97	Cabbage	0
	Liver, raw	2.64	Cauliflower	0.13
Sheep	Skeletal muscle	209.26	Potatoes	0
	Heart, raw	59.05	Asparagus	1.29
	Liver, raw	2.17	Peaches	1.61
Ram	Tenderloin, raw	162.80	Pears	2.74
	Rump, raw	168.50	Pineapple	1.05
	Heart, raw	59.50	Apple puree	3.14
	Liver, raw	2.60	Orange juice	0–1.77
Rabbit	Muscle, raw	21.00	Apple juice	1.29
	Liver, raw	11.10	Bearley seed	0
Chicken	Muscle, raw	4.55–9.67	Corn-seeds	0
	Liver, raw	0.61	Corn-flakes	9.51
Hen's eggs		0–0.81	Wheat, seeds	0.35–1.22
Cow's milk	fluid	0.53–3.91	Wheat, germ	1.06
	dry, not fat	15.00	Bread, Wasa	0.24
	Whole (per 100 ml)	0.63–1.02	Bread	0.81
Margarine		1.05	Brewer's yeast	1.60–3.29
			Rice	1.77

Sheep skeletal muscle contains more of it (209 mg/100 g wet muscle) (13) than any other food. In general, a diet rich in meat is considered to supply a large amount of carnitine, while a vegetable-based diet supplies little (14). Table 1 shows the carnitine contents of various foods. All these figures apply to raw foods; since carnitine is watersoluble (19), any cooking with water naturally causes losses of carnitine, as Mitchell (14) rightly pointed out, although she could not measure the amounts lost.

Borum et al. (15) and Schmidt-Sommerfeld et al. (16) measured the carnitine content of 42 liquid diet preparations given enterally or parenterally to adults or children. These diets' carnitine contents were determined by their protein components: the preparations whose protein came mainly from casein, eg, or soya contained little or no carnitine (< 0.1 mg/100 ml), whereas those based on milk protein or on beef protein contained between 0.8 and 10.6 mg of carnitine per 100 ml.

Intestinal absorption of carnitine

It is generally accepted that carnitine – the L form as well as the racemic form – is rapidly and completely absorbed by the intestinal mucosa. The various published overload tests provide only a limited amount of information, as they were performed in very diverse conditions and using noncomparable subjects. Thus Frohlich et al. (20) gave normal subjects 1 g of L-carnitine: the serum carnitine concentrations rose, reached a maximum after about 4 hours, and seemed to have returned to normal by 5½ hours after the beginning of the experiment. In another study, an 11-year-old boy with a systemic carnitine deficiency was given 500 mg of racemic carnitine: the plasma concentration of the substance rose for 3 hours, and had not returned to the initial level even 5 hours after reaching a maximum (2). And in yet another study, after a substantial dose (15 g) of L-carnitine had been given to a 10-year-old girl who also was suffering from carnitine deficiency, the plasma peak was reached 60 minutes later, and 6 hours after the ingestion the carnitine concentration was lower than at the start; in a young control subject, the maximum was at 30 minutes, but the return to the initial value was far from complete at 6 hours (21).

Mitchell (14) accepted both that only the free form is adsorbed and that intestinal enzymes can hydrolyse ingested acyl-carnitines.

Lowered serum carnitine concentrations have been observed in cases of malnutrition, malabsorption, Crohn's disease, and anorexia nervosa (22–25), and also following jejunoileal anastomose carried out in cases of morbid obesity (26). It is not known, however, whether these phenomena are attributable to a decrease of carnitine absorption and/or of lysine and methionine absorption.

Neither is known what level in the intestine and by what mechanism carnitine is absorbed, nor whether it follows the portal system (which is most likely for a water-soluble substance). The very great loss of carnitine from the blood of patients undergoing hemodialysis suggests that circulating carnitine is not strongly bound to a protein macromolecule (24, 27).

The carnitine in blood is taken up by the various tissues (28) and it is eliminated in the urine. In man, about a tenth of ingested L-carnitine (1 g) appears in the urine within 6 hours of its administration (20); and when the diet is rich in carnitine, more of it is eliminated in the urine (14).

