EDITORIAL

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THE ROLE OF CARNITINE IN THE PERINATAL PERIOD

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Abstract

Carnitine (2-hydroxy-4-trimethylammonium butyrate, vitamin BT) is a small hydrophilic molecule derived from protein-bound lysine, not degraded in the body but excreted via urine, bile and breast milk. Carnitine stimulates the catabolism of long-chain fatty acids (FAs), by transporting them to mitochondria for oxidation, and the intracellular decomposition of branched-chain ketoacids. It also helps to excrete toxic exogenous and nontoxic endogenous organic acids via urine. It further participates in the production of pulmonary surfactant, inhibits free radicals production and demonstrates other antioxidant properties. After delivery, infants dramatically increase energy demands for movement, growth, differentiation and maintenance of the body temperature that strongly depend on FAs oxidation which is facilitated by carnitine. At early stages of life, carnitine biosynthesis is less efficient than in adults and immature infants have less carnitine tissue reserves than term infants. Carnitine supplementation is recommended in newborns with aciduria, childhood epilepsy associated with valproate-induced hepatotoxicity, in kidney-associated syndromes, and premature infants receiving total parenteral nutrition. Concentrations of carnitine and acylcarnitines in neonatal blood have been postulated a useful tool for the diagnosis of type 1 diabetes, as well as the detection and monitoring of many inherited and acquired metabolic disorders. Taking into account the complex metabolic role of cellular FAs transporters, further studies are needed on indications and contraindications for carnitine supplementation in different clinical settings during early developmental period.

Key words: carnitine, dietary supplementation, fatty acids, neonate, pulmonary surfactant

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INTRODUCTION

Carnitine (Lat. *carnus* – meat), 2-hydroxy-4-trimethylammonium butyrate (Fig. 1), or vitamin BT, is a small hydrophilic molecule. Hydrophilicity of carnitine derives from two oxygen atoms of carboxyl group and one oxygen atom of hydroxyl group, which are able to create hydrogen bonds with water molecules. About ¾ of human body carnitine comes from the diet (mostly from red meat in adults and mother's milk in infants) (1, 2) and remaining ¼ is synthesized in the liver, kidney, brain (1, 3) and placenta (4). Carnitine nitrogen and hydroxybutyrate moiety are derived from protein-bound lysine (1). Protein-bound lysine is trimethylated during post-translational modification by protein-dependent methyltransferase using S-adenosylmethionine as a donor for the methyl groups (Fig. 1a). Trimethyllysine released from proteins in lysosomes (Fig. 1, 2), hydroxylated by ε-N-trimethyl lysine hydroxylase (dioxygenase) in the mitochondria (Fig. 1, 3b), is a substrate for the synthesis of carnitine by cytosolic enzymes: aldolase (Fig. 1, 4c), dehydrogenase (Fig. 1, 5d) and hydroxylase (Fig. 1, 6e) (1, 5). Human body carnitine is located mainly in skeletal and cardiac muscles (98%), the brain, liver and kidneys (1.5%) (Table I) (6,7). Carnitine is not degraded by human body metabolism but excreted via urine (Table I) (1, 5, 8-10), milk (5) or bile (5) as free carnitine or carnitine esters (1, 8, 9).

