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ORIGINAL ARTICLE

Adaptational modification of serine and threonine metabolism in the liver to essential amino acid deficiency in rats

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Abstract It is known that plasma serine and threonine concentrations are elevated in rats chronically fed an essential amino acid deficient diet, but the underlying mechanisms including related gene expressions or serine and threonine concentrations in liver remained to be elucidated. We fed rats lysine or valine deficient diet for 4 weeks and examined the mRNA expressions of serine synthesising (3-phosphoglycerate dehydrogenase, PHGDH) and serine/threonine degrading enzymes (serine dehydratase, SDS) in the liver. Dietary deficiency induced marked elevation of hepatic serine and threonine levels associated with enhancement of PHGDH mRNA expression and repression of SDS mRNA expression. Increases in plasma serine and threonine levels due to essential amino acid deficiency in diet were caused by marked increases in hepatic serine and threonine levels. Proteolytic responses to the amino acid deficiency may be lessened by storing amino radicals as serine and inducing anorexia through elevation of threonine.

Keywords Amino acid deficiency · Serine · Threonine · PHGDH · SDS

Abbreviations

PHGDH	3-Phosphoglycerate dehydrogenase
SDS	Serine dehydratase

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Introduction

Recently, acute phenotypes such as anorectic behaviour due to an amino acid deficient diet has been intensively studied (Gietzen and Rogers 2006; Maurin et al. 2005), and specific brain regions to recognize the amino acid deficiency are identified (Hao et al. 2005). Though these studies have been focused on an acute reaction for sensing the amino acid deficiency, it will be also worth studying adaptational modification, if any, of the amino acid metabolism after chronic feeding of essential amino acid deficient diet. A decrease in plasma level of any essential amino acid predisposes the protein metabolism to proteolysis in several tissues (Kadowaki and Kanazawa 2003; Vabulas and Hartl 2005). While deficient amino acid is utilized as substrates and/or regulators in many pathways, other 19 protein composing amino acids have to be excreted by deamination process, which could have lead to the cytosolic accumulation of toxic free ammonia. However, ammonia accumulation is not seen, but plasma serine and threonine levels are markedly elevated (Shikata et al. 2007). Since serine is a nonessential amino acid and threonine is an essential amino acid, it is reasonable to presume that serine biosynthesis should be enhanced and serine and threonine degradation should be attenuated. We hypothesized that increased serine and threonine were derived from excess amino acids produced by proteolysis and by inhibition of protein generation. We especially focused on liver, because liver is the principle organ responsible for recycling cytoplasmic components to provide nutrients to other tissues during the starvation.

3-Phosphoglycerate dehydrogenase (PHGDH; EC 1.1.1.95) plays a critical role in de novo serine biosynthesis in the liver (Greenberg and Ichihara 1957; Snell 1984), and serine dehydratase (SDS; EC 4.2.1.13) catalyses

conversion of serine and threonine to pyruvate and α-ketobutyrate, respectively (Snell 1975). PHGDH is the rate limiting enzyme in the phosphorylated pathway of serine biosynthesis, using 3-phosphoglycerate which is an intermediate of the glycolytic pathway, as a starting material (Greenberg and Ichihara 1957; Snell 1984). PHGDH is widely distributed in various tissues, and is significantly upregulated in proliferating, differentiating and neoplastic tissues (Davis and Fallon 1970). Patients with inherited PHGDH deficiency have reduced enzymatic activity, which leads to marked decrease of serine concentrations in plasma. They are reported to be afflicted with severe neurological symptoms including congenital microcephaly, intractable seizures, dysmyelination and psychomotor retardation (Jaeken et al. 1996; de Koning et al. 1999, 2004; Klomp et al. 2000). SDS is the enzyme that catalyzes the pyridoxal phosphate-dependent deamination of serine and threonine to produce pyruvate and α-ketobutyrate, respectively. Its activity is upregulated during gluconeogenic conditions, such as starvation, high-protein diet feeding or diabetes mellitus (Pitot and Peraino 1964; Ishikawa et al. 1965) to facilitate production of glucose from serine. By contrast, as SDS directly releases ammonia from amino acids, this enzyme should be down-regulated during catabolic states such as injuries (Lopez-Flores et al. 2005) or acidosis (Lopez-Flores et al. 2006) for adaptational changes. The changes in SDS activity are mainly regulated at transcriptional level (Ogawa et al. 1991). Under conditions of deficiency in a single amino acid, we studied changes in mRNA expression of PHGDH and SDS, and the phenotypic consequences were discussed in light of metabolic adaptation for essential amino acid deficiency.

