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Differential effects of dietary fatty acids on rat liver α-amino-β-carboxymuconate-ε-semialdehyde decarboxylase activity and gene expression

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Abstract

Hepatic α-amino-β-carboxymuconate-ε-semialdehyde decarboxylase (ACMSD; formerly termed picolinic carboxylase) [EC4.1.1.45] plays a key role in regulating NAD biosynthesis and the generation of quinolinate (quinolinic acid) from tryptophan. Quinolinate is a potent endogenous excitotoxin of neuronal cells. We previously reported that ingestion of fatty acids by rats leads to a decrease in their hepatic ACMSD activity. However, the mechanism of this phenomenon is not clarified. We previously purified ACMSD and cloned cDNA encoding rat ACMSD. Therefore, in this study, we examined the differential effect of fatty acids on ACMSD mRNA expression by Northern blot. Moreover, we measured quinolinic acid concentration in rats fed on fatty acid. When diets containing 2% level of fatty acid were given to male Sprague–Dawley rats (4 weeks old) for 8 days, long-chain saturated fatty acids and oleic acid did not affect ACMSD mRNA expression in the liver. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) strongly suppressed the liver ACMSD mRNA expression. In rats fed with high linoleic acid diet for 8 days, serum quinolinic acid was significantly increased as compared with the rats fed on a fatty acid-free diet under the condition of the approximately same calorie ingestion. These results suggest that the transcription level of ACMSD is modulated by polyunsaturated fatty acids, and suppressive potency of ACMSD mRNA is *n*-3 fatty acid family>linoleic acid (*n*-6 fatty acid)>saturated fatty acid. Moreover, this study provides the information that a high polyunsaturated fatty acid diet affects the production of quinolinic acid in serum by suppressing the ACMSD activity.

Keywords: α-Amino-β-carboxymuconate-ε-semialdehyde decarboxylase; Linoleic acid; Polyunsaturated fatty acid; Tryptophan; Quinolinic acid; Niacin

1. Introduction

Hepatic α-amino-β-carboxymuconate-ε-semialdehyde decarboxylase (ACMSD; picolinic carboxylase) [EC4.1.1.45] plays a key role in regulating NAD biosynthesis from tryptophan, as shown in Fig. 1. It has been reported that there is an inverse relationship between ACMSD activity and the production of NAD converted from tryptophan. ACMSD activity is greatly affected by many factors such as nutrients, hormones and diseases [1–7]. In rats, ACMSD has been generally detectable only in liver and kidney, and ACMSD activity in kidney was much higher than in liver [8]. This suggests that the conversion of tryptophan to NAD takes place mainly in the liver because of its low ACMSD activity.

The tryptophan catabolite quinolinate (quinolinic acid) has been reported to be associated with the pathogenesis of certain neurodegenerative diseases, since it acts as an excitotoxic agonist of *N*-methyl-D-aspartate receptor [9,10]. Quinolinate may therefore modulate the effects of

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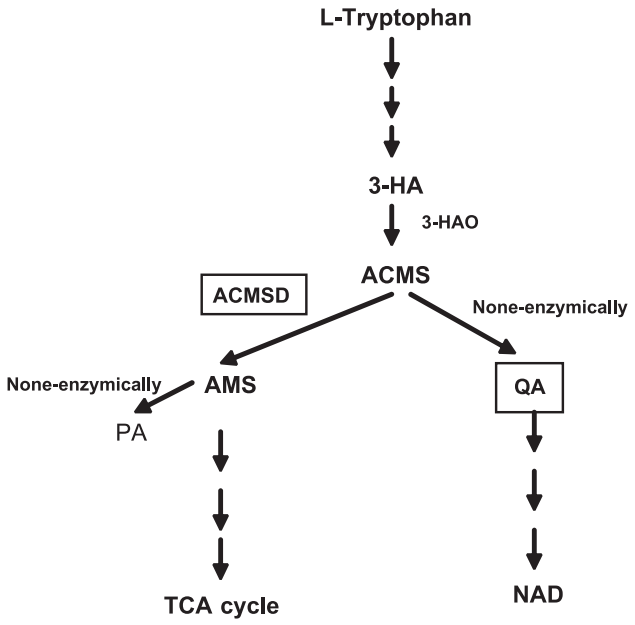