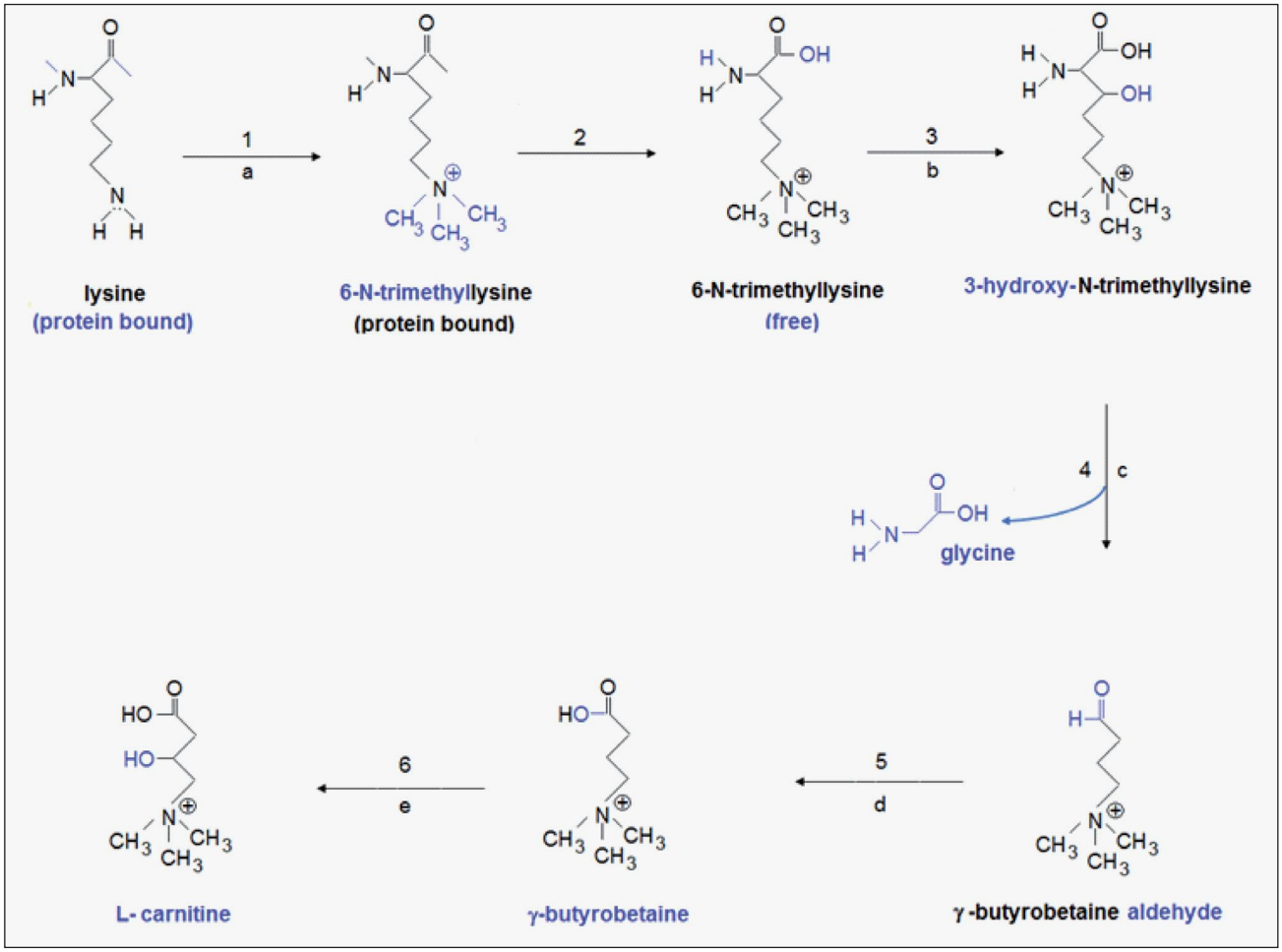

Fig. 1. Carnitine biosynthesis.

Enzymes: 1. S-adenosyl methionine: ε-N-lysine methyltransferase; **2.** Protease (lysosomes); **3**. ε-N-trimethyl lysine hydroxylase (mitochondria); **4.** β-hydroxy-ε-N-trimethyllysine aldolase (cytosol); **5.** γ-trimethylaminobutyraldehyde dehydrogenase (cytosol); **6.** γ-butyrobetaine hydroxylase.
Second substrates and products: a) S-adenosyl methionine → S-adenosyl homocysteine; b) 2-ketoglutarate + 0_2 →succinate + $C0_2$; d) NAD^+ → NADH + H^+; e) 2-ketoglutarate + 0_2 → succinate + $C0_2$.
Coenzymes: b) vitamin C, iron; **c)** pyridoxal phosphate; **e)** vitamin C, iron.

