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Review Article

Protection of the Brain by Carnitine

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Abstract: Protection of the Brain by Carnitine: Hideki IGISU, *et al.* Department of Environmental Toxicology, Institute of Industrial Ecological Sciences, University of Occupational and Environmental Health—Carnitine (β-hydroxy-γ-trimethylammonium butyrate) is widely distributed in the body including the nervous system. Its physiological function, viz. a carrier of long-chain fatty acids through the inner mitochondrial membrane, has been well established. In this review, mainly based on our experiments, we discuss the possibility that carnitine may have effects other than the "physiological" function and that it may be a potent protector of the brain. When mice were exposed to ammonia (intraperitoneal injection of ammonium acetate), they developed seizures and concentrations of brain energy metabolites were altered; ATP and phosphocreatine decreased while ADP, AMP, pyruvate and lactate increased. The seizures and changes in brain energy metabolites were clearly suppressed when the mice were pre-treated with carnitine. Furthermore, changes in energy metabolites in the brain caused by severe ischemia (decapitation) were also suppressed by carnitine. Since D-carnitine showed similar effects as those of L-carnitine, the effects seem due to function(s) of carnitine yet to be defined. Intrinsic substances including carnitine appear to deserve further studies for possible use in protecting the brain.
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Key words: Carnitine, Neurotoxicity, Brain protection

Protection of the brain is of great importance because its functions may be lost permanently once it is damaged to a certain degree. However, there seem to be mechanisms or structures in and around the brain which protect it. For instance, the skull and meninges may protect the brain from physical hazards. Cerebrospinal fluid which "suspends" the central nervous system may work as a "shock absorber". Indiscriminate entrance of chemicals into the brain from blood may be blocked by the blood-brain barrier.

There may also be metabolisms or intrinsic substances which can protect the brain. To find these and their mechanisms, if any, may provide clues to help in protecting the brain efficiently, especially from toxic chemicals. Here, we discuss two such substances—taurine and carnitine—mainly the latter, based on our findings.

Taurine

Taurine is a sulfur-containing amino acid ($H_2NCH_2CH_2SO_3H$) with a molecular weight of 125.1. It is present in a free form in various tissues including the nervous system. Although its role as a neurotransmitter has been considered, taurine is different from others in that the content in the brain decreases with development while the levels of neurotransmitters usually increase with maturing of the nervous system. The physiological functions of this amino acid in the brain therefore remain obscure. A number of experiments showed that taurine could suppress seizures whether they were induced by ouabain in rats or by pentylenetetrazole in mice when taurine was injected into the ventricles of the brain (Fig. 1)[1,2]. Since such anti-epileptic effects could not be seen when it was administered peripherally (e.g. intraperitoneally), taurine may not be used clinically unless practical methods are found to increase its levels in the brain. However, the above findings clearly indicate that there is an intrinsic substance that has the potential to protect the brain at least from chemically induced seizures.

Carnitine

Carnitine[3,4] was first found in muscles early in

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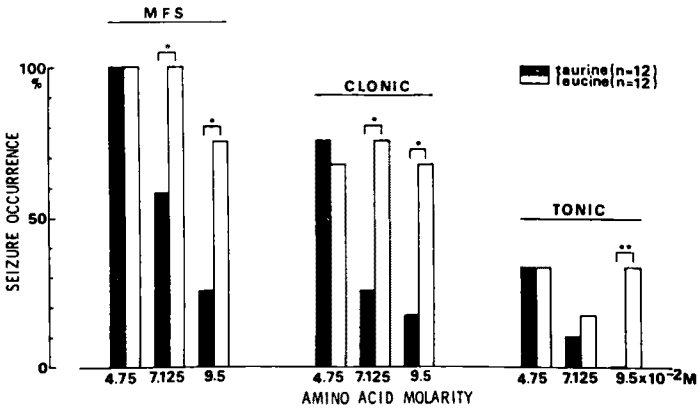
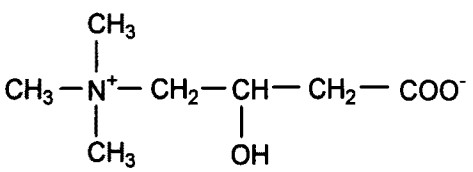
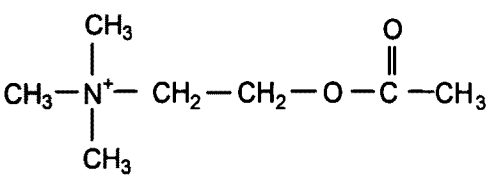