Fig. 1. Schematic diagram of tryptophan-NAD metabolism. 3-HA, 3-hydroxyanthranilate; ACMS, α-amino-β-carboxymuconate-ε-semialdehyde; AMS, α-aminomuconate-ε-semialdehyde; PA, picolinic acid; QA, quinolinic acid; TCA, tricarboxylic acid; NAD, nicotinamide adenine dinucleotide; 3-HAO, 3-hydroxyanthranilate 2,3-dioxygenase; ACMSD, α-amino-β-carboxymuconate-ε-semialdehyde decarboxylase.

excitotoxins. On the other hand, the tryptophan catabolite picolinic acid has been studied in the immune system of macrophages [11]. Picolinic acid induces the chemokine macrophage inflammatory protein in macrophage [11]. ACMSD was postulated to affect the production of quinolinate and picolinic acid (Fig. 1). However, the contribution of ACMSD to these processes has not been investigated and is still unknown.

We previously reported that ingestion of long-chain polyunsaturated fatty acids by rats leads to a decrease in their hepatic ACMSD activity, whereas long-chain saturated fatty acids do not affect its activity [3,4]. We also reported that this phenomenon was not attributed to the action of a glucocorticoid and insulin [5,12]. It was reported that in the rats fed a dietary linoleic acid, ACMSD protein levels in the liver were strongly suppressed as compared with the rats fed a fat-free diet [13]. In these previous studies, only the ACMSD activity and protein expression were measured but not its gene expression. On the other hand, it is not clear that these suppressive effects are caused by some special physiological activity (hormone-like) of essential fatty acids, such as prostaglandins.

Recently, we have purified ACMSD and cloned cDNA encoding ACMSD [14–16]. In this study, we examined whether dietary fatty acid altered liver ACMSD gene expression and what kind of fatty acid (*n*-3, *n*-6, *n*-9 fatty acid, and saturated fatty acid) affected ACMSD mRNA expression. Moreover, we examined whether dietary fatty acid affected the serum quinolinic acid concentration in rats.

2. Materials and methods

2.1. Reagents

Palmitic acid, stearic acid, oleic acid, linoleic acid and α-linolenic acid were purchased from Wako Pure Chemicals (Osaka, Japan). Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) were obtained from Nihon Kagaku Siryou Co. (Hokkaido, Japan). 3-Hydroxyanthranilic acid was purchased from Sigma Chemical Co. (St. Louis, USA).

2.2. Animals

Male Sprague–Dawley rats at the age of 3 weeks were purchased from CLEA Japan (Tokyo, Japan) and housed in

Table 1
Composition of diets (experiments 1–5)

Ingredient	Fatty acid-free	2% Fatty acid (experiment 1)	10% Fatty acid (experiments 2,3)	20% Fatty acid (experiments 2,4,5)
	(g/kg diet)			
Casein[a]	400.00	400.00	400.00	400.00
DL-Methionine	3.00	3.00	3.00	3.00
Cornstarch	150.00	150.00	150.00	150.00
Sucrose	350.00	330.00	250.00	150.00
Cellulose	50.00	50.00	50.00	50.00
Vitamin mixture[b]	10.00	10.00	10.00	10.00
Mineral mixture[b]	35.00	35.00	35.00	35.00
Choline bitartrate	2.00	2.00	2.00	2.00
Fatty acid[c]	0.00	20.00	100.00	200.00

[a] The amount of tryptophan in each diet was 4400 mg/kg diet. The niacin content of each diet was 30 mg/kg diet.
[b] AIN-76 [39].
[c] Test substance: experiment 1: palmitic acid ($C_{16:0}$), stearic acid ($C_{18:0}$), oleic acid ($C_{18:1}$), linoleic acid ($C_{18:2}$), α-linolenic acid ($C_{18:3}$), eicosapentaenoic acid ($C_{20:5}$), docosahexaenoic acid ($C_{22:6}$); experiment 2: linoleic acid; experiment 3: stearic acid, linoleic acid; experiment 4: linoleic acid; experiment 5: linoleic acid.