ROLE OF L-CARNITINE IN HUMAN METABOLISM

The main functions of carnitine in humans include: transport of FAs to the mitochondrial matrix and maintaining homeostasis of coenzyme A during mitochondrial oxidation of FAs (1), renal excretion of toxic exogenous (11) and non-toxic endogenous organic acids, catabolism of branched-chain ketoacids derived from branched-chain amino acids (2), inhibition of free radicals production (2, 12) and antioxidant action (2). Coenzyme A is necessary for activation and oxidation of the FAs from adipose tissue in the mitochondria for adenosine triphosphate, or ATP, synthesis. FAs oxidation reduced glucose oxidation in the tissues where glucose is not an essential fuel, and amino acid catabolism for gluconeogenesis and energy production (10). The yield of energy from total oxidation of FAs is 37.7 kJ/g as compared to 16.7 kJ/g from protein or carbohydrates. Blood free FAs released by adipocytes or derived from mother's breast milk are bound to serum albumins and transported to the tissues with high demand for energy, mostly skeletal and cardiac muscles. Some FAs enter target cells by passive transport, the majority of FAs enter cells by active transport mediated by three groups of transporters: integral membrane FAT/CD36 (FAs translocase /Cluster of differentiation 36), integral membrane FACS/ FATP (AcylCoA synthetase/FAs transport proteins) and FABPpm (Plasma membrane associated FAs binding protein) located at the external surface of cell plasma membrane (Fig. 2) (13, 14). FABPc (Cytoplasmic FAs binding proteins) are involved in intracellular transport of FAs (13, 14). In the skeletal and cardiac muscle, FAs are mainly oxidized in the mitochondria both via β-oxidation and in tricarboxylic acid (TCA) cycle, and some are stored in the cells as acylglycerols and phospholipids (14). Some long-chain

Table I. Carnitine in humans. AC - acylcarnitine, FC - free carnitine, TC – total carnitine.

Tissues					
Neonate (nmol of carnitine/mg noncollagen protein)					(16)
Muscle (birth weight): 8.4 ± 3.6 (≤ 1000 g); 14.0 ± 3.2 (≤ 1001-2500 g); 19.4 ± 2.6 (≥ 2500 g).					
Liver: 4.1± 1.5					
Heart: 4.7± 1.3					
Adults (µM)					(16)
Skeletal muscle: 2,000-4,600					
Heart: 3,500-6,000					
Brain: 200-500					
Plasma					
	TC (µM)	FC (µM))	AC (µM	AC/FC ratio	Reference
Preterm infants (28-34 gestational weeks)					
Day 1	24.3±12.4	16.0±9.8	11.5±1.0		(10)
Day 1(30-33wk)		43.0±5.6			(28)
Day 1 (33-36 wk)		37.5 ±3.1			(28)
Day 1 (≤ 36 wk)	29.0±1.8 (cord blood)				(36)
Day 1 (≤ 37 wk)	28.0±2.3	15.9±1.3	12.0±1.3		(34)
Day 7	33.0±33.0	19.1±15.6	11.0±8.3		(10)
Day 14	44.9±86.4	34.2±74.7	14.1±14.0		(10)
Day 28	44.6±17.7	32.8±14.5	13.2±19.7		(10)
	Low birth weight neonates				
Gestational age of 34.3±3.1 weeks and blood ammonium 62.9±3.8 µM:					
	29.5±8.5	16.5 ±5.4	12.9 ±4.8		(15)
Gestational age of 32.1±4.1 weeks and blood ammonium 38.9±8.4 µM:					
	29.1±10.7	20.7 ±3.1	8.4 ±4.0		(15)
Gestational age of 35.6±3.3 weeks and blood ammonium 24.5±2.9 µM:					
	33.7±5.4	25.5 ±3.2	8.2 ±4.6		(15)
	Healthy children/adults				
1 day	25.9 ±2.7				(5)
1 day		31.2±2.5			(28)
1 day (cord blood)	22.4±0.8				(36)
1 day (cord blood)	25.2±2.2	14.6±1.5	10.7 ±1.5		(34)
1 day	36.4±10.8	20.1 ±6.7	16.3 ±5.7	0.87 ±0.33	(11)
2-7 days	25.2±4.1	14.9 ±3.0	10.3 ±3.7	0.73±0.31	(11)
8-20 days	36.7±10.5	27.6 ±9.7	9.2 ±3.2	0.37 ±0.16	(11)
29 days - 1 year	47.6±7.7	35.5 ±6.5	12.0 ±3.1	0.35 ±0.10	(11)
1-6 years	54.4±9.9	41.7 ±7.9	12.8 ±5.9	0.32 ±0.16	(11)
2-5 years	47.7±6.3	45.6±5.1	7.1±3.6		(15)
6-10 years	56.2±11.4	41.4 ±10.0	14.7 ±6.0	0.38 ±0.19	(11)
12.6±5.4 years	50.0±10.3	37.1±6.1	12.9±6.8		(8)
10-17 years, boys	53.5±10.1	39.6 ±9.3	14.0 ±5.2	0.38 ±0.17	(11)
10-17 years, girls	53.2±8.9	39.3 ±8.1	13.9 ±5.1	0.37 ±0.16	(11)
Adult males	61.5±10.7	43.8 ±7.3	17.7 ±7.5	0.41 ±0.18	(11)
Adult females	46.1±9.3	34.2 ±7.1	12.0 ±5.2	0.36 ±0.15	(11)
Pregnant women	17.4±1.3				(5)