Fig. 1. Effects of amino acids (taurine and leucine) on occurrence of pentylenetetrazole(PTZ)-induced seizures. Seizure occurrence indicated as a percentage of the total number of animals that had seizures (MFS-minimal full seizure, CLONIC-clonic seizure, and TONIC-tonic seizure) during a 10-minute observation period following PTZ injection (Ref. 1).

this century and its structure was determined in 1927. Recognition of the neurophysiological function of acetylcholine stimulated physiological and pharmacological studies in the 1930s because the structure of carnitine is similar to that of acetylcholine (Fig. 2). Nevertheless, the studies did not disclose the physiological roles of carnitine. In the 1950s, carnitine was discovered to be an essential growth factor for Tenebrio moliter. (Hence, carnitine is sometimes called vitamin B_T after Tenebrio. Strictly speaking, however, carnitine cannot be called a vitamin, because humans can synthesize



Carnitine



Acetylcholine

Fig. 2. Carnitine compared with acetylcholine.

it.) Furthermore, it was found that carnitine accelerated oxidation of fatty acids in liver homogenate. These findings led to the discovery of the physiological function of carnitine: an essential carrier of long-chain fatty acids through the inner membrane of mitochondria (Fig. 3). This physio-

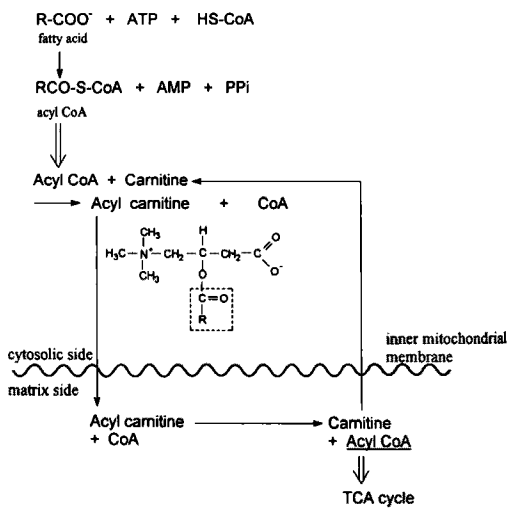


Fig. 3. Activation of the fatty acid and the function of carnitine. The fatty acid is first activated, i.e., thioester linkage is formed between the carboxyl group of a fatty acid and the sulfhydroxyl group of CoA (formation of acyl CoA). The acyl group is then transferred from the sulfur atom of CoA to the hydroxyl group of carnitine to form acyl carnitine. The acyl carnitine is shuttled across the inner mitochondrial membrane. The free carnitine returns to the cytosolic side in exchange for acyl carnitine.

logical function of carnitine has been firmly established since then.

Carnitine is widely distributed in the body and it is present in the brain[5] as well. Enzymatic activities essential for the synthesis of carnitine were found in the brain[6]. Carnitine was found to be taken up by the brain irrespective of the route of administration[7] but the role of carnitine in the brain is unknown because the brain utilizes glucose, not fatty acids, as the oxidative substrate for the production of energy (ATP).