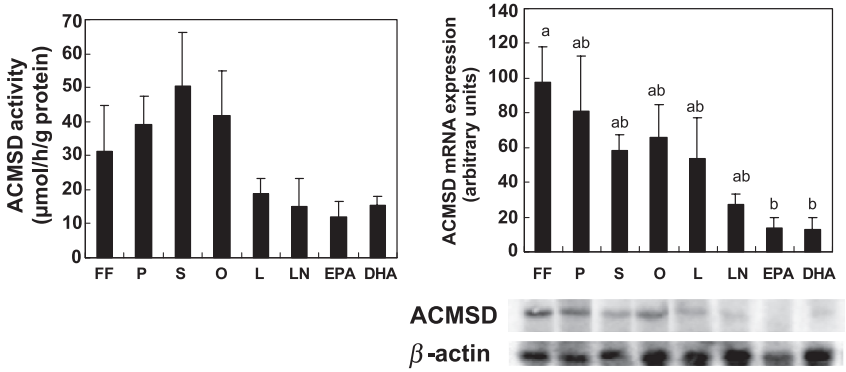

Fig. 2. Hepatic ACMSD activity and mRNA expression of rats fed diets containing 2% various fatty acids for 8 days (experiment 1). Values are means±S.E., n=3. Different superscript letters indicate significant difference, P<0.05. FF, fatty acid-free; P, palmitic acid ($C_{16:0}$); S, stearic acid ($C_{18:0}$); O, oleic acid ($C_{18:1}$); L, linoleic acid ($C_{18:2}$); LN, α-linolenic acid ($C_{18:3}$); EPA, eicosapentaenoic acid ($C_{20:5}$); DHA, docosahexaenoic acid ($C_{22:6}$).

individual cages at 22±1 °C with a 12-h light/dark cycle (lights on, 07:00–19:00 h). They were fed a commercial CE2 diet (CLEA Japan) which is adequate for normal growth. After this acclimation period of 4 days (body weight 73–85 g), they were fed one of the experimental diets shown in Table 1 for the next 8 days except for experimental 4. They were allowed free access to food and water until being killed by decapitation at the end of each experiment. All rats were fed with 40% casein diet because of a high protein diet increased ACMSD activity [1], this facilitated to detect hepatic ACMSD mRNA expression.

All rats were killed between 09:00 and 11:00 h, and their livers were immediately perfused via the portal vein with ice cold physiological saline solution (140 mmol/l NaCl) and excised. The liver samples were subjected to measurement of ACMSD activity and Northern blot analysis for determination of ACMSD mRNA expression. In all experimental animals, poor growth and dermatitis were not observed throughout the experiment. The care and treatment of the rats were carried according to the guideline prescribed in Faculty of Horticulture, Chiba University and the National Institutes of Health Guide for the care and use of laboratory animals [17].

2.3. Assay for ACMSD activity

Livers were homogenized in the three volumes of ice-cold buffer, 50 mmol/l potassium phosphate buffer (pH 7.0) containing 140 mmol/l potassium chloride, 5 mmol/l 2-mercaptoethanol, 1 mmol/l dithiothreitol, 1 mmol/l EDTA-2Na and 1 mmol/l phenylmethanesulfonyl fluoride, with a Potter–Elvehjem homogenizer. The homogenate was centrifuged at 105,000×g for 1 h at 4 °C. The activity of ACMSD in the cytosolic fraction was determined as previously described [14,18].