Dietary requirement for carnitine

In 1948, Fraenkel (29) reported that vitamin B_T (later recognized as carnitine) was essential for the growth of the mealworm, *Tenebrio molitor,* and of several other larvae of the same family. Small amounts of vitamin B_T are enough to ensure the normal growth and development of these insects. It was on the basis of these observations that carnitine was classified as a vitamin, a classification that has since been withdrawn. In fact, all mammals can synthesize carnitine themselves (5), and they have never been shown to have an absolute need for dietary carnitine. But I review here the results of studies on the subject.

First, there have been studies on laboratory animals. The introduction of 0.2 % DL-carnitine into a methionine-deficient (30) or a lysine-deficient (31) diet resulted in a resumption of growth in rats and in the reduction of a previously observed accumulation of lipids in the liver. On the basis of radioisotope experiments, Cederblad and Lindstedt (32) reported the following figures: for a total pool of 9200 µg of carnitine, the adult rat synthesized 486 µg and ingested 113 µg per day. But Christiansen and Bremer (33) thought that hepatic production of carnitine is sufficient to assure complete, though very slow (34), turnover. And the growth of young mice was not accelerated by a carnitine supplement, either in the food of the youngs or in that of their nursing mothers, when their dietary protein supply was adequate (35). Fraenkel (8) observed that rat liver and rat muscle contained the same amounts of carnitine, whether or not the substance was provided in the diet. However, the results of Tanphaichitr and Broquist (36) and of Tao et al. (37) were entirely different: a diet containing carnitine led to tissue concentrations of the substance that were 20 to 40 % higher than those observed when the diet was lacking in carnitine but contained the necessary amounts of lysine. This observation suggests that dietary carnitine plays a non-negligible role in meeting the needs of the rat (38).

Angelini et al. (21) suggested that in humans the dietary contribution of carnitine is between 8 and 11 mg per day, whereas Mitchell (14) considered these values to be serious underestimated. In an experiment to study the elimination of carnitine in urine, Cederblad (39) put women on a standard diet supplying 30.6 mg of carnitine daily for 9 days; this daily supply seems more plausible.

Many nutritionists accept that the human diet does not absolutely need to supply carnitine. They think that a healthy person can synthesize all the carnitine needed, provided the daily requirements for lysine (23 mg/kg body-weight) and methionine (31 mg/kg body-weight) are met. And the decreased carnitine elimination in urine when the diet supplies less can be considered an argument in favor this theory. We nevertheless think that the subject still deserves further study; until more is known, we are inclined to believe that exogenous carnitine is useful, especially because, as Mitchell (14) suggests, the amount of carnitine ingested may influence the amount synthesized by the body.

The neonate's carnitine requirements

Although the role of dietary carnitine in the adult is controversial, it is much less so in the neonate. Hahn (40) has classified mammals according to the amount of lipids transferred from mother to fetus: it is greater in the

rabbit and the guinea pig than in the rat and the sheep. In the latter two, carnitine transfer is also very slow (40, 41), and the blood levels of carnitine are higher in the mother than in the fetus. When radiolabelled carnitine is injected into the ewe, certainly the tracer appears in the tissues of the fetus, but always at lower concentrations than in the corresponding maternal tissues (40). In rabbits and guinea pigs (40), and also in humans (42), the serum levels of total carnitine and of acyl-carnitines are relatively high during the intra-uterine period. The cord blood contains more carnitine than the maternal blood does (42), which suggests that the substance is actively transported across the placenta to the fetus. The fetus retains the carnitine received from the mother, since the concentration seems higher in the umbilical artery than in the umbilical vein (42). A parallel decrease of plasma carnitine has been observed in women towards the end of the gestation period (42–44). This change is attributable partially to dilution by increased volume – the total pool of carnitine increases in the gestating rat (45) – but mainly to an increase in the fetal demand. A combination of this increased demand of the fetus with a systemic carnitine deficiency in the mother can have dramatic consequences for the mother (46, 47). Pregnant rabbits and ewes have increased acyl-carnitine concentrations (40), which implies that the available carnitine participates more in the metabolism of fatty acids.

In most mammals, the contribution of lipids to the supply of energy increases greatly in the hours following birth. A corresponding change in the need for carnitine would therefore be expected. And indeed, at that time, in animals and in humans, the blood and liver concentrations of total carnitine and of acyl-carnitines increase (41, 48, 53). In the liver of the piglet, for example, the amount of carnitine doubles in the first 24 hours of life (54); but if the piglet is without food during that day, the values remain unchanged. The introduction of milk into the diet of the newborn of course helps to accelerate lipid metabolism, but it also helps to supply carnitine.

