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L-Carnitine Administration Improves Lipid Metabolism in Streptozotocin-Induced Diabetic Rat

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ABSTRACT

The purpose of this study was to investigate the effects of L-carnitine administration on lipid metabolism in streptozotocin-induced diabetes. Diabetes was induced by a single intraperitoneal injection of streptozotocin (50 mg/kg b.w.) and was confirmed by determination of urinary glucose secretion. Diabetic rats in the three L-carnitine treated groups were given L-carnitine, 50 (D50), 100 (D100) and 200 (D200) mg/kg body weight, by subcutaneously every other day for four weeks, while animals in normal (N) and diabetic (DM) groups for control received saline by the same method. The daily weight gain was not different between normal and diabetic rats, but daily dietary intake was significantly higher in diabetic rats than in normal rat. Diabetic rats had a significantly lower carnitine concentration in both serum and liver compared to normal rats. Total carnitine concentration in serum was increased dose dependently upon carnitine administration, but statistic significance was shown only in D200 group. Diabetic rats had significantly higher serum triglyceride and cholesterol concentrations compared to normal rats. However there were no significant differences in liver. L-carnitine administration to diabetic rats significantly decreased serum triglyceride but not cholesterol concentrations. In liver, triglyceride and cholesterol concentrations were not altered by L-carnitine administration. These results indicated that streptozotocin induced-diabetic rats have decreased carnitine and increased lipid concentrations compared with normal rats. Also it indicated that L-carnitine administration has an effect on the normalization of serum triglyceride concentrations in diabetic rats.

KEY WORDS: L-Carnitine, triglyceride, total choesterol, diabetic rat.

INTRODUCTION

Carnitine (β-hydroxy-γ-trimethylaminobutyric acid) is a small water soluble-quaternary amine that plays an important role in lipid catabolism in which it serves as an essential cofactor for the transport of long chain fatty acids as acylcarnitine esters across the inner mitochondrial membrane.[1] Acquired or congenital carnitine deficiency results in impaired fat oxidation.[2] Carnitine administration has been demonstrated to reduce blood and tissue lipid accumulation in various conditions, including cardiovascular disease,[3][4] chronic alcoholism,[5] and dietary carnitine deficiency.[6] The lipid-lowering effect of carnitine administration is dose-dependent.[5][7] Thus, supplementary carnitine is effective at lowering the fat content of various tissues, particularly when lipids are elevated. More recently, carnitine was noted to be an important determinant of fatty acid production (lipogenesis) in laboratory animals.[8] In other studies, carnitine treatment has been demon-strated to enhance lipid utilization in humans[9] and animals.[10]

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Diabetes is associate with marked alteration in fat metabolism and tissue carnitine concentrations. Fats are increasingly mobilized as energy bearers for the cells that are suffering from starvation, but because of a relative deficiency of L-carnitine, they cannot be burned in appropriate amounts.[11] Several studies on carnitine metabolism have reported decreased plasma and liver carnitine levels in human and experimental diabetic rats. It has been observed that carnitine administration has a hypoglycemic effect on diabetic rats,[12][13] and lead to an improvement in glucose metabolism accompanied by a saving in insulin secretion.[14] Also, acetyl-L-carnitine at a dose of 150 mg/kg/day given for one month normalizes nerve conduction velocity in streptozotocin-induced diabetes with no adverse effect.[15] Recent research suggests that carnitine is also crucial in the regulation of carbohydrate metabolism in addition to its role in the oxidation of fatty acids.[16] However, less understood is the role that carnitine plays in carbohydrate metabolism, either directly, or indirectly through its action on fatty acids.

Therefore, in this study, we studied the effects of administration of various concentrations of carnitine on lipid metabolism in streptozotocin-induced diabetic rats.