Carnitine and toxicity of ammonia

Ammonia is one of the most commonly used chemicals in industry. Because of its toxicity, ammonia has been classified as a "specified chemical substance" (class 3) in Japan. Permissible exposure limits in the air are: 25 ppm (the value adopted by the Japan Association of Industrial Health[8]), 25 ppm as the time-weighted average and 35 ppm as the short-term exposure limit (American Conference of Governmental Industrial Hygienists[9]). On the other hand, ammonia is believed to play a major role in the pathogenesis of brain dysfunctions in several disorders associated with hyperammonemia including hepatic failure, inborn errors of the urea cycle function and Reye's syndrome[10]. Hence, ammonia may be regarded as an intrinsic neurotoxin as well as an extrinsic toxin. O'Connor and his colleagues first reported that carnitine suppressed the toxicity of ammonia in mice[11,12] but contradictory results have also been presented[13,14]. Moreover, if the findings of O'Connor *et al.* are correct, the mechanisms of the effects of carnitine in suppressing the toxicity of ammonia are not clear.

The mechanism of the neurotoxicity of ammonia itself has not been fully clarified. It is known that ammonia can inhibit some enzymatic activities in the TCA cycle and that it activates phosphofructokinase, one of the rate limiting enzymes in glycolysis[10]. Bates *et al.*[15] showed by means of nuclear magnetic resonance spectroscopy, that energy metabolism was impaired *in vivo* in rats with hyperammonemia associated with hepatic failure caused by carbon tetrachloride. We directly induced hyperammonemia in mice by injecting ammonium acetate intraperitoneally (i. p.) and measured the energy metabolites in the brain by chemical (enzymatic) methods. Our findings[16] were consistent with those of Bates *et al.*[15] In addition, we analyzed the behavior of the animals with hyperammonemia by recording it on a video tape. In this way, we examined effects of carnitine in hyperammonemia clinically as well as biochemically. It should be noted, however, that the doses of ammonium acetate we used in our experiments were much higher than the ammonia concentration to which humans are possibly exposed in occupations or in the general environment.

Suppression of ammonia-induced seizures by carnitine

When mice were given a high dose of ammonium acetate (>15 mmol/kg body weight, i.p.), they developed seizures. On administration of L-carnitine (i.p.) 30 min prior to ammonium acetate, the latency to the first fit was prolonged and the frequency of seizures during the observation period (10 min) was significantly decreased (Fig. 4)[17]. Our results therefore indicated that L-carnitine was effective clinically against ammonium-induced seizures in mice.

In previous studies including that of O'Connor *et al.*, the clinical effectiveness of carnitine was judged mainly by the mortality rate[11-14]. The use of such a "gross" criterion may have underlain the inconsistencies of the results. However, our results based on detailed analysis of behavior recorded on a video tape showed that L-carnitine did suppress seizures caused by hyperammonemia[17]. Our results did not show any effect of carnitine on the mortality rate. This may have reflected the shortness of the observation period in our experiments.

Effects on energy metabolites in the brain

As mentioned earlier, hyperammonemia causes alterations in the levels of energy metabolites in the brain: phosphocreatine, ATP and ECP (energy charge potential) decrease while ADP, AMP and lactate increase. These changes were suppressed by L-carnitine (Table 1). In addition, increase in ammonia in the brain was suppressed[17].

Previous results of biochemical analysis of the

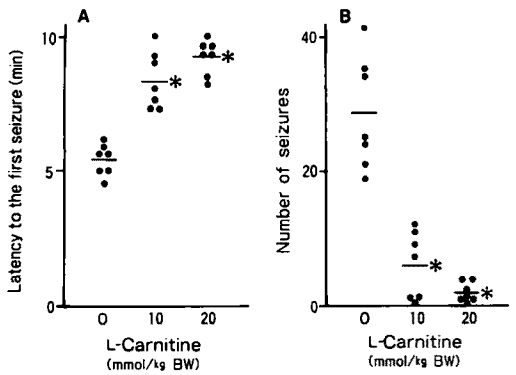


Fig. 4. Effects of L-carnitine on ammonium-induced seizures (Ref. 17).