Materials and methods

Animals and diets

Our experiments were reviewed and approved by the Animal Care Committee of Ajinomoto Co., Inc. Wistar rats (Charles River Japan Inc., Yokohama, Japan) were housed individually in a hanging cage made of stainless steel wire. The animal room was maintained with constant temperature (23 ± 2°C) and humidity (55 ± 10%) with a 12-h light/dark cycle (lights on 7.00 to 19.00). Feeding with the control diet began at 7 weeks of age; the control diet was based on AIN93G standard diet, modified by replacing casein with a free amino acid mixture of the same amino acid composition (Tables 1, 2).

At 9 weeks of age, rats were divided into four groups: control, pair feeding (PairFed), lysine deficiency (LysDef) and valine deficiency (ValDef) groups. LysDef and ValDef diets were adjusted with glutamine to make them isonitrogenous with the control diet ($N = 6$ in each group and total number is 24). The animals were fed these diets ad libitum for an additional 4 weeks. The PairFed group was fed the control diet adjusted to the same amount as that in the ValDef group. Body weight and amount of food intake were measured from Monday to Friday. On day 28 after dividing into groups, animals were anesthetized by diethyl ether and sacrificed to collect blood and liver.

To obtain time-course data of rats fed ValDef diet, rats kept under the same condition as the previous experiment

Table 1 Diet composition

%, w/w	
Amino acid mixture	20.0
L-Cystine	0.3
Corn starch	62.9
Cellulose	5.0
Soybean oil	7.0
AIN93G Mineral Mix	3.5
AIN93G Vitamin Mix	1.0
Choline bitartrate	0.25
t-Butyl hydroquinone	0.0014
Energy (kcal/g)	3.5

Table 2 Amino acid composition in each diet

%, w/w	Control	LysDef	ValDef
Alanine	2.55	2.55	2.55
Arginine	3.28	3.28	3.28
Asparagine·H_2O	3.6	3.6	3.6
Aspartic acid	3.16	3.16	3.16
Cystine	0.5	0.5	0.5
Glutamate	9.16	9.16	9.16
Glutamine	9.16	16.22	12.74
Glycine	1.62	1.62	1.62
Histidine	2.54	2.54	2.54
Isoleucine	4.45	4.45	4.45
Leucine	8.13	8.13	8.13
Lysine·HCl	8.82	0	8.82
Methionine	2.43	2.43	2.43
Phenylalanine	4.5	4.5	4.5
Proline	9.37	9.37	9.37
Serine	5.06	5.06	5.06
Threonine	3.81	3.81	3.81
Tryptophan	1.08	1.08	1.08
Tyrosine	4.85	4.85	4.85
Valine	5.73	5.73	0
Amino acid-total	93.82	92.06	91.67
Starch	6.18	7.94	8.33
Total	100	100	100

were fed ValDef diet at 9 weeks of age. Before changing to ValDef diet, rats which were fed control diet were anesthetized by diethyl ether and blood and liver were collected to obtain the basal data. Then rats fed ValDef diet were anesthetized by diethyl ether and blood and liver were collected on days 1, 2, 7, 14 and 21 after changing the diet ($N = 6$ in each group and total number is 36).

At least two replicates of each experimental group were made. No mortality was observed during the studies.

Amino acid analysis and quantification of mRNA expression

Amino acid concentrations in the plasma and liver were measured according to the protocol of Noguchi et al. 2006. For quantification of mRNA expression, total RNA was isolated from the liver by the acid guanidinium isothiocyanate-phenol-chloroform method (Isogen; Nippon Gene, Tokyo, Japan). Total RNA (2 μg) was used for reverse transcription reaction (final volume, 8 μl) with 80 U of SuperScript™ II RNase H Reverse Transcriptase (Invitrogen), dNTP and random primers for 60 min at 42°C according to the manufacturer's instructions.