In an earlier section, we mentioned that milk contains significant amounts of carnitine. After 24 hours of nursing, the milk of a mother rat contains 10 times more carnitine than her plasma does (48). In women, adaptation of the carnitine concentrations is observed: 0.63 mg/100 ml during the first 3 days of nursing, 1.02 mg during days 4 to 7, and 0.73 mg a month after the delivery (16). Hahn (41) showed that the injection of labelled carnitine into nursing mother rats resulted first in the appearance of the tracer in the milk, and then in its accumulation in various tissues of the babies. In addition, the accumulation of carnitine in the adipose tissue of the newborn coincides with the initiation of the milky diet, suggesting that the oral intake of carnitine is important during this period (82).

Recall that McGarry and Foster (48, 52) showed that the carnitine in milk is of hepatic origin: a short time before parturition in the rat, the level of carnitine in the liver rises sharply, returning to its usual value only after 3 to 8 days of nursing. When newborns or premature babies are given a diet deficient in carnitine, they have lower blood concentrations of carnitine than do babies fed on mother's milk or cow's milk or receiving a carnitine supplement (49, 51, 55, 57). Borniche et al. (58) found that the addition of

carnitine to the diet accelerated weight gain in the nursing baby and in the young child with postinfection anorexia.

To achieve an optimal capacity to oxidize fatty acids, then, a nursing baby depends much more on exogenous carnitine than does an adult (6, 51). Yet if exogenous carnitine should be totally lacking from diet, the serum concentrations of total carnitine and acyl-carnitines remain stable, although reduced by 45 and 35 %, respectively (6). Thus carnitine seems to be synthesized already at this age, although apparently in inadequate amounts. This observation slightly modifies the opinion of Strack et al. (59), who classed carnitine unequivocally as an essential nutrient for young babies.

Exogenous carnitine in certain diseases

We shall now briefly review the various diseases in which an exogenous supply of carnitine (the DL form, or more often the hydrochloride form [= bicarnesine], or preferably the L form [60]) can be helpful.

It should be remembered that patients in hospital are often given a diet in which the amount of protein is limited, or even inadequate. One might therefore wonder whether the carnitine pool in hospitalized patients reflects this. In addition, it has been shown that, in dogs and in humans, severe septicemia or serious trauma leads to a drop in the carnitine content of muscles (61). If it should turn out that the capacity to oxidize fatty acids is thereby diminished, a supply of carnitine would allow the energy needs (which are considerable in these two conditions) to be better met. Tao and Yoshimura (62) suggested adding carnitine to the perfusate of patients being fed intravenously in order to increase their utilization of fats.

Many studies (see 3) have demonstrated a slump in the plasma concentrations of carnitine in hemodialysed patients. This observation can be accounted for, at least partially, by carnitine losses into the dialysis fluid. Oral or intravenous administration of carnitine prevents this fall, reduces the hypertriacylglycerolemia observed in these patients, and improves their muscular performance.

In subjects with type-IV hyperlipoproteinemia, the ingestion of 900 mg of DL-carnitine (chloride form) per day for 2 months lowers triacylglycerolemia but not cholesterolemia (64). The daily administration of 750 mg of L-carnitine chloride to diabetic patients with hyperlipemia for 4 to 6 months leads to a 24 % reduction of the total lipemia (65).

Certain myopathies accompanied by an excess of lipids are due to a carnitine deficiency; the level of carnitine is low in the skeletal muscles and sometimes also in the blood (7). In some patients, a daily 2- to 6-g supplement of DL-carnitine brings muscular improvement, but no accompanying increase of the muscle concentrations of carnitine (66).

Frohlich et al. (26) suggested carnitine treatment for patients who had undergone jejunoileal anastomosis because of morbid obesity. Carnitine has also been prescribed in a whole series of disorders: malabsorption, malnutrition, anorexia, and rickets (7, 67, 69). In these cases the dietary carnitine deficiency is naturally associated with a more generalized deficiency, especially of amino acids, which makes it difficult to demonstrate

the carnitine deficiency. And in human ischemic myocardia, carnitine increases tolerance to stress (70).

