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DHA regulates lipogenesis and lipolysis genes in mice adipose and liver

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Abstract Docosahexaenoic acid (DHA) is one kind of ω-3 polyunsaturated fatty acids (PUFAs) and plays an important role in lipid metabolism. In this research, mice were daily intragastric administrated with DHA for 3 weeks. Subcutaneous adipose tissue and liver were separated every week, RNA was extracted. Peroxisome proliferator-activated receptor (*PPARγ*), Sterol regulatory element binding protein-1c (*SREBP-1c*), Fatty acid synthetase (*FAS*), Hormone sensitive lipase (*HSL*) and triglyceride hydrolase *TGH* genes expression were detected by quantitative PCR. Data showed that, DHA up-regulated *PPARγ*, *HSL* and *TGH* in adipose tissue, but it had no effect on *SREBP-1c* and *FAS* expression. However, in liver there were some differences in regulating these genes. *PPARγ*, *SREBP-1c* and *FAS* were down-regulated, *HSL* was up-regulated and *TGH* had no change. These results indicated that DHA played different regulating roles in lipid metabolism in different tissues. In adipose tissue, DHA increased the expression of lipogenesis and lipolysis genes. In liver lipogenesis genes were decreased, but lipolysis genes were increased by DHA. In conclusion, DHA could reduce body fat mass through regulating lipogenesis and lipolysis genes.

Keywords DHA · Mice · Lipogenesis genes · Lipolysis genes

Introduction

Obesity has become one of the most popular diseases in recent years. Researches on how to prevent obesity and cure relative diseases caused by obesity become very hot. DHA is an essential ω-3 PUFAs, and plays an important role in growth and functions as an important composition of nervous tissue and biomembrane [1, 2]. Many researches found that PUFAs can regulate lipid mobilization in many kinds of animals [3–5]. Dietary DHA not only affected tissue DHA concentration but also modified the expression of genes related to fatty acid metabolism [6]. ω-3 PUFAs impact lipid and sugar mobilization through regulating some transcription factors and enzymes. As transcription factors, *PPARγ* and *SREBP-1c* are known to regulate expression of many enzymes. *SREBP-1c* up-regulates the expression of *FAS*, and promotes fat synthesis [7–10]. Supplementation with long chain ω-3 PUFAs in human diet produced a decrease in fasting plasma triglyceride (TG) (−35%) and accompanied by a remarkable increase in the concentration of LPL mRNA in adipose tissue (+55%) [4]. ω-3 PUFAs also has positive therapeutic effect on cardiovascular diseases and hypertriglyceridemia [11–13]. Recent studies mainly focused on lipogenesis, however, there was few research on lipolysis. In our study, DHA was intragastric administrated to mice for 3 weeks, lipogenesis and lipolysis genes were analyzed. Results showed that DHA can decrease lipogenesis and increase lipolysis. It can provide both-around information for the treatment of obesity and other relative diseases.

Materials and methods

Animals

Male Kunming mice (2 weeks old) were purchased from the Fourth Military Medical University (Xi'an, China). These mice were maintained in a temperature-controlled

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room (25°C) on a 12-h light/dark cycle. The animals were fed a standard rodent chow diet, and had free access to food and water for 1 week of an acclimatization period. The mice were then divided into three groups randomly, control group (control), low concentration group (low) and high concentration group (high), each group had 15 mice, and each group had five repetition. Low and high concentration groups were daily intragastric administrated 6.25 and 12.5 g/kg DHA (Sigma) respectively, and control group was daily intragastric administrated 0.9% sodium chloride for 3 weeks. Every week five mice of each group were weighed after one-night fast and then killed by decapitation. Subcutaneous adipose tissue and liver were surgically removed and frozen in liquid nitrogen.

Gene cloning

Total RNA was extracted from adipose tissue and liver using Trizol reagent (Invitrogen, USA). First strand cDNA was prepared with RevertAidTM First Strand cDNA Synthesis Kit (Fermentas). Primers of *β-actin*, *PPARγ*, *SREBP-1c*, *FAS*, *HSL* and *TGH* genes were designed (Table 1). PCR reaction conditions were summarized in Table 1. The 50 μl PCR reaction contained 2 μl tissue-specific cDNA, 4 μl $MgCl_2$ (25 mmol/l), 0.5 μl *Taq* DNA polymerase (Fermentas), 5 μl dNTPs (2.5 mmol/l), 5 μl 10× buffer and 1 μl of each primer (10 μmol/l). Product was examined by agarose gel electrophoresis (AGE).