Quantitative PCR was performed using TaqMan polymerase with detection of SYBR green fluorescence (Schmittgen and Zakrajsek 2000; Simpson et al. 2000) using an ABI PRISM 7900HT Sequence Detection System (Applied Biosystems, CA, USA). The expression levels of beta-actin (Gene ID: 81822), PHGDH (Gene ID: 58835) and SDS (Gene ID: 25044) mRNAs were measured individually. When necessary, cDNA solutions were diluted in order to obtain the results within the range of measurement. In order to normalize, the relative expression level of each gene was obtained by dividing the expression levels of PHGDH and SDS by the expression levels of beta-actin as a housekeeping gene. The following sense and antisense sequences were employed: 5′-TCTGAAGAATGCTGGG ACCT-3′ (sense) and 5′-GCTTAGCGTTCACCAAGTT CA-3′ (antisense) for PHGDH, 5′-CTTGGGTGTGAACA CTGTGG-3′ (sense) and 5′-CAGTCACAGCCTCCTGG TCT-3′ (antisense) for SDS and 5′-CTCCAAGTATCC ACGGCATAG-3′ (sense) and 5′-AAGCAATGCTGTCA CCTTCC-3′ (antisense) for beta-actin.

Statistical analysis

Data are presented as mean ± standard error of the mean. Changes in amount of food intake and body weight were analysed by two-way analysis of variance (ANOVA) followed by Fisher's LSD method. The other data were analysed by one-way ANOVA followed by Fisher's LSD method, and when normality or equal variance tests failed, Kruskal–Wallis one-way ANOVA on Ranks was performed, which was followed by the Student–Newman–Keuls method.

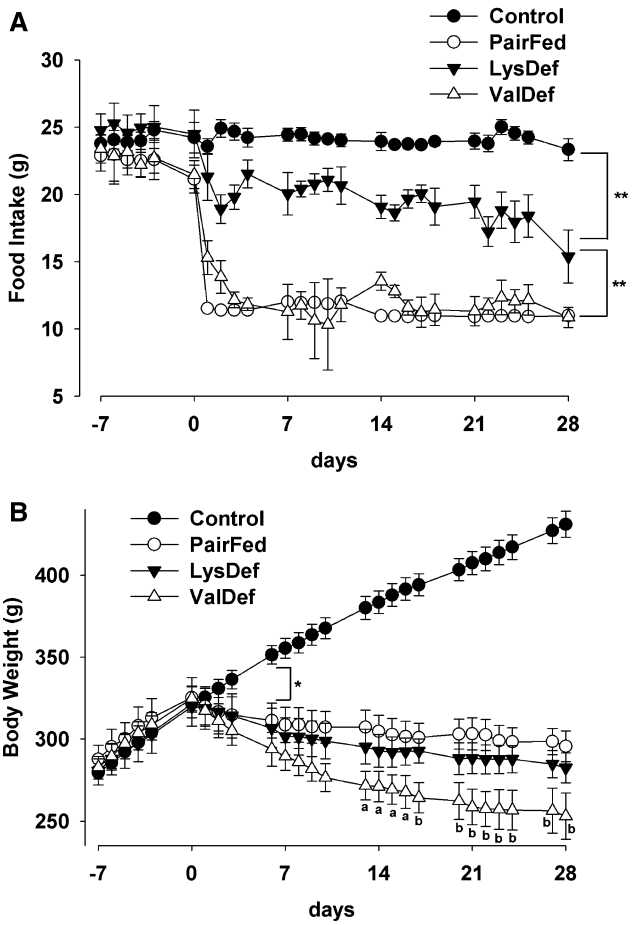

Fig. 1 Changes in food intake and body weight of rats fed each experimental diet. Two-way ANOVA followed by Fisher's LSD method was performed ($N = 6$ in each group). **a** The significant differences of daily food intake between experimental groups are shown as $^{**}P < 0.01$. **b** The significant differences of body weight between control and other groups are indicated as $^{*}P < 0.05$ on day 7. The significant differences between ValDef group and PairFed group are indicated as letter "*a*" and the significant differences between ValDef group and LysDef group are indicated as letter "*b*"

Results

Body weight and food intake

The food intake of the LysDef group was significantly lower than that of control group, and the food intake of ValDef group was significantly lower than that of LysDef group (Fig. 1a). While daily body weight gains were observed in the control group, body weights in PairFed, LysDef and ValDef groups decreased continuously and were significantly lower than that in the control group after day 6 (Fig. 1b). The body weight of ValDef group was

Table 3 Plasma amino acid concentrations of rats fed each experimental diet on day 28