Conclusion

To conclude this review of carnitine in the human diet, it must of course be recognized that at present there are far more unanswered questions, or at least questions without definite answers, than definitively answered ones.

Carnitine is widely distributed in foods, especially those of animal origin. It is certainly absorbed by the intestine; but in what form, at what level, how, and at what rate? Even though it has a low molecular weight and acts at low doses in a metabolic pathway essential for the living cell, beta-oxidation, carnitine must be considered a nutrient and not a vitamin. It is clear that the adult animal organism can synthesize it, but it is not known whether such synthesis can meet the requirements for carnitine, nor below what level of dietary carnitine the cells lose some of their capacity to oxidize fatty acids. Although dietary carnitine seems to be useful but not indispensable in adults, it is undeniably more important during the neonatal period, especially in the hours and days following birth; but it is not known whether it is really a growth factor that must be supplied in the diet of the nursing infant.

Acknowledgment

The author is indebted to Dr. Brigitte Picandet for a critical review of the manuscript.

Summary

The oxidation of long-chain fatty acids is carnitine-dependent. Indeed, only when they are bound to carnitine, in the form of acyl-carnitines, do fatty acids penetrate into the mitochondria to be oxidized. To meet the need for carnitine, animals depend on both endogenous synthesis and an exogenous supply. A diet rich in meat supplies a lot of carnitine, while vegetables, fruits, and grains furnish relatively little.

Although it has a low molecular weight and acts at low doses in a vital metabolic pathway, carnitine should not be considered a vitamin, but rather a nutritive substance. Indeed, it seems that the diet of the adult human need not necessarily furnish carnitine: the healthy organism, given a balanced nutrition (sufficiently rich in lysine and methionine), may well be able to meet all its needs. Furthermore, it seems that a reduction of the exogenous supply of carnitine results in a lowering of its elimination in the urine.

However, dietary carnitine is more important during the neonatal period. The transition from fetal to extrauterine life is accompanied by an increased role of lipids in meeting energy needs. This change is accompanied by a rise in the body of the levels of carnitine, which is mainly supplied in the maternal milk.

Finally, this review briefly surveys the illnesses in which a dietary carnitine supplement proves useful.

Zusammenfassung

Die Oxydation der langkettigen Fettsäuren ist carnitinabhängig. So dringen diese Fettsäuren nur an Carnitin gebunden, d. h. als Acylcarnitin, in die Mitochondrien ein, um dort oxydiert zu werden. Der tierische Organismus deckt seinen Bedarf an Carnitin durch exogene Zufuhr und endogene Synthese. Eine fleischreiche Nahrung führt dem Organismus viel Carnitin zu, während Gemüse, Obst und Getreide relativ wenig davon enthalten.

Obwohl es sich um ein relativ kleines Molekül handelt, das in geringer Menge in einem lebenswichtigen Stoffwechselsystem wirkt (die Beta-Oxydation), darf Carnitin nicht als Vitamin angesehen werden, sondern vielmehr als eine Nährsubstanz. Es scheint nämlich nicht unbedingt notwendig zu sein, daß die Ernährung dem erwachsenen Menschen Carnitin zuführt. Der gesunde Organismus kann bei einer ausgeglichenen Ernährungsweise (ausreichende Zufuhr von Lysin und Methionin) seinen Bedarf vollständig selbst decken. Dies um so mehr, als eine Senkung der exogenen Zufuhr von Carnitin eine geringere Ausscheidung über den Harn zur Folge hat.

Dem in Nahrungsmittel enthaltenen Carnitin kommt jedoch beim Neugeborenen eine größere Bedeutung zu. Der Übergang vom pränatalen zum postnatalen Leben bewirkt eine Erhöhung des Stellenwertes der Lipide bei der Deckung des Energiebedarfs. Diese Veränderung wird von einem Anstieg des Körpergehalts an Carnitin begleitet, das im wesentlichen durch die Muttermilch zugeführt wird.

Zum Abschluß gibt dieser Bericht eine knappe Darstellung der Krankheiten, bei denen sich eine ergänzende Zufuhr von Nahrungs-Carnitin als nützlich erweist.

Key words: carnitine, foods, dietary requirements, adult, neonate.

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