MATERIALS AND METHODS

1. Experimental animals and protocol

Thirty male Sprague Dawley rats weighing 205.3 ± 12.5 g were used. Diabetes was induced by a single intraperitoneal injection of streptozotocin (45 mg/kg b.w.) and was confirmed by determination of urinary glucose secretion, then randomly divided into four groups; diabetic control group for control and three experimental groups for L-carnitine treated groups. Each group consists of six rats. Each rat in the three L-carnitine treated groups was given carnitine 50, 100 and 200 mg/g body weight, subcutaneously every other day for four weeks, while animals in the diabetic and normal groups for control received saline by the same method. The animals were fed AIN-76 diet for four weeks. The rats were housed in the laboratory maintained at constant temperature (22 ± 2℃) and controlled 12 hrs light/dark cycle during the experimental period. The animals were given free access to food and water during the entire experimental period. The day after four weeks of experimental period, animals were anesthetized and sacrificed following 15 hrs fast. Blood samples were taken from the trunk after decapitation, centrifuged at 4℃, 3000 rpm for 30 min and serum was separated and stored at −70℃ until assayed. Liver was collected and frozen at −70℃ until assayed. To evaluate the liver carnitine palmitoyltransferase-I (CPT-I) activity, liver was immediately used for extraction.

2. Analysis of lipids

Serum total cholesterol levels were measured by using commercial kits from Asan Pharm. Co. (Seoul, Korea) based on the cholesterol oxidase method.[17] Serum triglyceride levels were measured by the lipase-glycerol phosphate method[18] using commercial kits (Asan Pharm. Co., Seoul Korea). The liver tissues were minced thoroughly while on ice, and representative aliquots of each were used for determining the concentrations of total cholesterol and triglycerides in liver by the method as described above in serum.

3. Carnitine assay

Nonesterified carnitines (NEC), acid-soluble acylcarnitines (ASAC), and acid-insoluble acylcarnitines (AIAC) in serum and liver extracts were determined by the radioenzymatic procedure of Cederblad and Lindstedt,[19] as modified by Sachan *et al.*[20] In this method AIAC was precipitated with perchloric acid and centrifugation leaving the ASAC and NEC in the supernatant. An aliquot of the supernatant was assayed to determine the NEC and another aliquot hydroyzed with 0.5 mol/L KOH to assay all acid soluble carnitines (ASAC + NEC). ASAC is calculated as the difference between the NEC and the total acid soluble carnitines. The pellets containing the AIAC were drained, washed, and hydrolyzed in 0.5 mol/L KOH for 60 min in a hot water bath at 60℃. In each case carnitine was assayed using carnitine acetyl transferase (Sigma Chemical Co., St. Louis, MO, USA) to esterify the carnitine to a [^{14}C]acetate from [1-^{14}C]acetyl CoA (Amersham, Arlington Heights IL USA). Radioactivity of samples was determined in a Beckman LS3801 liquid scintillation counter (Beckman Instruments, Palo Alto, CA).

4. CPT-1 activity assay

Liver mitochondria were prepared by the procedure of Johnson and Lardy.[21] The liver was homogenized in cold, tris-buffered 0.25 M sucrose and the mitochondria were isolated from the homogenate by differential centrifugation, washed and resuspended three times. After the final wash, the mitochondria were resuspended in the buffer. The mitochondrial protein content was determined by the method of Bradford by using γ-globuline as the standard. A modified procedure of Guzman[22] was employed to measure CPT-I activity. Final concentrations in a total volume of 1 ml at 37℃ were: 80 mM of sucrose, 70 mM imidazole (pH 7.0), 1 mM EGTA, 1 ug antimycin A and 2 mg bovine serum albumin. A 5 min preincubation period was initiated by the addition of myristoyl-CoA. The reaction was started with L-carnitine (0.4 mCi/mmol l-[methyl-^{3}H] carnitine) and stopped after 5 min by adding 4 ml of 1.0 M perchloric acid.

5. Statistical analysis

All values are expressed as group means ± SD. Significance of difference was determined by students t-test and analysis of variance (ANOVA) with Duncans multiple range test using SAS version 6 (SAS Istitute, Cary, NC, USA). $P < 0.05$ was considered significant.

RESULTS

1. Food intake, weight gain and food efficiency

There are no significant differences on initial body weight among the groups (data not shown). Food intake was significantly higher in diabetic rats than in normal, however weight gain was not different between two groups (Table 1). These results indicates that food ef-

ficiency ratio was significantly lower in diabetic rats than in normal rats.