(μmol/l)	Control	PairFed	LysDef	ValDef
Alanine	574.0 ± 22.9	423.2 ± 17.8*	416.2 ± 27.7*	452.5 ± 52.3*
Arginine	141.6 ± 5.9	89.6 ± 3.3*	122.6 ± 6.9	127.2 ± 8.5
Asparagine	73.1 ± 4.7	64.4 ± 4.2	51.4 ± 3.7	60.3 ± 5.8
Aspartic acid	9.1 ± 0.4	6.8 ± 1.9	10.4 ± 1.5	9.9 ± 1.1
Cystine	61.6 ± 2.1	53.9 ± 2.1	31.9 ± 3.2*	46.8 ± 7.1*
Glutamate	104.5 ± 4.8	77.8 ± 18.3	89.8 ± 5.8	91.2 ± 9.1
Glutamine	456.4 ± 12.9	467.5 ± 14.0	466.4 ± 47.9	454.7 ± 34.3
Glycine	236.5 ± 9.9	218.9 ± 8.8	230.4 ± 14.4	289.6 ± 20.2*
Histidine	64.0 ± 2.0	54.7 ± 2.3	81.8 ± 6.9*	94.8 ± 6.0*
Isoleucine	82.3 ± 4.0	75.8 ± 4.9	50.5 ± 2.9*	57.1 ± 6.4*
Leucine	139.9 ± 6.7	128.6 ± 11.0	91.2 ± 6.4*	91.1 ± 9.2*
Lysine	568.3 ± 26.5	364.0 ± 25.2*	106.4 ± 18.7*	439.7 ± 26.2*
Methionine	83.5 ± 4.7	89.0 ± 3.9	38.9 ± 2.2*	57.1 ± 6.7*
Phenylalanine	67.4 ± 3.6	71.2 ± 3.5	59.0 ± 3.9	54.6 ± 7.3
Proline	317.5 ± 26.7	299.7 ± 28.5	159.9 ± 28.1*	149.1 ± 11.3*
Serine	282.1 ± 10.4	241.6 ± 13.4	590.4 ± 83.6*	889.7 ± 111.5*
Threonine	406.5 ± 18.4	227.8 ± 6.1	1717.0 ± 133.4*	2140.3 ± 243.6*
Tryptophan	81.6 ± 5.2	45.1 ± 4.3	66.5 ± 7.5	29.0 ± 3.1*
Tyrosine	131.9 ± 7.3	72.5 ± 3.4*	75.1 ± 11.4*	64.6 ± 3.2*
Valine	190.8 ± 9.8	164.1 ± 9.7	141.3 ± 10.9*	80.5 ± 16.2*

Values are mean ± SEM. $N = 6$ in each group

*Significantly different ($P < 0.05$) from the control

significantly lower than those of PairFed group and LysDef group from day 13 and day 17, respectively.

Plasma and liver amino acid concentrations

The plasma lysine and valine concentrations were significantly lower in LysDef and ValDef groups than in the other three groups, respectively, on day 28 (Table 3). Both LysDef and ValDef groups showed increases in plasma concentrations of only three amino acids: histidine, serine and threonine. The magnitudes of these increments were approximately 1.5-fold for histidine, twofold to threefold for serine and fourfold to fivefold for threonine.

As illustrated in Fig. 2, hepatic serine concentration reached 6788.3 ± 1362.2 μmol/kg in LysDef group and 10592.7 ± 1542.4 μmol/kg in ValDef group, while that in control group remained at 479.8 ± 36.4 μmol/kg. Similarly, hepatic threonine concentration reached 8933.9 ± 2151.2 μmol/kg in LysDef group and 13679.6 ± 2438.0 μmol/kg in ValDef group, while that in the control group remained at 462.7 ± 19.0 μmol/kg. Remarkable elevations of hepatic serine and threonine concentrations—14- to 22-fold and 19- to 30-fold, respectively—occurred in both LysDef and ValDef groups on day 28. The time-courses of increments in hepatic serine and threonine concentrations after switching to ValDef diet are presented in Fig. 2b, c, where significant increases in serine and threonine were detected on days 2 and 14, respectively, which were followed by continuous elevation. The time-courses of increases in plasma serine and threonine concentrations are illustrated in Fig. 2d; the increments in serine and threonine concentrations reached significant levels on days 7 and 14, respectively, concomitant with the increase in hepatic serine and threonine levels.