Table I. Cd.

Urine					
	Preterm infants (gestational age of 28-34 weeks)				
Day 1	25.5±16.0	13.6±11.2	12.9±12.0		(10)
Day 4	50.7±141	17.2±37.4	12.7±21.5		(10)
Day 7	39.8±43.2	25.6±34.4	14.3±12.2		(10)
Day 10	59.7±67.4	45.0±54.3	19.9±23.2		(10)
		Adolescents			
	TC (μM/g creatinine)	FC (μM/g creatinine)	AC (μM/g creatinine)		
12.6±5.4 years	187.3±126.6	111.3±88.3	76.0±38.0		(16)

FAs may be initially β-oxidized in peroxisomes, then transported as carnitine-bound to mitochondria, for final β-oxidation and TCA cycle (Fig. 2) (2). Short- and medium-chain FAs may be transported directly from blood to the mitochondrial matrix through cell membrane, cytoplasm and mitochondrial membranes (1). Long-chain FAs (with aliphatic tails of 14-24 carbons) require carnitine for their transport from the cytoplasm to the mitochondria (Fig. 2). In the cytoplasm of muscle cells, long-chain FAs bind with cytoplasmic CoA in a reaction catalyzed by FAs CoA synthase (FACS), creating long-chain FAsCoA which are not able to penetrate the inner mitochondrial membrane. Carnitine palmitoyltransferase I (CPT I) located at the outer mitochondrial membrane transfers long-chain FAs from FAsCoA to carnitine, releasing free CoA and creating long-chain FAs carnitine (FAcarnitine). FAcarnitine is translocated through the inner mitochondrial membrane to the mitochondrial matrix by carnitine FAs translocase (CFAT). Subsequently, carnitine palmitoyltransferase II (CPT II) located at the mitochondrial matrix side of the inner mitochondrial membrane transfers long-chain FAs from FAcarnitine to CoA located at mitochondrial matrix, creating FAsCoA complex and releasing free carnitine which may return to the cytoplasm for another cycle (5). In the mitochondrial matrix, FAsCoA are subjected to β-oxidation generating energy and acetylCoA, a substrate for the production of ketone bodies in the liver and substrate of mitochondrial TCA cycle for the ATP production in the liver and other tissues (5). The excess of acetylCoA, and short- and medium-chain acylCoAs (2) in the mitochondrial matrix is harmful for the macroorganism because it disturbs aerobic glycolysis by inhibiting mitochondrial pyruvate decarboxylase, an important enzyme for glycolysis. AcetylCoA, as well as short- and medium-chain acylCoAs also inhibit the activity of carbamyl phosphate synthetase (the first step in urea synthesis) (15). Harmful acetyl groups accumulated in the mitochondrial matrix , as well as short- and medium-chain acyls blocking CoA may be connected with carnitine by carnitine acetyltransferase (CAT) and removed from the mitochondrial matrix (and human body) as acetyl or short- and medium-chain acyls carnitine (Fig. 2). Acetylcarnitine is transported from skeletal or cardiac myocytes mitochondrial matrix to cytoplasm via inner mitochondrial membrane CFAT. Further, it may be transported to the cells of the nervous system where it may provide acetyl groups for the biosynthesis of neuronal acetylcholine that may be critical for the development of the neonatal brain (2). Body excess of short-chain (including acetate) and medium-chain FAcarnitine are excreted via urine (8, 9).