Real-time quantitative PCR

We measured the expression of *PPARγ*, *SREBP-1c*, *FAS*, *HSL*, and *TGH* mRNA from samples of adipose tissue and liver by real time quantitative PCR. The 20 μl real-time reaction system contained 12.5 μl SYBR Premix EX Taq (Takara, Japan), 0.5 μl Forward Primer (10 μmol/l), 0.5 μl Reverse Primer (10 μmol/l), 1 μl cDNA, 10.5 μl ddH_2O. Reactions were incubated in an TP800 Real-time System (Takara, Japan) for 10 s at 95°C, followed by 32 cycles of 95°C for 5 s and 60°C for 30 s, 95°C at 15 s, 60°C at 30 s, 95°C at 15 s.

Using real-time quantitative PCR to analyze the expression of these genes, the method of $2^{-\Delta\Delta C}$t was also used. Relative quantification of gene expression was evaluated by utilizing the comparative critical threshold (C_t). The C_t values for each gene reaction were subtracted from the respective C_t value of the *β-actin* control, resulting in the ΔC_t value. The largest ΔC_t value was arbitrarily used as a constant that was subtracted from all other ΔC_t values to determine $\Delta\Delta C_t$ value. Fold changes were then generated for each gene by calculating $2^{-\Delta\Delta C}$t.

Data analysis

Software SPSS 13.0 was used for statistical analysis. The expression of genes was analyzed with one-way ANOVA and LSD multiple comparison. Results were considered statistically significant if $P < 0.05$ (*) and extremely significant if $P < 0.01$ (**). All data from samples were shown as means ± standard error (SEM).

Results and analysis

DHA affected average daily gain (ADG) of mice

To investigate the effect of DHA on mice body weight, ADG was used to describe it. Every week before mice were killed, body weight (BW_n) was weighed. ADG was obtained by formula $(BW_n - BW_{n-1})/7$. Data showed that ADG had a significant decrease with time and dose increasing ($P < 0.01$) (Fig. 1). In control group, the ADG decreased gradually, it might be caused by sodium chloride.

Table 1 Sequence of primers and T_m

Gene and accession number	Primer sequences (5′–3′)	Amplicon size (bp)	T_m (°C)
β-actin (NM_007393.2)	Forward: ACTGCCGCATCCTCTTCCTC	399	53.8
	Reverse: CTCCTGCTTGCTGATCCACATC		
PPARγ (U01664)	Forward: ACCACTCGCATTCCTTTGAC	261	52.1
	Reverse: CCACAGACTCGGCACTCAAT		
SREBP-1c (AB017337)	Forward: CTGGAGACATCGCAAACAAGC	277	59.7
	Reverse: ATGGTAGACAACAGCCGCATC		
FAS (BC046513)	Forward: AGTGTCCACCAACAAGCG	280	55.9
	Reverse: GATGCCGTCAGGTTTCAG		
HSL (NM_010719)	Forward: GGAGCACTACAAACGCAAC	357	57.9
	Reverse: TCCCGTAGGTCATAGGAGAT		
TGH (NM_053200)	Forward: CTTGGCTCCTTGAGATTTG	455	53.3
	Reverse: AGTTGGCAATGTTGTCCTG		

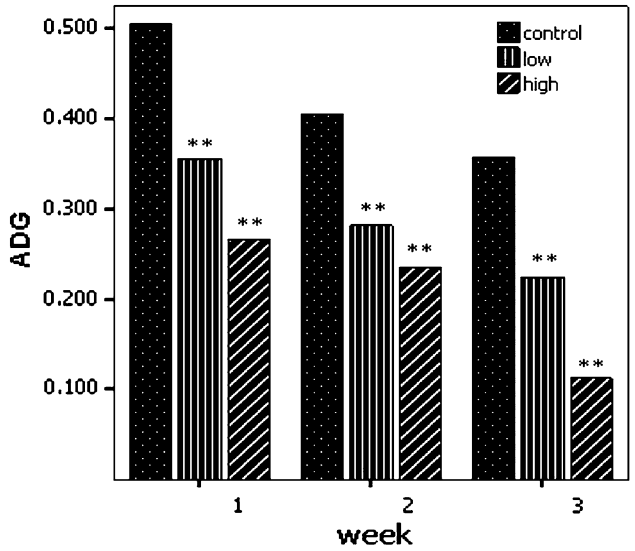

Fig. 1 Effect of increasing concentrations of DHA on mice ADG. Values are means ± SEM. ** $P < 0.01$