PHGDH and SDS mRNA levels

In LysDef and ValDef groups, expression levels of PHGDH mRNA increased markedly to more than 100-fold higher than those of control and PairFed groups, while SDS mRNA expression was significantly attenuated on day 28 (Fig. 3a, b). The time-courses of changes in hepatic PHGDH and SDS expression after switching to ValDef diet are depicted in Fig. 3c, d. Figure 3c shows that the significant increment of PHGDH expression was detectable on day 1 followed by a continuous elevation. In contrast, as is shown in Fig. 3d, SDS expression significantly decreased on day 14, and declined continuously throughout the remainder of the experimental period.

Discussion

The results of the present study demonstrated that elevation of serine and threonine in the plasma and liver were associated with up-regulation of mRNA expression of PHGDH and down-regulation of mRNA expression of SDS in the liver. Of all the essential amino acids, we chose diets

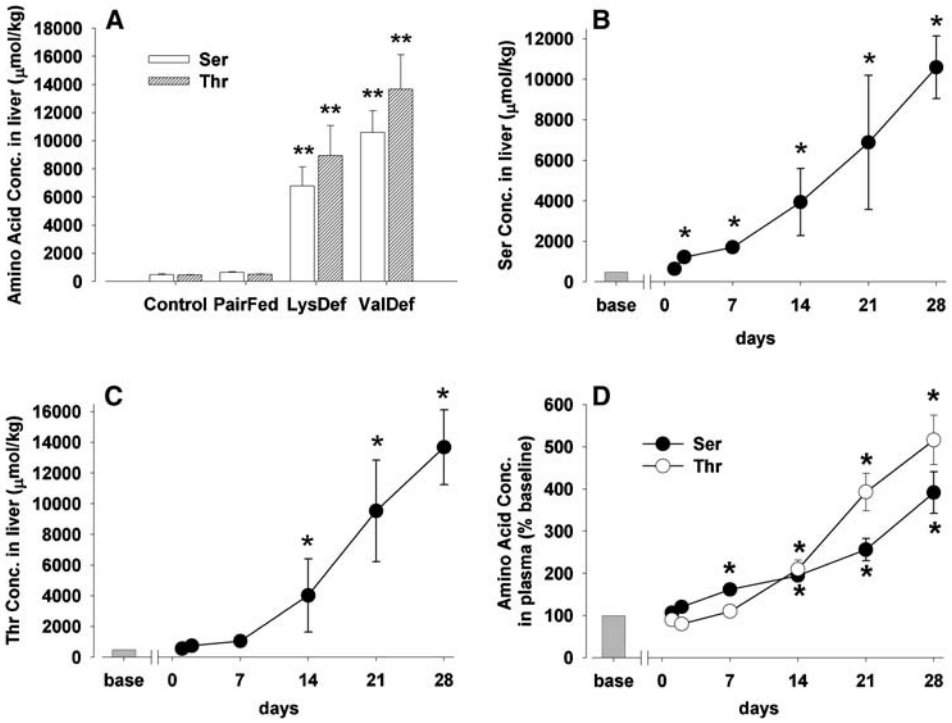

Fig. 2 Serine and threonine concentrations of liver and plasma in each experimental diet group. The data were analysed by one-way ANOVA followed by Fisher's LSD method, and when normality or equal variance tests failed, Kruskal–Wallis one-way ANOVA on Ranks was performed, which was followed by the Student–Newman–Keuls method. Significant differences from the appropriate control or baseline are indicated as $*P < 0.05$ and $**P < 0.01$ ($N = 6$ in each group). **a** Hepatic serine and threonine concentrations in each group. **b** Time-course data of hepatic serine concentrations in rats fed ValDef diet. Basal data indicates the hepatic serine concentration of rats fed control diet before changing to ValDef diet. **c** Time-course data of hepatic threonine concentrations in rats fed ValDef diet. Basal data indicates that of rats fed control diet before changing to ValDef diet. **d** Plasma serine and threonine concentrations of rats fed ValDef diet. Basal data indicates those of rats fed control diet before changing to ValDef diet, respectively