L-carnitine is also involved in the catabolism of endogenous organic acids (including ketoacids derived from branched-chain amino acids: valine, leucine, and isoleucine), and renal excretion of endogenous and exogenous acids derived from xenobiotics, such as some antibiotics and valproic and salicylic acids (2, 11). Complexes of branched-chain ketoacids with carnitine are transported to the liver, where they are oxidized or utilized as substrates for glyconeogenesis (2). It is worthy to mention that carnitine chelates cadmium, lead and ferric cations (2, 12), thus inhibiting free radical production. It has been suggested that anemia due to iron deficiency associated with hyperlipidemia may be related to iron chelation by carnitine (2).

Interestingly, carnitine α-carbon (Fig. 1) demonstrates antioxidant actions by scavenging free radicals and carnitine molecule effectively protects thiol groups of proteins against oxidative action of hydrogen peroxide and free radicals (2). Carnitine decreases peroxidative damage of the unsaturated FAs built into membrane phospholipids that stabilize cell membranes and ion canals (2). In neonates, carnitine seems to act as an inductor of pulmonary surfactant production by phospholipid repair activity (3).

ROLES OF CARNITINE IN NEONATES

Tissues

Like in adults (7), neonatal tissues carnitine concentration was highest in the skeletal muscles, lesser in heart and liver, but markedly lower than in adults (Table I) (16). Assuming that carbohydrates are the main fetal energy substrates, the importance of L-carnitine in fetal metabolism may be explained by carnitine regulation of glycolysis by stimulation

