Role of Carnitine in Lipid Metabolism

Peggy R. Borum

Departments of Food Science and Human Nutrition and Biochemistry, Gainesville, Florida 32611

A major function of lipids in modern nutrition is to serve as a substrate for production of metabolic energy. Mechanisms regulating the production of metabolic energy under a wide variety of physiological conditions are required for survival of the species. The critical role of carnitine in the production of energy from long-chain fatty acids is well recognized. As illustrated in Fig. 1, carnitine also has a role in the production of metabolic energy from several substrates in addition to long-chain fatty acids. Thus, adequate carnitine status and carnitine nutriture are essential in maintaining health (1).

ROLE OF CARNITINE IN β-OXIDATION OF LONG-CHAIN FATTY ACIDS

In the late 1950s and early 1960s, the role of carnitine in the transport of long-chain fatty acids into the matrix of the mitochondria was documented (2,3). Experimental work of the last 20 years has enhanced our knowledge of the role of carnitine palmitoyltransferase I, carnitine acylcarnitine translocase, and carnitine palmitoyltransferase II, as diagrammed in Fig. 2. The role of carnitine and the three proteins needed for transport of long-chain fatty acids into the mitochondrial matrix has been reviewed (4) and will not be repeated at this time. The discovery that malonyl CoA is an inhibitor of carnitine palmitoyltransferase I has added to our understanding of the coordinated metabolic regulation of fatty acid oxidation and fatty acid synthesis. Many questions remain concerning the regulation of the carnitine transport process during the normal physiological cycles of feasting and fasting as well as during a variety of disease states. Since the first description of human carnitine deficiency in 1973 (5), many carnitine deficient patients have been described with a wide variety of symptoms. In addition to patients with what appears to be a genetic carnitine deficiency, there are a large number of patients who have a carnitine deficiency that is secondary to their primary disease. Our understanding of the carnitine transport system for long-chain fatty acids allows us to explain some of the symptoms that appear to be the result of impaired fatty acid oxidation. However, many of the symptoms are unexpected, and we have diffi-
The role of carnitine in the production of metabolic energy from a variety of substrates is illustrated in FIG. 1. It is usually assumed that medium chain fatty acids are oxidized via a carnitine independent pathway. In fact, dietary medium chain triglycerides have been suggested as a nutritional intervention modality to bypass the carnitine transport mechanism in patients at risk for impaired carnitine status. However, more than a decade ago Groot and Hulsmann (6) demonstrated that the oxidation of octanoate by rat skeletal muscle mitochondria required carnitine. Data from several investigators (4) indicate that the requirement for carnitine results from the activation of octanoate to the coenzyme A level outside the inner mitochondrial membrane barrier.
FIG. 2. Role of carnitine in the β-oxidation of long-chain fatty acids in the mitochondria.
as diagrammed in Fig. 3. In skeletal muscle, the activation of both long-chain fatty acids and medium-chain fatty acids appear to be catalyzed by the same enzyme at a site exterior to the inner mitochondrial membrane. Thus, utilization of either palmitate or octanoate as an energy source by skeletal muscle requires carnitine for transport of the acyl coenzyme A moiety into the mitochondrial matrix.

A vast quantity of data support the carnitine independent oxidation of octanoate by hepatic tissues. However, a recent report by Otto (7) suggests that when the ATP/ADP ratio is decreased, octanoate oxidation by either hepatocytes or mitochondria isolated from hepatic tissue is shifted from an almost total reliance upon a carnitine independent pathway to an increased reliance upon a carnitine dependent pathway. The data indicate that this increased reliance of octanoate oxidation upon a carnitine dependent pathway reflects an increased reliance upon extramitochondrial activation of octanoate. Although the exact mechanism for the inhibition of intramitochondrial fatty acid activation by a depressed extra- or intramitochondrial ATP/ADP ratio is unknown, the author has proposed two hypotheses (7). First, some metabolite or other unknown factor, the level of which is determined by the ATP/ADP ratio, might directly inhibit the matrix medium-chain fatty acyl CoA synthetase. Second, the inhibition of this enzyme may result from a decreased availability of the intramitochondrial ATP required for fatty acid activation, as a consequence of the reduced intramitochondrial ATP/ADP ratio and/or the rapid transport of extramitochondrial ATP in exchange for intramitochondrial ADP.

Many questions remain to be answered concerning the role of carnitine in the oxidation of medium-chain fatty acids. However, available data demonstrate that in the clinical setting we can no longer assume that nutritional support of patients with medium-chain triglycerides will be successful, regardless of the carnitine status of the patient. Similarly, in the biochemical laboratory we can no longer routinely use octanoate in comparison with long-chain fatty acids to distinguish between metabolic effects occurring before or after the carnitine dependent steps of fatty acid oxidation.