effects of carnitine in ammonium intoxication are not consistent[12-14]. This also seems at least partly due to technical problems. The brain must be processed appropriately not only for accurate determination of phosphate compounds (ATP, ADP, AMP and phosphocreatine) but for the measurement of lactate and ammonia. Lactate in the brain increases by more than 300% within 15 seconds when the brain is left on ice[18]. The brain ammonia concentration also increases rapidly after decapitation[19,20]. In previous experiments attention was not necessarily paid to these aspects[12-14]. For instance, in some, the brain was frozen after it was removed from the skull. In our study, the whole body of a small animal (mouse) was rapidly frozen in liquid nitrogen (freeze clamp). Furthermore, the tissue was homogenized in liquid nitrogen and extracted at low temperature (−15 °C).

A close correlation was found between seizure activities and ATP concentrations in the brain, and ATP concentrations decrease under prolonged seizures[21]. We therefore examined the effects of L-carnitine in mice with hyperammonemia not so severe as to cause seizures, and found that here

Table 1. Effects of L-carnitine on brain energy metabolites in ammonium intoxication

	Control	L-Carnitine (mmol/kg b. wt.)		
		0	10	20
	(group I)	(group II)	(group III)	(group IV)
Ammonia	0.48±0.07	5.95±0.28[a]	3.38±0.22[a,b]	3.08±0.25[a,b]
Phosphocreatine	3.42±0.11	2.33±0.12[a]	3.38±0.09[b]	3.74±0.05[b]
ATP	2.72±0.10	2.21±0.09[a]	2.77±0.07[b]	2.63±0.08[b]
ADP	0.574±0.023	0.706±0.036[a]	0.578±0.024[b]	0.536±0.013[b]
AMP	0.049±0.006	0.239±0.027[a]	0.081±0.015[b]	0.042±0.007[b]
ECP	0.899±0.005	0.815±0.010[a]	0.892±0.008[b]	0.903±0.002[b]
Creatine	7.42±0.17	8.43±0.28[a]	7.52±0.19[b]	7.13±0.17[b]
Glucose	2.05±0.11	1.61±0.16	1.64±0.13	1.70±0.14
Pyruvate	0.104±0.011	0.107±0.002	0.103±0.010	0.098±0.009
Lactate	1.82±0.09	4.48±0.20[a]	3.85±0.11[a,b]	3.21±0.15[a,b,c]
Lactate/pyruvate	18.5±1.8	41.7±1.5[a]	39.4±3.6[a]	34.4±3.9[a]

All values are expressed in terms of μmol/g tissue (wet wt.) except for ECP (([ATP] +1/2[ADP])/([ATP] +[ADP] +[AMP])). Controls (group I) were injected with saline solutions only.
Animals in other groups were injected with saline solution containing no carnitine (group II) or carnitine (groups III and IV), and then with 15 mmol ammonium acetate/kg b. wt. Data are the mean±S.E.M. values for 7 animals.
[a] Significantly different from group I ($P<0.05$). [b] Significantly different from group II ($P<0.05$). [c] Significantly different from group III ($P<0.05$). (Ref. 17).

Table 2. Effects of L- and D-carnitine on brain energy metabolites in intoxication with lower dose of ammonia

		Treatmentment before ammonium acetate injection		
	Control	Saline	L-Carnitine	D-Carnitine
	(N=6)	(N=15)	(N=9)	(N=7* or 8)
	Group I	Group II	Group III	Group IV
Ammonia	0.48±0.09	3.13±0.08[a]	2.04±0.15[b]	2.88±0.17
Phosphocreatine	3.47±0.11	3.31±0.07	3.81±0.05[b]	3.63±0.10[b]
ATP	2.74±0.11	2.69±0.06	2.99±0.06[b]	2.73±0.07
ADP	0.585±0.024	0.568±0.016	0.515±0.021	0.545±0.019
AMP	0.046±0.007	0.112±0.010[a]	0.073±0.007[b]	0.094±0.009
ECP	0.899±0.006	0.882±0.005	0.908±0.003[b]	0.891±0.005
Creatine	7.35±0.18	7.48±0.09	7.38±0.14	7.06±0.22
Pyruvate	0.110±0.010	0.120±0.005	0.100±0.007	0.111±0.011
Lactate	1.83±0.11	3.39±0.08[a]	2.62±0.14[b]	3.23±0.18*
Lactate/pyruvate	18.9±2.1	28.8±1.3[a]	26.9±1.7	30.8±3.3*