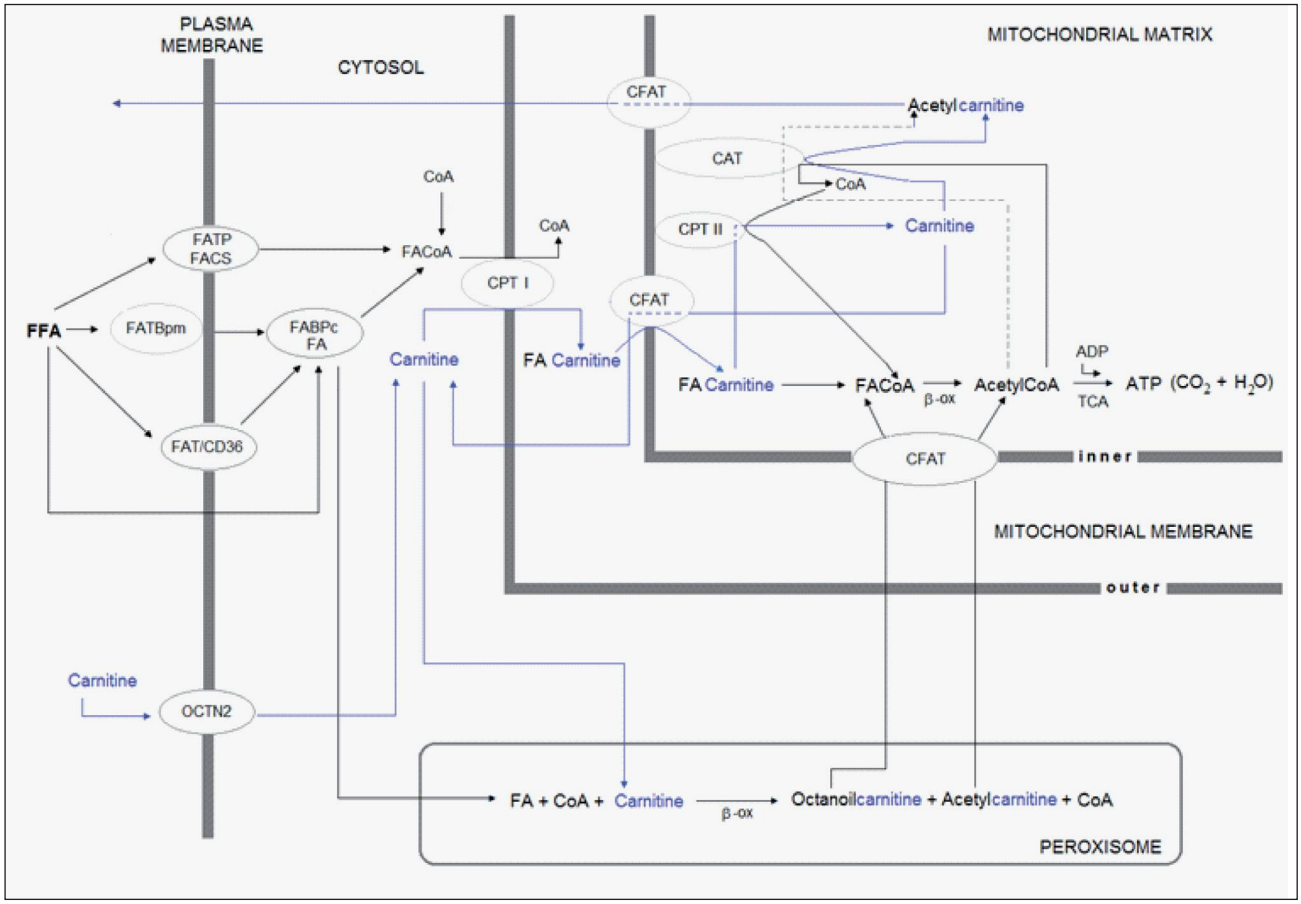

Fig. 2. Carnitine in fatty acids metabolism.

β-OX – β-oxidation; **CAT** – carnitine acetyltransferase; **CFAT** – carnitine fatty acids translocase; **CPT I** – carnitine palmitoyltransferase I; **CPT II** – carnitine palmitoyltransferase II; **CoA** – coenzyme A; **FA** – fatty acids; **FABPc** – fatty acids binding proteins (cytoplasmic); **FABPpm** – fatty acids binding protein (plasma membrane bound); **FAcarnitine** – fatty acids carnitine; **FACoA** – fatty acids coenzyme A; **FAT/CD 36** – fatty acids translocase/cluster of differentiation 36; **FATP/FACS** – fatty acids transport protein/fatty acids CoA synthetase; **FFA** – free fatty acids; **OCTN2** – sodium-ion dependent, high affinity human carnitine transporter; **TCA** – tricarboxylic acids cycle.

of pyruvate decarboxylase activity and mitochondrial respiratory chain (3). It is noteworthy that about 25% of energy necessary for the development of fetal brain is derived from FAs β-oxidation (3).

During parturition, endogenous energy sources such as fetal glycogen stores are substantially depleted. In this situation, newborns depend on an increased rate of FAs oxidation and ketogenesis (3). For instance, neonatal adaptation to a colder environment, rather than the intrauterine, strongly depends on the thermogenesis maintained by FAs derived from the brown fatty tissue and transported to the mitochondrial matrix by carnitine for oxidation (10). The amount of carnitine available for the neonate depends on endogenous synthesis, carnitine stores accumulated during intrauterine life, uptake from mother's breast milk and level of renal excretion. In premature infants, carnitine biosynthesis is limited. This limitation is a result of a low transport of 6-N-trimethyllysine to mitochondria (Fig. 1, 3b), low activity of cytoplasmic hydroxylase (Fig. 1, 6e), and deficiency of cofactors in carnitine biosynthesis (Fig. 1b,c,e) (3, 5). Some authors state that human milk is the principal source of carnitine (60-70 nmol/mL) for the neonate (5).

Fetal tissue carnitine increases in direct relation to gestational age and maximal placental carnitine transfer is far in excess of estimated carnitine requirements (3). Carnitine biosynthesis at early stages of life is less efficient than in adults (17) and immature infants have less carnitine tissue reserves than term infants (18). With the interruption of transplacental carnitine transport at birth, the premature infant depends on exogenous intake of carnitine as the neonatal carnitine biosynthesis is inadequate. Premature newborns of less than 34 weeks gestation requiring total parenteral nutrition develop nutritional carnitine deficiency with impaired FAs oxidation and ketogenesis (19). In newborns (16), similarly as in adults (6), tissue carnitine concentration has been found highest in the skeletal muscle, which correlated positively with gestational age and body dimensions. In contrast, liver and heart carnitine concentrations are lower than that in skeletal muscle (16).