ROLE OF CARNITINE IN PEROXISOMES

β-Oxidation of long-chain fatty acids occurs in peroxisomes as well as in mitochondria. The peroxisomal β-oxidation system oxidizes saturated and unsaturated acyl CoAs with chain lengths from 7 to 22 or more carbons. The β-oxidation system of peroxisomes differs from the β-oxidation system of mitochondria in several ways. The enzymes that catalyze the reactions of the β-oxidation process in mitochondria differ from the enzymes that catalyze the reaction of β-oxidation in peroxisomes. The intermediates of the β-oxidation process in the two locations also differ (8). Carnitine functions in the mitochondrial β-oxidation process by transporting into the mitochondria long-chain acyl CoA moieties formed in the cytoplasm. In contrast to mitochondria, peroxisomes have a significant capability to activate long-chain fatty acids to the coenzyme A level. As a result, the free long-
FIG. 3. Role of carnitine in the β-oxidation of medium-chain fatty acids in the mitochondria.
chain fatty acids enter the peroxisomes and are activated within the peroxisomal interior. Peroxisomes contain carnitine octanoyltransferase of a high specific activity and with peak specific activities for 5 to 8 carbon acyl CoA derivatives with gradually decreased activity for longer chain acyl CoA derivatives (9). Evidence is mounting to support involvement of carnitine in shuttling acetyl residues and medium chain acyl residues out of the peroxisome. Thus, a long-chain fatty acid enters the peroxisome in a carnitine independent manner and is shortened to several acetyl CoA moieties and a medium-chain CoA moiety that are transported out of the peroxisome in a carnitine-dependent manner (Fig. 4).

ROLE OF CARNITINE IN KETONE BODY METABOLISM

Ketone bodies are a critically important source of metabolic energy during extended periods of little or no carbohydrate intake. However, uncontrolled ketogenesis leads to ketoacidosis and death. Thus, the inability to initiate ketogenesis or to discontinue ketogenesis results in severe pathophysiological consequences.

Hepatic ketogenesis is known to be stimulated by increased hepatic carnitine concentration and decreased malonyl CoA concentration (10,11). The physiological control mechanism increasing the hepatic carnitine concentration remains unidentified. Whether or not the increased carnitine has any effect in addition to that of increasing the concentration of a substrate for carnitine palmitoyltransferase I

FIG. 4. Role of carnitine in the oxidation of fatty acids in peroxisomes.
also remains uncertain. Elucidation of the role of carnitine in the production of ketone bodies, utilization of ketone bodies, and the interrelationship of ketogenesis and gluconeogenesis are exciting areas for further research.

**ROLE OF CARNITINE IN THE PRODUCTION OF ENERGY FROM AMINO ACIDS**

Although amino acids are not generally considered a major energy source, they may become a significant energy source during periods of catabolism. The branched-chain amino acids have been proposed as a good energy source for peripheral tissues during a variety of metabolic stresses. The nitrogen moiety can be transaminated to keto acids such as pyruvate to form alanine. The alanine is transported to the liver where the amino group is metabolized to urea for excretion, and the carbon chain is metabolized to glucose for use as an energy source in a variety of tissues. The keto acids of the branched-chain amino acid can then be utilized for metabolic energy by a process that is stimulated by carnitine (12,13). The mechanism of stimulation remains to be completely elucidated but appears to involve the conversion of a CoA metabolite to a carnitine linked metabolite that is transported out of the mitochondria and leaves behind free coenzyme A (14,15) to be utilized in the continued metabolism of the branched-chain keto acids for metabolic energy. It is easy to speculate that during a carnitine deficiency the catabolism of branched-chain keto acids may be slowed, which may in turn affect the transamination step and possibly impact upon the glucose alanine cycle. Such speculations begin to implicate carnitine having a role in the production of metabolic energy involving pathways usually associated with carbohydrate and protein metabolism.

**ROLE OF CARNITINE IN THE PRODUCTION OF ENERGY FROM PYRUVATE**

Pyruvate is an excellent source of metabolic energy and can itself be derived from either carbohydrate sources or amino acids. The utilization of pyruvate for energy is modulated by the activity of the pyruvate dehydrogenase complex. The regulation of the pyruvate multienzyme complex has been investigated in complex metabolic preparations under a variety of different metabolic states. The regulatory process appears to vary with different types of tissues and under different physiological conditions. The ratio of free coenzyme A to coenzyme A bound to fatty acids, branched-chain keto acids, or short-chain organic acids exerts regulatory control on the activity of pyruvate dehydrogenase (16–18). Since carnitine in turn influences the ratio of free coenzyme A to bound coenzyme A, carnitine has a role in the production of metabolic energy from pyruvate. Once again carnitine’s role in energy metabolism involves carbohydrate and protein sources for metabolic energy in addition to its better known role in the production of metabolic energy from lipid sources.
CONCLUSIONS

A more detailed understanding of the critical role of carnitine in regulating the production of metabolic energy from lipid sources is emerging. Carnitine also has a regulatory role in the production of metabolic energy from protein and carbohydrate sources. The role of carnitine in the integrated regulation of the production of metabolic energy from all fuel sources is probably of greater physiological consequence than has been realized in the past.

REFERENCES