All values are expressed in terms of μmol/g brain (wet wt.) except for ECP. Each value represents the mean ±S.E.M.
Controls (group I) were injected with saline solutions only. Animals in other groups were injected with saline solution containing no carnitine (group II) or carnitine (groups III and IV), and then with ammonium acetate (12 mmol/kg b.wt.) which caused no seizures.
[a] Significantly different from group I ($P<0.05$). [b] Significantly different from group II ($P<0.05$). (Ref. 22).

again carnitine was effective in maintaining the concentrations of energy metabolites (Table 2)[22], showing that the above results (Table 1) were not secondary to the inhibition of seizures.

Effects on ammonia concentration

The effects of L-carnitine in intoxication with ammonia were apparently systemic because L-carnitine lowered the ammonia concentration not only in the brain but also in the blood (Table 3)[17]. Some investigators suggested dilution of ammonia in the peritoneal cavity[14]. Since the control animals were given the same amount of physiological saline in our experiments, the effects of simple dilution could be ruled out, but our results did not rule out dilution due to osmosis by carnitine or suppression of absorption of ammonia in the peritoneal cavity. However, Bobyleva-Guarriero *et al.*[23] showed that L-carnitine significantly ameliorated mitochondrial dysfunction in hyperammonemia compared with controls treated with 0.6 M NaCl. Moreover, O'Connor *et al.*[7] reported that L-carnitine was effective in hyperammonemia whether it was administered intramuscularly or subcutaneously. The "osmoprotective hypothesis"[24] was therefore not substantiated.

It has been shown that L-carnitine can activate the hepatic urea cycle[25,26], the major system which removes ammonia from the body. And this might underlie the systemic effect of carnitine. Although the urea concentration was similar in the animals treated with carnitine and the controls in our experiments[27], it did not negate differences in the turnover rate in the cycle. In the brain, ammonia is removed mainly in astrocytes by amidation of glutamate to glutamine, catalyzed by glutamine synthetase[10] which requires ATP. It is therefore possible that the improved energy metabolism (by carnitine) further stimulated ammonia-removing system in the brain.

Effects on cerebral ischemia

As carnitine could prevent the impairment of brain energy metabolism caused by ammonia, the question was raised whether carnitine is effective for the prevention of a change in energy metabolism due to a more direct cause, that is ischemia. To our knowledge, this had not been examined before.

When a mouse was decapitated and the head was freeze-clamped after being left on ice, the concen-

Table 3. Effects of L-carnitine on blood ammonia concentration (μmol/ml)

Control	L-Carnitine (mmol/kg b. wt.)		
	0	10	20
(group I)	(group II)	(group III)	(group IV)
0.06±0.00	4.18±0.18[a]	2.48±0.16[a,b]	2.36±0.16[a,b]

Controls (group I) were injected with saline solutions only. Animals in other groups were injected with saline solution containing no carnitine (group II) or carnitine (groups III and IV), and then with 15 mmol ammonium acetate/kg b. wt. Data are the mean±S.E.M. values for 8 animals.

[a] Significantly different from group I ($P<0.01$). [b] Significantly different from group II ($P<0.01$). (Ref. 17).