Carnitine is involved in the production of pulmonary surfactant. At the end of gestation, in lungs of fetal rats striking

increases in main surfactant (complex of 90% lipids and 10% of lung-specific apoproteins), total phosphatidylcholine and dipalmitoylcholine (main surfactant components), and carnitine, as well as short-chain acylcarnitine content were found (20). It should be mentioned that dipalmitoyl phosphatidylcholine particularly lowers the surface tension in the alveoli (21). A deficiency in fetal lung surfactant is the primary cause of the respiratory distress syndrome (RDS), the most severe complication observed in preterm infants (20) and the most frequent cause of mortality of premature infants (21). Corticosteroids had proven to be effective for the stimulation of surfactant production and are accepted worldwide; however possible adverse effects on the mother and her fetus have led to the discussions about the use of corticosteroids. Compared with an untreated control group, treatment of rat mothers with L-carnitine resulted in significant lung increases in both total phospholipid and dipalmitoyl phosphatidylcholine (22). Furthermore, antenatal combination therapy with carnitine and betamethasone significantly reduces the necessary betamethasone dose, incidence of RDS and mortality of premature newborns (23). Decreased serum levels of carnitine in preterm infants with RDS during the first week of life may be caused by the increased consumption of carnitine in lung tissue for surfactant synthesis (24). In line, antenatal carnitine administration accelerates lung maturity by increasing pulmonary surfactant in both human and animal studies (25).

Plasma concentrations

Mother

Plasma carnitine concentration in pregnant women is substantially lower than in nonpregnant (Table I) (2, 5, 11). In comparison with maternal plasma, larger amounts of long-chain acylcarnitines were found in umbilical arterial plasma, and larger amounts of short-chain carnitines, mostly acetylcarnitine, in umbilical vein plasma (26). That may indicate that carnitine is a supplier of long-chain FAs to the fetus and a scavenger of harmful acetyl groups from the fetus. Similarly, maternal plasma concentrations of acylcarnitine were always lower than acylcarnitine concentrations in their milk, and premature infants mother's breast milk carnitine concentration was similar to mother's breast milk carnitine concentration of the term infants (27).

Full term neonates

Carnitine concentration variation in full term newborn blood was from 25.9±2.7 μmol/L (5) to 36.4±10.8 μmol/L (Table I) (11). In the first 2 weeks of life, free carnitine (FC) level showed a good correlation with age (28). In healthy breast-fed children, carnitine plasma concentration decreases after the first day of life, then subsequently increases reaching adult concentration at 6 months, and no further significant changes in plasma carnitine concentration and no sex-related differences are observed (Table I). The term neonates plasma carnitine and acylcarnitine (AC) strongly correlated with their umbilical cord plasma (29).

Carnitine and AC in blood of neonates are a useful tool in the diagnosis of type 1 diabetes (30), as well as the detection and monitoring of many inherited and acquired metabolic disorders (31). However, it should be taken into consideration that gestational age and age at sampling influence metabolic profiles in premature infants (32).

Preterm neonates

In very low birth weight infants (median 29 weeks/1210 g), a significant increase (in comparison to full term neonates) in the cord blood concentrations of butyryl-, isovaleryl-, hexanoyl- and octanoyl-carnitines was observed, thus suggesting enhanced short- and medium-chain FAs β-oxidation in human preterm feto-placental unit (33). Maternal-fetal gradients for these compounds were also increased in very low birth weight infants (33). Cord plasma levels of FC, AC, and total carnitine (TC) were significantly higher in preterm newborns in comparison with term newborns (34), but the total blood pool of FC and TC was significantly lower in preterm newborns than in term newborns (35). A positive correlation was found between FC, gestational age and birth weight. In addition, a positive correlation was found between AC and red blood cell count as well as hematocrit (35). The plasma carnitine and AC of the preterm neonates weighing less than 1500 g strongly correlates with maternal plasma carnitine and AC concentration (29).

There are divergent data in the reports on premature neonates blood carnitine concentration. Some papers report that postnatal concentrations of FC in blood and most AC were significantly higher in very preterm (gestational age, 22-27 weeks) and preterm (less or equal to 36 weeks) infants compared with term infants (Table I) (28, 34, 36). Other reports stated that preterm infants with (25) or without (37) RDS have significantly lower free plasma carnitine concentration than normal term babies.

The inability of preterm neonates to synthesize sufficient amounts of carnitine is clearly emphasized by the observation that their plasma concentration decreases when they are fed with carnitine-free nutrition (5). Some reports indicate that in premature newborns, when no exogenous carnitine is supplied, its plasma concentration rapidly decreases during the first three days of life (26, 37). After 5 days of parenteral nutrition without carnitine, premature infants had reduced plasma carnitine concentration in comparison to premature infants fed with milk with carnitine, an observation in support of insufficient carnitine synthesis in premature infants (17).