2. Lipid concentrations in serum and liver

Diabetic rats had a significantly higher serum triglyceride and cholesterol concentrations than those of normal rats but not in liver cholesterol concentration. However, only triglyceride concentrations in liver had a significantly increased in diabetic rats. L-Carnitine administrations did not have any effect on serum cholesterol, liver choleaterol and triglyceride concentrations. L-Carnitine administrations to diabetic rats significantly decrease serum triglyceride but the triglyceride-lowering effect was not dose-dependant of carnitine administration (Table 2).

3. Carnitine concentrations in serum and liver

Diabetic rats had a significantly lower carnitine concentration in both serum and liver compared with normal rats. Total carnitine concentrations in serum increased dose dependently by carnitine administration. The levels of carnitine in serum and liver as shown in Table 3. TCNE level in serum and liver were significantly lower in diabetic rats than in normal rats. L-carnitine treatment induced dose dependent increase of carnitine levels in serum but not in liver. L-carnitine treatment of dose 100 and dose 200 induced increase on liver carnitine levels of

Table 1. Food consumption, body weight gain and food efficiency ratio in rat

	Control		Carnitine treated diabetes		
	Normal	Diabetes	D50	D100	D200
Food consumption(g/day)	16.4 ± 1.5*	23.2 ± 1.5	22.8 ± 2.6	24.3 ± 2.5	23.7 ± 4.4
Weight gain(g/d)	3.1 ± 0.4	3.0 ± 1.0	2.4 ± 0.8	2.8 ± 1.5	2.3 ± 1.2
Food efficiency ratio[a)]	18.7 ± 2.0*	12.7 ± 3.5	10.7 ± 3.6	11.7 ± 6.3	10.2 ± 5.7

Values are mean ± SD, *: Values with normal rats are significantly different compare to control diabetic rats by Student t-test. Values with different superscripts are significantly different by ANOVA with Duncan's multiple range test at $p < 0.05$. Feed efficiency ratio was calculated as weight gain/dietary intake during the experimental period. Dose(mg/kg b.w. /day): D50 (dose 50), D100 (dose 100), D200 (dose 200).

Table 2. Triglyceride and total cholesterol concentrations in serum and liver

		Control		Carnitine treated diabetes		
		Normal	Diabetes	D50	D100	D200
Serum (mg/dL)	Triglyceride	153.1 ± 30.8*	322.2 ± 39.8[a]	229.5 ± 37.7[b]	238.2 ± 28.5[b]	234.6 ± 21.1[b]
	Cholesterol	64.0 ± 1.3*	95.4 ± 1.5	77.7 ± 2.5	80.3 ± 3.0	78.3 ± 3.0
Liver (mg/wet. g)	Triglyceride	14.6 ± 3.7*	22.8 ± 3.6	17.9 ± 3.0	19.5 ± 4.4	19.4 ± 4.1
	Cholesterol	3.2 ± 0.7	2.5 ± 1.0	2.8 ± 1.4	3.6 ± 0.9	2.6 ± 0.9

Values are mean ± SD. *: Values with normal rat are significantly different compare to corresponding values of diabetic control rat by Student's t-test at $p < 0.05$. Values with different superscrips are significantly different among the diabetic groups by ANOVA with Duncan's multiple range test at $p < 0.05$. Dose (mg/kg body weight /day): D50 (dose 50), D100 (dose 100), D200 (dose 200).

Table 3. Carnitine concentrations in serum and liver

		Control		Carnitine treated diabetes		
		Normal	Diabetes	D50	D100	D200
SERUM (nm/mL)	NEC	41.2 ± 7.5	54.9 ± 20.7	69.2 ± 16.4	76.7 ± 19.8	89.1 ± 36.9
	ASAC	38.4 ± 6.5	29.1 ± 4.8	43.2 ± 30.3	69.0 ± 19.3	78.7 ± 35.5
	AIAC	-	-	-	-	-
	TCNE	81.9 ± 13.6*	62.1 ± 19.5[b]	112.4 ± 29.5[ab]	145.7 ± 37.4[ab]	167.8 ± 57.5[a]
LIVER (nm/g wet wt.)	NEC	1441.2 ± 420.4	779.7 ± 310.3[b]	828.7 ± 338.7[ab]	1493.5 ± 284.9[a]	1349.8 ± 790.8[ab]
	ASAC	1401.5 ± 381.3	753.5 ± 348.5	718.1 ± 246.4	1356.4 ± 310.4	1327.4 ± 839.3
	AIAC	-	83.93 ± 17.4[a]	38.6 ± 33.0[b]	12.2 ± 5.9[b]	32.7 ± 18.7[b]
	TCNE	2802.9 ± 762.6*	1617.1 ± 651.7[b]	1577.6 ± 564.3[ab]	2859.6 ± 579.2[a]	2696.9 ± 1617.2[ab]