Table 4. Effects of ischemia and L-carnitine on brain energy metabolites in mice

	No ischemia		Ischemia for 15 seconds		Ischemia for 30 seconds	
	Control	L-Carnitine	Control	L-Carnitine	Control	L-Carnitine
Phosphocreatine	3.10±0.10(8)	3.49±0.07(8)*	1.04±0.06(9)	1.31±0.06(9)*	0.51±0.03(8)	0.66±0.04(8)*
ATP	2.69±0.08(8)	2.85±0.07(8)	1.92±0.08(9)	2.23±0.08(9)*	1.20±0.10(8)	1.51±0.08(8)*
ADP	0.598±0.031(8)	0.569±0.020 (8)	0.829±0.035(9)	0.772±0.019(9)	0.856±0.051(8)	0.852±0.016(7)
AMP	0.063±0.007(8)	0.057±0.007(8)	0.414±0.037(9)	0.312±0.037(9)	1.044±0.060(8)	0.828±0.076(8)
ECP	0.892±0.006(8)	0.902±0.003(8)	0.738±0.013(9)	0.789±0.014(9)*	0.524±0.020(8)	0.610±0.024(7)*
Creatine	7.30±0.14(8)	7.09±0.18(8)	9.35±0.21(9)	9.48±0.18(9)	10.73±0.11(8)	10.55±0.12(8)
Pyruvate	0.127±0.004(7)	0.094±0.004(6)*	0.146±0.005(9)	0.134±0.005(9)	0.128±0.015(7)	0.140±0.010(8)
Lactate	1.81±0.12(7)	1.71±0.10(7)	6.26±0.37(9)	6.49±0.24(9)	6.84±0.18(8)	6.61±0.22(8)
Lactate/pyruvate	13.6±0.6(6)	18.3±2.2(6)	43.2±2.7(9)	49.0±2.1(9)	57.0±5.0(7)	49.3±4.5(8)

Controls were injected with saline and those in the L-carnitine group with 20 mmol L-carnitine/kg b.wt. Thirty minutes later, the animals in the no ischemia group were freeze-clamped without decapitaion. Mice in other groups were decapitated and the brain was made ischemic for 15 or 30 seconds. All values are expressed in terms of μmol/g tissue except for ECP. Each value represents the mean±S.E.M. The number of samples in each group is given in parenthesis.

* $P<0.05$ as compared with the control group. (Ref. 18).

Table 5. Effects of L-carnitine and its analogues on brain ammonia and energy metabolite concentrations in mice with hyperammonemia

	Control (group I)	Saline (group II)	L-Carnitine (group III)	D-Carnitine (group IV)	Acetyl-L-Carnitine (group V)
Ammonia	0.38±0.05	5.09±0.12*	2.24±0.14†	2.82 ±0.05†	3.16±0.33†‡
Phosphocreatine	3.16±0.12	2.49±0.11*	3.64±0.13†	3.11±0.21†	3.69±0.11†§
ATP	2.68±0.09	2.38±0.07*	2.57±0.08	2.48±0.07	2.87±0.08†‡§
ADP	0.494±0.019	0.618±0.035*	0.456±0.038†	0.515±0.048	0.511±0.015
AMP	0.080±0.016	0.208±0.028*	0.068±0.008†	0.119±0.022†	0.082±0.017†
ECP	0.899±0.006	0.839±0.014*	0.905±0.007†	0.880±0.013†	0.903±0.006†
Creatine	7.89±0.29	8.16±0.25	7.13±0.22†	7.45±0.31	7.61±0.15
Glucose	1.70±0.06	1.47±0.07*	2.23±0.14†	1.86±0.10	2.13±0.12†
Pyruvate	0.125±0.008	0.132±0.012	0.093±0.013	0.116±0.018	0.095±0.010
Lactate	2.20±0.15	4.31±0.16*	2.76±0.15†	3.18±0.17†	3.04±0.27†
Lactate/pyruvate	17.8±1.4	33.7±2.7*	32.7±3.3	31.7±4.8	33.5±3.7

Results are means±S.E.M. for six animals. All values are expressed in terms of μmol/g tissue except for ECP. Controls (group I) were injected with saline solutions only. Animals in other groups were injected with saline solution containing no carnitine (group II), 20 mmol L-carnitine/kg (group III), 20 mmol D-carnitine/kg (group IV) or 20 mmol acetyl-L-carnitine/kg (group V), and 30 min later with 15 mmol ammonium acetate/kg. The animals were freeze-clamped 10 min after the injection of the second saline or ammonium acetate.