Urinary excretion of carnitine

Pregnancy increases woman's urinary loss of carnitine and reduces plasma carnitine concentration (38). Urinary excretion of FC per day is significantly lower in infants 0 to 3 years old and in children 3 to 10 years old than in adults (29). The carnitine pool of the human fetus mainly depends on the transplacental transport of carnitine and its precursors from maternal plasma (3) and on fetal renal carnitine excretion (5). There are differences of opinion concerning urinary excretion of carnitine. Some authors report that urinary excretion of FC and most of AC are significantly

higher in preterm infants (gestational age 22-27 weeks) compared with infants born at term (39), others state that renal excretion of carnitine is similar in both ill preterm and normal fetuses and increases with gestational age similarly to other excreted products (40). The third possibility is that premature infants have impaired reabsorption of carnitine and AC at the proximal renal tubules, which makes them dependent on exogenous supply (5).

CARNITINE SUPPLEMENTATION IN INFANTS

Carnitine supplementation was introduced based on observations that intravenous carnitine supplementation has little, if any, side effects (5) and the assumption that preterm infants are at risk for carnitine deficiency (10), caused by immaturity of synthesis, low renal carnitine reabsorption and delayed oral feeding (40). In 1985, it was reported that premature infants over 10 days old fed parenterally without carnitine developed lower carnitine levels in the heart, liver and kidneys than those 24 hours after birth. Infants receiving oral or intravenous carnitine had higher carnitine tissue reserves than those who did not (18). During oral supplementation of low birth weight premature infants, a fraction of supplemented carnitine was taken up by tissues and entered intermediary metabolism (41), promoting ketone body formation (5, 42, 43) and improving FA oxidation (44). Modest increases in growth and nitrogen accretion were reported after carnitine parenteral neonatal supplementation (5). In a case of preterm infant (24 weeks/799 g) fed with a medium-chain triacylglycerols, or MCT, formula from 30 to 100 days of life because of steatorrhea, who developed carnitine deficiency with hepatomegaly and liver damage (confirmed by needle biopsy) and high urinary loss of AC and dicarboxylic acids, carnitine treatment was effective (45). Borum and Bennet recommend carnitine supplementation in newborns who have propionic, methylmalonic or isovaleric acidemia and aciduria, and possibly other forms of organic aciduria (46) where carnitine is conjugated with abnormal metabolites and excreted via urine (5). A panel of pediatric neurologists recommended carnitine supplementation in childhood epilepsy associated with valproate-induced hepatotoxicity, in kidney-associated syndromes, and premature infants receiving total parenteral nutrition (47).

Authors of older reports (5, 18, 41-44, 46, 47) were quite enthusiastic about carnitine supplementation. Newer publications (48-52) raised some doubt. In 2006, carnitine supplementation was reported to increase plasma and red blood cells TC concentrations that had a positive effect on catch-up growth and may have improved periodic breathing in premature neonates, but did not improve respiratory, gastroesophageal and infectious morbidity or nitrogen balance (48). In a 2010 publication, L-carnitine-supplemented parenteral nutrition (10 mg/kg/day) improved fat metabolism but failed to support compensatory growth in premature infants (49). Earlier this year, Winter et al. reported that 82% of their infant patients weighing less than 5 kg were carnitine-deficient and should have been supplemented with carnitine, however there was no statistical correlation among carnitine levels, hypoglycemia and hyperglyceridemia (50). However, after having searched the main medical databases including the Cochrane database, Cains and Stalker found no evidence to support the routine supplementation of parenterally fed neonates with carnitine (51). Kumar et al. evaluated randomized trials from 1966 to 2004 on carnitine supplementation for prevention and treatment of preterm infants with recurrent apnea, and came to a conclusion that despite the plausible rationale for the treatment of prematurity apnea with carnitine, there are insufficient data to support carnitine use for this indication (52).

In conclusion, taking into account the complex metabolic role of cellular FAs transporters, further studies are needed on indications and contraindications for carnitine supplementation in different clinical settings during early developmental period.

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