Prevention of Ammonia and Glutamate Neurotoxicity by Carnitine: Molecular Mechanisms

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Carnitine has beneficial effects in different pathologies and prevents acute ammonia toxicity (ammonia-induced death of animals). Acute ammonia toxicity is mediated by excessive activation of the NMDA-type of glutamate receptors, which mediates glutamate neurotoxicity. We showed that carnitine prevents glutamate neurotoxicity in primary cultures of cerebellar neurons. This supports the idea that the protective effect of carnitine against ammonia toxicity is due to the protective effect against glutamate neurotoxicity. We are studying the mechanism by which carnitine protects against glutamate neurotoxicity. Carnitine increases the binding affinity of glutamate for metabotropic glutamate receptors. The protective effect of carnitine is lost if metabotropic glutamate receptors are blocked with specific antagonists. Moreover, activation of metabotropic glutamate receptors by specific agonists also prevents glutamate neurotoxicity. This indicates that the protective effect of carnitine against glutamate neurotoxicity is mediated by activation of metabotropic glutamate receptors. The molecule of carnitine has a trimethylamine group. Different compounds containing a trimethylamine group (carbachol, betaine, etc.) also prevent ammonia-induced animal death and glutamate-induced neuronal death. Moreover, metabotropic glutamate receptor antagonists also prevent the protective effect of most of these compounds. We summarize here some studies aimed to identify the mechanism and the molecular target that are responsible for the protective effect of carnitine against ammonia and glutamate neurotoxicity. Finally it is also shown that carnitine inhibits the hydrolysis of inositol phospholipids induced by activation of different types of metabotropic receptors, but this effect seems not responsible for its protective effects.

Key words: Carnitine; ammonia; neurotoxicity; glutamate; phospholipid hydrolysis.

L-CARNITINE: FUNCTIONS AND DEFICIENCIES

L-Carnitine is an endogenous molecule important in mammalian metabolism. L-Carnitine, in plasma or tissues, is present in free form or bound to fatty acids as acyl-L-carnitine derivatives.

L-Carnitine metabolism attracted more attention with the discovery of the first L-carnitine deficiency syndrome. The main function of L-carnitine is to facilitate the transport of long-chain fatty acids into the mitochondria, where they are used for fatty acid oxidation. L-Carnitine also modulates the intramitochondrial coenzyme A (CoA)/acyl-CoA ratio and facilitates the removal of short- and medium-chain fatty acids accumulating in

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mitochondria as a result of normal or abnormal metabolism. Alteration of these processes
impairs energy production and causes accumulation of triglycerides. The clinical conse-
quences of L-carnitine deficiencies include metabolic encephalopathy, lipid storage myopa-
thy, or cardiomyopathy (Breningstall, 1990; Carter, 1992; Fritz, 1959).

L-Carnitine is acylated by L-carnitine acyltransferases (e.g. palmitoyltransferase) and
it is transported into the mitochondrial matrix by L-carnitine translocases, which exchange
L-carnitine with acyl-L-carnitine. In the mitochondrial matrix, acyl-L-carnitine is used to
form acyl-CoA by acyltransferases (Fritz, 1959; Haeckel et al., 1990).

Primary genetic disorders of L-carnitine metabolism are due to inherited enzyme defi-
ciencies, for example, carnitine palmitoyltransferase (CPT I or CPT II) deficiencies. Sec-
ondary deficiencies (reduction in plasma concentration) may be due to a number of condi-
tions affecting intermediary metabolism: organic acidemias, inherited fatty acid oxidation
disorders due to deficiencies in enzymes or proteins involved in mitochondrial β-oxidation
or respiration or in the urea cycle. Some nongenetic disorders also result in reduced plasma
L-carnitine, for example, AIDS, chronic haemodialysis, or treatment with sodium valproate
or with antibiotics that contain pivalic acid. In most cases carnitine deficiency is associated
with hyperammonemia (Breningstall, 1990; Haeckel et al., 1990; Walter, 1996).

**THERAPEUTIC EFFECTS OF L-CARNITINE**

L-Carnitine treatment has been used in inherited and acquired disorders to restore L-
carnitine levels. Propionyl-L-carnitine administration has been used as a therapy for ischemic
heart. In both ischemic heart and ischemic brain there is a reduction in L-carnitine, and L-
carnitine treatment overcomes this deficit (Calvani et al., 1999; Leipala et al., 1991). Diabetic
patients show L-carnitine deficiency in myocardium and impaired cardiac function. This
alteration is improved by propionyl-L-carnitine treatment (Paulson et al., 1992). Treatment
with L-carnitine causes benefits also in cases of skeletal muscle ischemia (Hülsmann, 1997).

L-Carnitine therapy has also been used in neurological diseases, such as encephalo-
pathies associated with mitochondrial myopathies (Campos et al., 1993), brain ischemia
(Matsuoka, 1992; Slivka et al., 1990), hepatic encephalopathy (Therrien et al., 1997), and
Alzheimer’s disease (Scorizziello et al., 1997). The therapeutic use of L-carnitine in AIDS
has also been recently reported (Raulin, 2000).

**L-CARNITINE PREVENTS AMMONIA TOXICITY**

Hepatic encephalopathy is one of the main causes of death in Western countries. Hyper-
ammonemia is considered one of the main factors responsible for hepatic encephalopathy.
Elevated levels of ammonia accompany a number of human diseases, such as cirrhosis and
acute liver failure, inborn errors of the urea cycle, and Reye’s syndrome (acute hepato-
cerebral dysfunction). Reye’s-like syndrome is also induced by valproate, an anti-epileptic
drug that may cause hepatotoxicity, hyperammonemia, hypoketonemia, and a decrease of
L-carnitine levels. L-Carnitine treatment of patients with valproate-induced hepatotoxicity
restores plasma ammonia levels and improves hepatic function (Bohan et al., 2001; Böhles
et al., 1996).