Values are mean ± SD. *: Values with normal rats are significantly different compare to control diabetic rats by t-test. Values with different superscripts are significantly different by ANOVA with Duncan's multiple range test at $p < 0.05$. Dose (mg/kg b.w./day): D50 (dose 50), D100 (dose 100), D200 (dose 200), NEC: Nonesterified acylcarnitine, ASAC: Acid soluble acylcarnitine, AIAC: Acid-insoluble acyl carnitine, TCNE: Total carnitine

Table 4. Carnitine palmitoyl transferase-I concentration in liver

	Control		Carnitine treated diabetes		
	Normal	Diabetes	D50	D100	D200
CPT-I (nmol/minute/mg protein)	9.0 ± 1.3*	5.5 ± 1.5	8.5 ± 2.5	10.6 ± 3.0	8.9 ± 3.0

Values are mean ± SD. *: Values with normal rat are significantly different compare to corresponding values of diabetic control rat by Student's T-test at $p < 0.05$. Values with different superscripts are significantly different by ANOVA with Duncan's multiple range test at $p < 0.05$. Dose (mg/kg b.w./day): D50 (dose 50), D100 (dose 100), D200 (dose 200), CPT-I: Carnitine palmitoyl transferase-I.

NEC, ASAC and TCNE, whereas dose 50 did not.

4. Liver CPT-I activity

The activity of CPT-I are shown in Table 4. Diabetic rats had a significantly lower liver CPT-I activity than that of normal rats. Liver CPT-I activity was not changed statistically by L-carnitine treatment with dose 50, increased by L-carnitine treatment with dose 100, and then dropped by L-carnitine treatment with dose 200.

DISCUSSION

The unique role of carnitine is intramitochondrial translocation of fatty acids[23] as well as in inter organ transport of fatty acids and their metabolites.[24][25] In present study, we examined the lipid-lowering effect of L-carnitine administration on streptozotocin-induced diabetic rats.

There are considerable evidences that carnitine administration causes decrease of lipids in human and in animals. For example, oral administration of carnitine decreased plasma triglycerides in both normolipidemic and hyperlipidmic subjects.[3][4] L-carnitine administration is involved in the decrease of total serum cholesterol and triglyceride in rat fed with a cholesterol enriched diet.[26] Infants given L-carnitine developed significantly lower plasma triglycerides and free fatty acids at two and three months of age.[27] In reverse, the consequence of decreased fat oxidation resulting from carnitine deprivation was forced to store the fatty acids as triglycerides in adipose tissue.[2] The present data also showed that streptozotocin-induced diabetic rats had a significantly higher serum triglyceride and cholesterol concentrations and liver triglyceride than those of normal rats. L-carnitine administration (50 mg/kg/48 hr) for four weeks decreased significantly the serum triglyceride, however the triglyceride-lowering effect was not dose-dependent in our diabetic rats (Table 2). Diabetic rats consumed more diet than normal control rats, however their weight gain was not different between normal and diabetic rats (Table 1). It may be argued that increased serum triglyceride levels of the diabetic rats were due to increased amounts of diet consumed compared to normal control. This is most unlikely because all L-carnitine administered diabetic rats and diabetic control rats consumed on average identical quantities of diet but their serum triglyceride was far from identical.

Diabetes is associated with marked alteration in fat metabolism and tissue carnitine concentrations. Fats are increasing mobilizated as energy, but because of a relative deficiency of carnitine, fat metabolism is reduced.[11] Liver carnitine is increased at the expanse of cardiac (and possibly skeletal) muscle, which exhibits a reduction in total carnitine value.[28] In addition, the ratio of acyl/free carnitine is elevated in the heart. Reduced plasma carnitine, increased urinary excretion of carnitine, and raised blood and tissue triglyceride levels.[29][30] Paulson and Shug's study[31] further demonstrated a significant diminution in the severity of diabetes by carnitine administration (3 g/kg, or 180 g/60 kg person, given intravenously) in human. These results, taken together, are indications of deranged fat metabolism in diabetes: carnitine therapy should, in theory, be of value.