* $P<0.05$ when compared with group I by Student's *t*-test. † $P<0.05$ when compared with group II by analysis of variance with Dunnett's test. ‡ $P<0.05$ when compared with group III by analysis of variance with Tukey's test. § $P<0.05$ when compared with group IV by analysis of variance with Tukey's test. (Ref. 27).

trations of energy metabolites were prominently and rapidly changed in the brain[18]. Within 15 seconds, phosphocreatine and ATP decreased while creatine, ADP, AMP, pyruvate and lactate increased. These changes were further enhanced after 30 seconds of ischemia. The decrease in phosphocreatine was more marked than that of ATP (Table 4). Brain ischemia therefore caused a decrease in the amount of high energy phosphate compounds, especially phosphocreatine, and it activated glycolysis (increased production of lactate). These findings were consistent with those of previous studies[28]. However, when the animal was given L-carnitine (i.p.) 30 min before decapitation, the concentrations of phosphocreatine and ATP were significantly higher than in the untreated mouse (Table 4). ECP was also higher in mice treated with L-carnitine. These results suggest that L-carnitine may protect the brain from ischemic attack[18].

It should be noted here that, even without decapitation, the phosphocreatine concentration was higher and that of pyruvate was lower in mice treated with L-carnitine[18]. In human muscle, L-carnitine can accelerate the metabolism of pyruvate to CO_2 associated with comparable activation of pyruvate dehydrogenase[29]. The same reaction might take place in the brain and might stimulate the energy producing system in the brain.

Mechanism of effects of carnitine

Carnitine therefore appears to have the potential to protect the brain from ammonia and ischemia. The precise mechanisms, however, have not been clarified. As mentioned earlier, carnitine might have accelerated the removal of ammonia from the body (and the brain) through activation of the urea cycle and glutamine synthetase[17]. In cerebral ischemia, acyl CoA increases and it inhibits the activities of several enzymes (e.g. pyruvate dehydrogenase and adenine nucleotide translocase), while carnitine may lower the acyl CoA concentration by transferring the acyl group to carnitine[30,31]. Nevertheless, these explanations cannot be complete because in our experiments not only L form but also D-carnitine was effective both in hyperammonemia and in ischemia (Tables 2,5,6, Fig. 5)[18,27], though

Table 6. Effects of ischemia (30 s) and D-carnitine on brain energy metabolites

	Control	D-Carnitine
Phosphocreatine	0.58±0.04(8)	0.88±0.07(8)*
ATP	1.28±0.11(8)	1.63±0.08(9)*
ADP	0.923±0.024(8)	0.869±0.042(9)
AMP	0.914±0.078(8)	0.630±0.063(9)*
ECP	0.555±0.029(8)	0.661±0.021(9)*
Creatine	10.22±0.12(8)	10.16±0.18(9)
Pyruvate	0.128±0.011(8)	0.130±0.007(9)
Lactate	5.85±0.13(8)	6.00±0.17(9)
Lactate/pyruvate	48.8±5.4(8)	47.3±3.1(9)

Controls were injected with saline and those in the D-carnitine group with 20 mmol D-carnitine/kg b.wt. Thirty minutes later, all brains were made ischemic for 30 seconds. All values are expressed in terms of μmol/g tissue except for ECP.

Each value represents the mean±S.E.M. The number of samples in each group is given in parenthesis. * $P<0.05$ as compared with the control group. (Ref. 18).