2.4. RNA isolation and Northern analyses

Total RNA was extracted from rat liver using Qiagen Rneasy Midi Kit (Qiagen GmbH; Hilden, Germany). RNA concentration of the preparations was evaluated by measuring A260. After DNase treatment, 20 μg of total RNA were separated by electrophoresis on denaturing formaldehyde gels, transferred to nylon membranes and ultraviolet cross-linked to filters. The blots were hybridized in a solution containing 0.125 mol/l Na_2HPO_4 (pH7.2), 0.25 mol/l NaCl, 7% (w/v) sodium dodecyl sulfate (SDS), 1 mmol/l EDTA, 50% formamide, 10% (w/v) polyethylene glycol 6000, 20 μg/ml denatured salmon sperm DNA and Dig-labeled probe at 42 °C overnight. The membranes were then washed in 2× SSC, 0.1% SDS at RT twice for 5 min, and 0.1× SSC, 0.1% SDS at 42 °C for 15 min, followed by a using digoxigenin (DIG) luminescent detection kit (Roche Molecular Biochemicals, Germany) according to the manufacturer's instructions. Blots were exposed to Kodak X-ray films for 15 min at RT (experiment 2) or were exposed to image analysis using LAS-1000 (Fuji Photo Film Co., Ltd., Tokyo, Japan) (experiment 1, experiments 3–5). Results obtained were normalized according to the signals from hybridization with β-actin and expressed in arbitrary units.

2.5. Digoxigenin-labeled probes

We selected two probes: beta-actin and a probe comprising the cDNA of ACMSD [19].

Table 2
Body weight gain, food intake and liver weight in rats (Experiment 2)*,**

	0% Linoleic acid	10% Linoleic acid	20% Linoleic acid
Body weight gain (g/8 days)	51.2±4.2	54.2±2.1	49.6±2.2
Food intake (g/8 days)	122±4[a]	110±4[a]	80.0±5.0[b]
Calorie intake (kcal/8 days)	439±15[a]	451±15[a]	365±21[b]
Daily calorie intake (kcal/day)	54.8±1.7[a]	56.4±1.7[a]	45.6±2.4[b]
Liver weight (g)	7.87±0.24	7.28±0.32	7.50±0.15

* Values are means±S.E., n=5.
** Means in a row with different superscript letters differ, P<0.05.

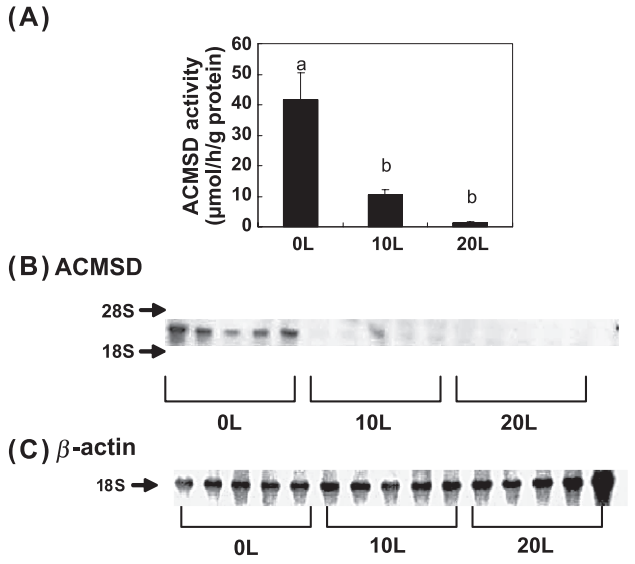

Fig. 3. Hepatic α-amino-β-carboxymuconate-ε-semialdehyde decarboxylase (ACMSD) activity and mRNA expression of rats fed diets containing 0–20% linoleic acid for 8 days (experiment 2). Values are means±S.E., n=5. Different superscript letters in a dose response study indicate significant difference, P<0.05.

The oligonucleotide probe 5′-CTA CCA AAG GAA TGG CCT GAT-3′ and 5′-TGG TCT CCG ATG GCA GCA TTC CTA -3′ were used for the ACMSD, 5′-GTG GGC CGC CCT AGG CAC CAG-3′ and 5′-CTC TTT AAT GTC ACG CAC GAT TTC-3′ were used for β-actin. The ACMSD and β-actin probe was labeled with digoxigenin-dUTP using the PCR DIG probe synthesis kit (Roche Molecular Biochemicals) according to the manufacturer's instructions. The kit enables the synthesis of probes by incorporation of DIG-dUTP into the PCR product.

2.6. Quantification of quinolinate

Quinolinate was quantified by an electron capture negative chemical ionization gas chromatography/mass spectrometry assay as previously described [20,21].