deficient in lysine or valine, because plasma lysine concentration is most highly conserved regardless of nutritional condition due to its capacity for reservation and slower catabolism (Flodin 1997), while valine deficiency is associated with severe phenotypes in rats (Hutchison et al. 1983). The changes in PHGDH and SDS activities are mainly regulated at the transcriptional level and the protein expression level corresponds linearly to the expression level of mRNA (Kanamoto et al. 1991; Ogawa et al. 1991; Achouri et al. 1999). Actually, time-course data of PHGDH and SDS mRNAs (Fig. 3) showed that a significant increment of PHGDH mRNA expression on day 1 preceded a significant decrement of SDS mRNA expression on day 14. In accordance with the gene expression patterns described above, elevations of serine concentrations in either the liver (Fig. 2b, c) or plasma (Fig. 2d) preceded that of threonine. The accordance of changes of mRNAs with the hepatic elevation of serine and threonine levels (Figs. 2, 3) indicates that accumulation of hepatic serine and threonine can be mainly attributable to the marked synthetic enhancement indicated by the increased PHGDH mRNA expression and the simultaneous alleviation of degradation indicated by the decreased SDS mRNA expression. As the reservoir sizes of serine and threonine in the muscle or kidney are smaller than that of the liver, the majority of plasma serine and threonine should be derived from the liver where serine and threonine were accumulated at remarkably high levels.

In order to make the nutritional condition among groups to be comparable, we put PairFed group whose nutritional condition is almost the same as ValDef group except for the valine content. Since the nutritional condition of carbohydrates, lipids or amino acids except for valine are comparable between these groups, it can be concluded that changes of mRNA expressions of PHGDH and SDS, and serine and threonine concentrations in plasma and liver were attributable to the deficiency of valine itself. Although we did not put PairFed group for LysDef group, it is possible to conclude similarly that changes shown in LysDef group are due to lack of lysine itself. This is because no signs of increment of serine and threonine levels in plasma or liver were seen nor the increment of PHGDH mRNA expression nor the decrement of SDS mRNA expression were seen in PairFed group for ValDef

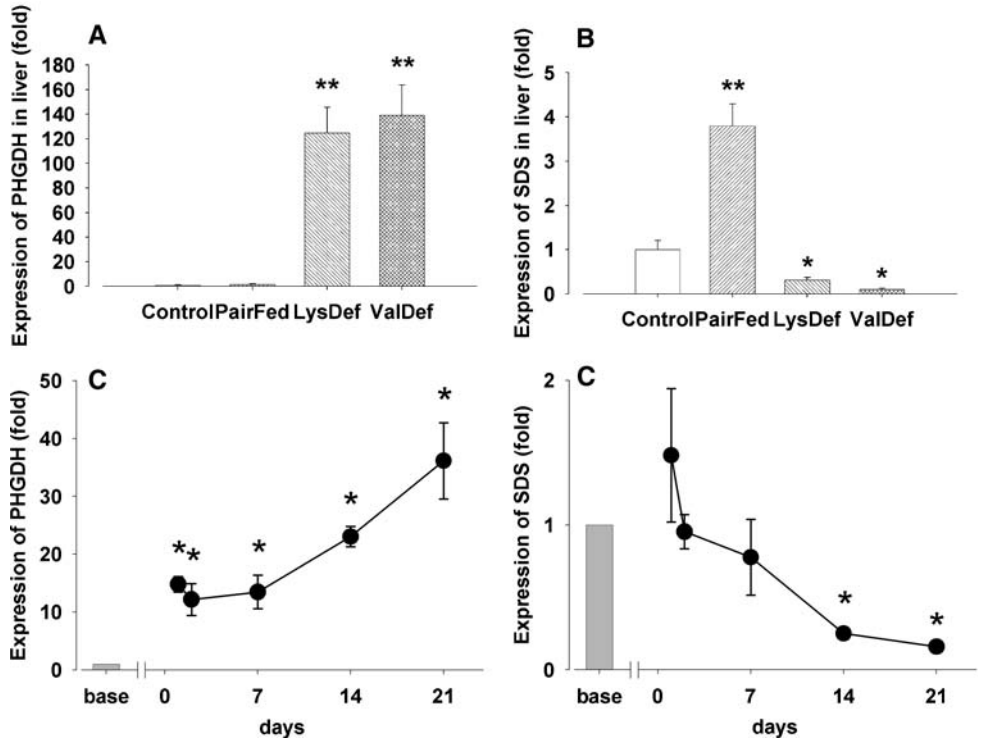

Fig. 3 mRNA expression changes of PHGDH and SDS in the livers of rats fed each experimental diet. The data were analysed by one-way ANOVA followed by Fisher's LSD method, and when normality or equal variance tests failed, Kruskal–Wallis one-way ANOVA on Ranks was performed, which was followed by the Student–Newman–Keuls method. Significant differences from the appropriate control or baseline are shown as $*P < 0.05$ and $**P < 0.01$ ($N = 6$ in each group). **a** PHGDH mRNA expressions in liver on day 28. **b** SDS mRNA expressions in liver on day 28. **c** Time-course data of hepatic PHGDH expressions in rats fed ValDef diet. Basal data indicates that of rats fed control diet before changing to ValDef diet. **d** Time-course data of hepatic SDS expressions in rats fed ValDef diet. Basal data indicates that of rats fed control diet before changing to ValDef diet