The hepatic carnitine pool was the characterized in several animal models with genetic or chemicaly-induced diabetes. In db/db mice, Stearns and Benzo[32] found decreased hepatic free carnitine but unchanged acylcarnitine concentrations at the age of 9 or 12 weeks, and the carnitine concentrations had normalized at 21 weeks. In this mice, the liver triglyceride concentration increased approximatly tenfold at all time points, suggesting that the development of fatty liver may be independent from the hepatic carnitine concentrations. In agreement with Stearns and Benzo,[32] also Reddi *et al.*[33] found decreased total carnitine concentrations in the liver from db/db mice. Interestingly, in blood and other organs (kidney, brain, heart, skeletal muscle and pancreas) the carnitine concentration was not reduced in comparison to control mice. The present data support previous other studies that functional carnitine deficiency may be defined as that pool of total carnitine (Table 3).

The results of these studies including present study differ from the findings in rats treated with streptozotocin[30][34] or alloxan.[35][36] Fogle and Bieber[34] and Brooks *et al.*[30] described a significant increase in the hepatic total carnitine concentration in rat with streptozotocin-induced diabetes mellitus. This increase was independent of the carnitine content of the diet and could be reversed by treatment with insulin. Similarly, McGarry *et al.*[35] found an increase in the total hepatic carnitine content in alloxan-diabetic rats in comparision to control rats. They speculated that the increase in the hepatic carnitine concentration could be due to the increased glucagon/insulin ratio in the plasma of these animals. Indeed, it has been shown that glucagon increase carnitine transport into the liver. However, in contrast to McGarry *et al.*,[35] Henderson *et al.*[36] did not find an increase in the total liver carnitine content in rats with alloxan-induced diabetes. Interestingly, in sheep with alloxan-induced diabetes, the hepatic carnitine concentration is even more increased than rats. Snoswell *et al.*[37]

and Handerson *et al.*[36] found more than tenfold increase in the free, short-chain acyl and total carnitine concentrations in the liver from alloxan-diabetic sheep 2 weeks after induction of diabetes. In comparision to non-diabetic control sheep, the portal-venous difference of total carnitine was clearly increased in diabetic sheep, suggesting that increased biosynthesis accounts for this dramatic increase in the hepatic carnitine content.[37] Thus, the hepatic carnitine content appears to increase in animals with chemically-induced diabetes mellitus due to increased transport of carnitine into the liver and/or due to increased biosynthesis. Since fatty liver develops even when the hepatic carnitine content is normal or increased, absolute carnitine deficiency is not the cause for hepatic accumulation of fat in diabetes. Studies investigating the administration of carnitine to reduce hepatic fat accumulation in patients with diabetes are so far lacking.

CPT-I is the rate-limiting enzyme for fatty acid oxidation and is the first step specific to fatty acid oxidation.[38] Liver CPT-I activity in diabetic rats decreased significantly compared to normal control rats (Table 4), which indicates diabetic rats in our study is retarded fatty acid oxidation. In a different study, the changes of CPT-I mRNA abundance, produced by hyperthyroidism and hypothyroidism, paralleled the changes in CPT-I activity in the rat liver. This suggests that the CPT-I is regulated at the transcriptional level by thyroid hormones.[39] Transcriptional of the rat liver CPT-I gene was also elevated by both high fat diets and exercise, suggesting that control of CPT-I gene expression is a key feature in the regulation of fatty acid oxidation during exercise.[40] On the other hand, the activity of rat liver CPT-I was not statistically changed by L-carnitine treatment with dose 50, but increased by L-carnitine treatment with dose 100, and then dropped by L-carnitine treatment with dose 200 in present study (Table 4). Further study about the relationship between carnitine administration and CPT-I activity is needed.

In conclusion, these results demonstrate that streptozotocin induced-diabetic rats have decreased carnitine and increased lipid concentrations compared with normal rats. It is especially noteworthy that L-carnitine administration (at dose of 50 mg/kg b.w./48 hr for four weeks) to diabetic rats recover serum triglyceride concentrations to near normal levels.

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