2.7. Statistical analysis

Data are shown as means±S.E. Data were analyzed by a one-way ANOVA, which was followed by an inspection of difference by Tukey's multiple-range test. The differences between two groups were analyzed by Student's unpaired t-test (in experiments 3 and 5). Differences with P<0.05 were considered significant.

3. Results

3.1. Effect of fatty acids on liver ACMSD mRNA expression (experiments 1–4)

In the first experiments, rats were fed diets containing 2% fatty acid (palmitic acid, stearic acid, oleic acid, linoleic acid, α-linolenic acid, EPA or DHA) to investigate the effects of long-chain fatty acids on the liver ACMSD mRNA expression. In a previous experiment, 10% long-chain polyunsaturated fatty acids strongly suppressed liver ACMSD activity [4]. Therefore, in this experiment, we selected 2% level fatty acid diet in order to study the suppressive potency of each fatty acid on ACMSD mRNA expression. ACMSD mRNA expression (2.6 kbp) of the rats fed 2% EPA and DHA were significantly lower (P<0.05) than that of the fatty acid-free group (experiment 1, Fig. 2). On the other hand, palmitic acid, stearic acid and oleic acid did not suppress the liver ACMSD activity and mRNA expression. N-3 fatty acids suppress the liver ACMSD activity and mRNA expression even at only the 2% level in diets. The potency of suppression of liver ACMSD mRNA was greater in n-3 fatty acid family than in linoleic acid (n-6 fatty acid), oleic acid (n-9 fatty acid) and long-chain saturated fatty acid.

In the next experiment, we investigated the effects of 0% (fatty acid-free), 10%, 20% linoleic acid on liver ACMSD activity and mRNA expression to observe a dose dependence study. The final body weight and body weight gain were not different among the groups (Table 2). Food intake and calorie intake were higher in the 0% and 10% linoleic acid-fed rats than that in the 20% linoleic acid-fed rats. Daily calorie intake was not different between the 0% linoleic acid group and the 10% linoleic acid group. Hepatic ACMSD activity was strongly suppressed in response to the amount of linoleic acid in the diet. ACMSD mRNA expression of the rats fed 10% and 20% linoleic acid were suppressed entirely (experiment 2,

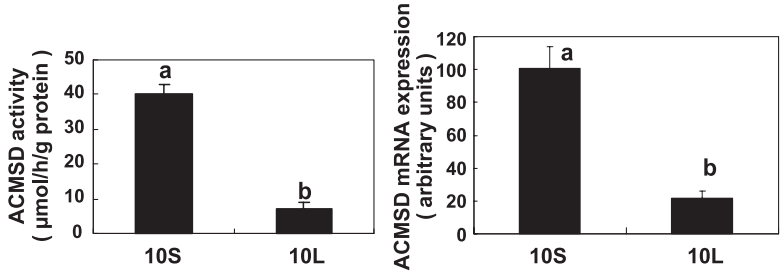

Fig. 4. Hepatic ACMSD activity and mRNA expression of rats fed diets containing 10% stearic acid or 10% linoleic acid for 8 days (experiment 3). Values are means±S.E., n=5. Different superscript letters indicate significant difference, P<0.05.

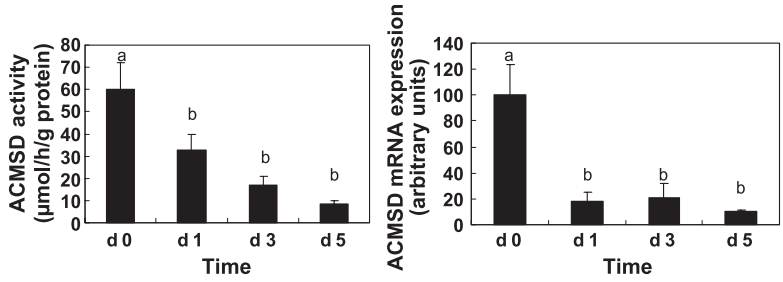

Fig. 5. Effect of the dietary shift to 20% linoleic acid diet on hepatic ACMSD activity and mRNA expression in rats previously adapted to 0% linoleic acid diet (experiment 4). Values are means±S.E., n=5. Different superscript letters in a time-course study indicate significant difference, P<0.05.