diet, whose food intake was set much lower than that of LysDef group. Although difference in calories intake was minimized between PairFed and ValDef groups, body weight of PairFed group was maintained significantly higher than the amino acid deficient groups from day 13 on (Fig. 1b). Higher weight loss in the amino acid deficient groups may signify extra calorie consumption for adapting to the essential amino acid deficiency metabolically. SDS is generally known as a gluconeogenic enzyme, as its activity is strongly enhanced by starvation, diabetes mellitus or feeding with a high-protein diet (Snell 1984). In fact, enhanced SDS expression level was observed in the PairFed group in the present study (Fig. 3b), which was attributed to the insufficient calorie intake. However, SDS expression levels were significantly attenuated in LysDef and ValDef groups, probably not to suppress gluconeogenesis but to somehow adapt to the essential amino acid deficiency, as will be discussed later.

Excess amino acids released by proteolysis are usually degraded to ammonia and are transported as glutamate and/or glutamine to the liver and kidneys, where ammonia is freed and processed in the urea cycle (Desvergne et al. 2006). However, hepatic concentrations of ammonia and urea in LysDef and ValDef in the present study were not high enough to indicate that the majority of amino acids released by proteolysis had been converted into these metabolites. Highly accumulated serine and threonine in the liver could be regarded as acceptors for amino radicals to lessen the contribution of the common degradation pathway of ammonia to urea. Storage of amino radicals as serine and threonine is assumed to be much less toxic than storage as ammonia, which shows toxicity as hepatic encephalopathy. Ammonia neurotoxicity involves altered energy metabolism, abnormal neurotransmitter function and changes in ionic homeostasis (Albrecht and Jones 1999). As hepatic ammonia level remains at around 3,000 μmol/kg, the marked increases in hepatic serine and threonine in the deficient groups were able to absorb fivefold to eightfold greater amounts of amino radicals than ammonia. Furthermore, from the viewpoint of energy profits, conversion of glutamate to serine requires less energy than that to urea (Salway et al. 2004), which will be beneficial in the deficient groups where energy intake is significantly decreased.

A greater anorectic effect of essential amino acid deficiency was observed in the ValDef group than in the LysDef group (Fig. 1a). The anorectic response to amino acid imbalanced diet has been explained by a sensing mechanism in the anterior piriform cortex in the brain (Gietzen and Rogers 2006). When rodents ingest amino acid imbalanced diet, the amount of uncharged tRNAs increase in the cells in the anterior piriform cortex, which triggers activation of general control non-derepressible-2 (GCN2) to stop feeding behaviour. GCN2 pathway is known as the conserved pathway from yeast to mammals to sense amino acid imbalances in a cell. In rodents, this pathway is already demonstrated to cause acute anorectic effect to amino acid imbalanced diet (Gietzen and Rogers 2006). However, different magnitude of anorectic effects between LysDef diet and ValDef diet cannot be explained under this scheme. Further study should be done to demonstrate the possible differences of GCN2 pathway between the ingestion of LysDef diet and ValDef diet. On the other hand, excessive threonine intake is known to evoke anorexia (Anderson and Ralten 1992). As is shown in Table 3, increases of plasma threonine were observed in both LysDef group and ValDef group. This elevation of plasma threonine could cause the suppression of intake of each diet and it might also be one of the adaptational mechanisms to avoid surfeit ingestion of amino acid deficient diet.

In conclusion, we found that increases in plasma serine and threonine levels due to essential amino acid deficiency in the diet are caused by marked increases in hepatic serine and threonine levels resulting from either enhancement of PHGDH or attenuation of SDS gene expression. As a low-protein diet are also known to enhance PHGDH and attenuate SDS gene expression (Mauron et al. 1973), this type of adaptational modification of amino acid metabolism is assumed to be a basic biological reaction under conditions of a nitrogen-scarce diet. However, the mechanisms involved in enhancement of the expression of PHGDH and attenuation of SDS by amino acid deficiency remain unclear.

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