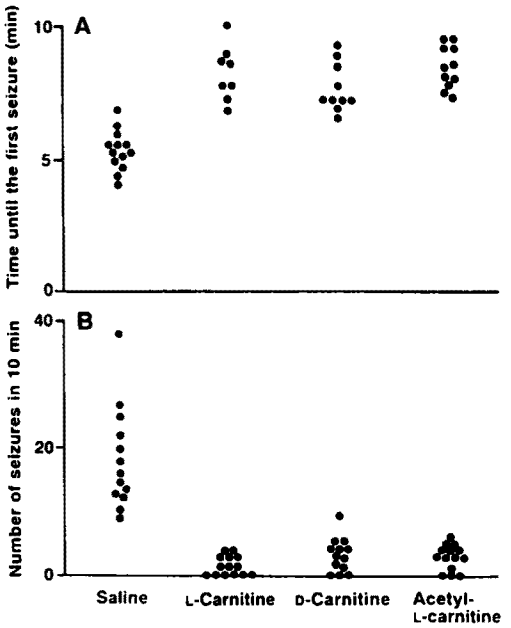


Fig. 5. Effects of L-carnitine and its analogues on ammonium-induced seizures (Ref. 27).

D-carnitine does not occur naturally and it even competitively inhibits carnitine acetyltransferase activity[32].

However, in ischemic dog hearts, Folts *et al.*[33] found that D,L-carnitine was as effective as L-carnitine in suppressing both electrocardiographic changes and a decrease in phosphocreatine and ATP concentrations.

These findings suggest that carnitine may have functions other than the well established "physiological" function.

Conclusion

The most important thing in the prevention of brain damage is to suppress the generation of harmful substances or factors and prevent their entry into the body, specifically into the brain. However, this is not always possible or sufficient, so that the utilization of intrinsic substances which have the potential to protect the brain may be very useful.

It is obvious that much more study is necessary before practical application of these substances is considered, because the experiments presented here were all done in animals under extreme conditions.

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英文論文の和文要旨

カドミウム曝露の腎臓への影響の指標：N-acetyl-β-D-glucosaminidase を中心に

川田智之

カドミウム（Cd）取り扱い作業者および Cd 汚染地区住民を対象にして，Cd 曝露の臨界臓器である腎臓への影響が低分子量蛋白の排泄量増加を中心に研究されてきた．最近 10 年間では，尿中 N-acetyl-β-D-glucosaminidase（NAG）や β_2-microglobulin（BMG）などのいくつかの尿蛋白が，Cd の腎臓への影響を知る早期の感度のよい指標として提案されている．これまでの研究における Cd 曝露者の尿中 Cd 平均値は 10μg/g・creatinine を越える例が多かったが，現在の日本や欧米諸国では，職域でもこの Cd 曝露レベルはまれであり，低い曝露量での影響指標が求められている．因果関係における関連の一致性という視点から，尿中 Cd と NAG の関連は確かなものである．NAG は，pH 変化に対する安定性，測定の簡便さ，低コスト，および測定の信頼性という点で優れている．尿中 NAG は 10μg/g・creatinine 未満の Cd 値における微少な腎影響を検出するためにも推奨できる指標の一つである．
(*J Occup Health 1995; 37: 69–73*)

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カルニチンによる脳防御

伊規須英輝，松岡雅人，井料佳久

カルニチンは，神経系を含む全身に広く分布している．その「生理的」機能，つまり，長鎖脂肪酸のミトコンドリア内膜通過のためのキャリヤーであることは充分確立されている．本稿では，主に我々の実験結果にもとづいて，カルニチンが「生理的」機能以外の作用をもち，脳防御作用を持ちうることを論じた．すなわち，マウスにアンモニア負荷を行うと，けいれんと脳内エネルギー代謝産物濃度の変化（ATP やクレアチンリン酸の低下，ADP, AMP, ピルビン酸，乳酸の上昇など）が見られるが，これらはいずれもカルニチンにより抑制された．また，重篤な脳虚血時の脳内エネルギー代謝産物濃度の変化もカルニチン投与により減少した．D-カルニチンが，L-カルニチンと同様の効果を示したことから，これらはこれまでに確立されているカルニチンの作用とは異なった機序によることが考えられた．カルニチンを含む内因性物質の脳防御作用の可能性は注目に値するように思われる．
(*J Occup Health 1995; 37: 75–82*)

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