Fig. 3). We got the same results using competitive RT-PCR method (not shown).

In experiment 3, rats were fed on the diets which replace 10% linoleic acid with 10% stearic acid. Hepatic ACMSD activity and mRNA expression of the rats fed linoleic acid were lower (P<0.05) than that of stearic acid (experiment 3, Fig. 4).

In experiment 4, rats were fed a 0% linoleic acid diet (fatty acid-free) for a week to increase liver ACMSD activity. They were switched to a 20% linoleic acid diet and killed at 0, 1, 3 and 5 days after the diet change. Rats were fed with 20% linoleic acid diet, because a high linoleic acid diet decrease liver ACMSD activity and mRNA expression entirely, this facilitates to observe a time course study of ACMSD expression. Hepatic ACMSD activity decreased gradually after the shift from a linoleic acid-free to a 20% linoleic acid (experiment 4, Fig. 5). However, ACMSD mRNA expression decreased greatly at day 1 after the diet switch and then continued through day 5.

3.2. Effect of fatty acid on serum quinolinic acid concentration (experiment 5)

Rats were divided into two groups and each fed a 0% linoleic acid (fatty acid-free) diet and a 20% linoleic acid diet (Table 1) for the next 8 days. Final body weight, body weight gain and liver weight were not significantly different between two groups (not shown). Although food intake was higher in the 0% linoleic acid-fed rats than in the 20% linoleic acid-fed rats, calorie intake was not significantly different between two groups (Table 3). The concentration of serum quinolinic acid of the linoleic acid diet group increased 2-fold above the fatty acid-free group under almost the same calorie ingestion conditions (experiment 5, Fig. 6). Serum quinolinic acid concentration per milligram of tryptophan intake in the linoleic acid group was about 2.6 times that in the fatty acid-free group.

Table 3
Food intake and calorie intake in rats (experiment 5)*,**

	0% Linoleic acid	20% Linoleic acid
Food intake (g/8 days)	95.1±2.9[a]	71.5±1.3[b]
Calorie intake (kcal/8 days)	342±10	329±6
Daily calorie intake (kcal/day)	42.8±1.3	41.1±0.7

* Values are means±S.E., n=6.

** Means in a row with different superscript letters differ, P<0.05.

4. Discussion

Dietary polyunsaturated fatty acids reduce rat liver fatty acid synthesis rates and the activities of fatty acid synthetase, acetyl-CoA carboxylase, citrate cleavage enzyme, malic enzyme, and glucose-6-phosphate dehydrogenase more effectively than do either monounsaturated or saturated fatty acids [22–25]. We previously reported that ingestion of 2% polyunsaturated fatty acids such as EPA and DHA by rats leads to a decrease in their hepatic ACMSD activity [4]. In this study, we investigated the effect of several kinds of fatty acids on the rat liver ACMSD mRNA expression. Suppression of liver ACMSD mRNA expression was observed in rats fed polyunsaturated fatty acid diets. Especially, n-3 fatty acids such as α-linolenic acid, EPA and DHA strongly suppress liver ACMSD and mRNA activity even at only the 2% level in diets. The potency of suppression of liver ACMSD mRNA was greater in n-3 fatty acid than in linoleic acid (n-6 fatty acid) which is greater than saturated fatty acid. Linoleic acid, α-linolenic acid, EPA and DHA give rise to eicosanoids, physiologically and pharmacologically active compounds (hormone-like) known as prostaglandins, thromboxanes, and leukotrienes. The eicosanoids rising from n-3 fatty acid have mainly platelets anti-aggregatory, anti-inflammatory, vasodilatator effects, whereas eicosanoids from n-6 fatty acid show the opposite effects. Sanada and Egashira [26] reported that the suppressive effect of linoleic acid was alleviated by indomethacin, cyclooxygenase inhibitor, under the experiment using primary culture of rat hepatocytes. However, indomethacin itself had a potency to suppress the hepatocyte ACMSD activity in culture. Further studies will be necessary to elucidate the participation of eicosanoids in the suppressive effect of liver ACMSD. On the other hand, it was reported that the tryptophan catabolite picolinic acid selectively induces the chemokine macrophage inflammatory protein-1α and -1β in macrophages [11]. It is not still clear the relationship between physiological function of ACMSD and immune system or picolinic acid, and further study will be needed.

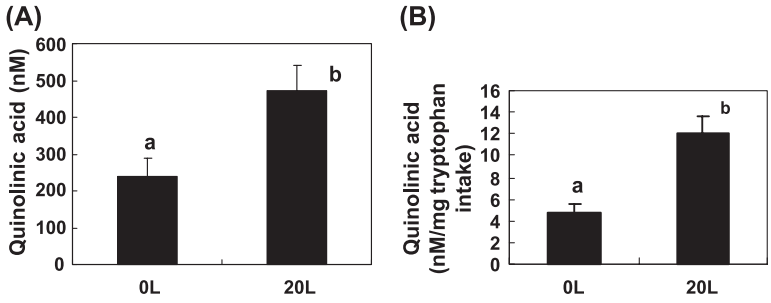

Fig. 6. Effect of dietary 20% linoleic acid on serum quinolinic acid concentration under the condition of the approximately same calorie intake (experiment 5). (A) Serum quinolinic acid concentration (nM). (B) Serum quinolinic acid concentration (nM)/mg tryptophan intake. Values are means±S.E., n=6. Different superscript letters indicate significant difference, P<0.05.

ACMSD activity decreased gradually until 5 days after the dietary change to a 20% linoleic acid diet from a linoleic acid-free diet, while ACMSD mRNA expression decreased quickly by 1 day (experiment 4, Fig. 5). The apparent response in ACMSD mRNA expression that was inconsistent with the change of the enzyme activity might be attributed to the difference of turnover between ACMSD mRNA and its enzyme.

During the metabolism of tryptophan, ACMSD is able to affect directly the production of quinolinate. Quinolinate is non-enzymically generated from ACMS in the absence of ACMSD activity. This metabolite is a potent endogenous excitotoxin, which functions as an agonist of the *N*-methyl-D-aspartate receptor [9,10]. Intra-striatal injection of quinolinic acid, which provokes neuronal death, is used as an animal model of Huntington's disease [27–30]. Moreover, quinolinate is considered to have roles in the pathogenesis of epilepsy [31,32], in Alzheimer's disease [33], and in dementia resulting from AIDS [34]. It has been reported that levels of quinolinate are elevated in cerebrospinal fluid and brain tissue of patients with the AIDS dementia complex [35]. In addition, quinolinic acid is a cation chelator and an inhibitor of both hepatic phophoenolpyruvate carboxykinase and gluconeogenesis [36]. Quinolinic acid may initiate lipid peroxidation in brain [37]. Quinolinic acid is an important substrate for the synthesis of nicotinamide-containing nucleotides, particularly in case of restricted niacin availability [38]. Therefore, accumulation of the L-tryptophan pathway metabolite in certain circumstances may be of functional and clinical significance. In this experiment, we showed that high linoleic acid diet significantly increased quinolinic acid in serum (experiment 5). Saito et al. [21] reported that systemic administrations of pyrazinamide (ACMSD inhibitor) increased quinolinic acid concentrations of serum and brain in rats. The elevated serum quinolinic acid in rats fed 20% linoleic acid appears to be due to the decrease the ACMSD activity. So, in tryptophan–niacin conversion, ACMSD is an important enzyme regulating the generation of quinolinic acid.

In conclusion, hepatic ACMSD mRNA expression in rats fed with polyunsaturated fatty acids was strongly suppressed and the potency of suppression of mRNA expression was greater in *n*-3 fatty acid family than in linoleic acid (*n*-6 fatty acid) which is greater than saturated fatty acid. These results suggest that the transcription level of ACMSD is modulated by polyunsaturated fatty acids. Moreover, this study provides the information that a high fatty acid diet affects the production of quinolinic acid in serum by suppressing the ACMSD activity.

Acknowledgements

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