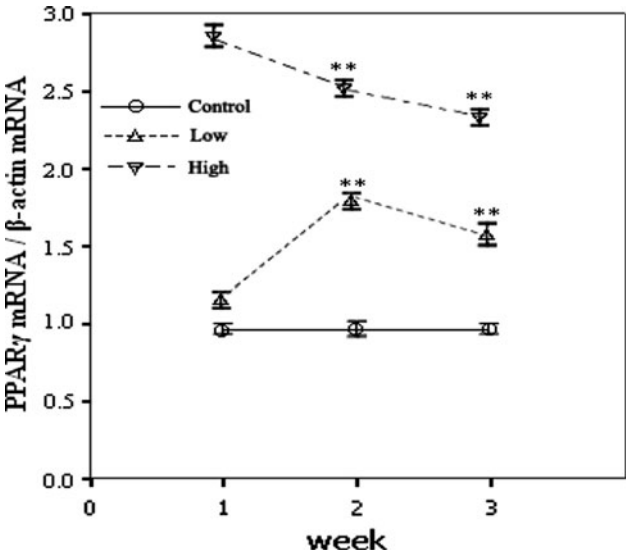

Fig. 2 Effect of DHA on *PPARγ* expression in mice adipose for 3 weeks. Quantitative PCR analysis of the expression level of *PPARγ*. *β-actin* was used as an internal control. Values are means ± SEM of experiments from 15 mice, each has five repetition. ** $P < 0.01$

Effect of DHA on lipogenesis genes mRNA expression in adipose and liver

To examine the potential effect of DHA on lipogenesis, real-time PCR was used to determine the expression level of *PPARγ*, *SREBP-1c* and *FAS*, which were seen as lipogenesis genes. The *β-actin* was used as the internal standard to correct for small RNA loading differences. Results showed that in adipose tissue *PPARγ* mRNA expression increased significantly with time (Fig. 2) and DHA dose increasing (150, 152 and 127% compared with control for every week) ($P < 0.05$), however, *SREBP-1c* didn't change in adipose tissue ($P > 0.05$) (Fig. 3). Compared with control group, there was no significant difference of *FAS* expression neither in low concentration group nor in high concentration group ($P > 0.05$) (Fig. 4). In liver DHA down-regulated *PPARγ* mRNA expression (51, 54 and 60% compared with control for every week) ($P < 0.05$). There was no time-dependent effect in previous 2 weeks, but in the 3rd week it had a significant decrease ($P < 0.01$) (Fig. 5). On the other hand, *SREBP-1c* (22, 27 and 31% compared with control for every week) ($P < 0.05$) and *FAS* (11, 21 and 28% compared with control for every week) ($P < 0.05$) were both down-regulated by DHA, and in the 3rd week in high concentration group *SREBP-1c* and *FAS* expressed the lowest level ($P < 0.01$) (Figs. 6, 7).

Effect of DHA on lipolysis genes mRNA expression in adipose and liver

To examine the potential effect of DHA on lipolysis, *HSL* and *TGH* were chosen as lipolysis genes because they are important genes in lipid hydrolysis process. *β-actin* was also used as the internal standard. The expression levels of these two genes at different time and doses were analyzed. Data showed that in mice adipose tissue DHA can up-regulate the expression of *HSL* (63, 69 and 82% compared with control for every week) and *TGH* (64, 69 and 76% compared with control for every week), and the level achieved the maximum in the 3rd week ($P < 0.01$) (Figs. 8, 9). The level change also depended on DHA dose (Figs. 8, 9). *HSL* increased significantly (41, 42 and 39%

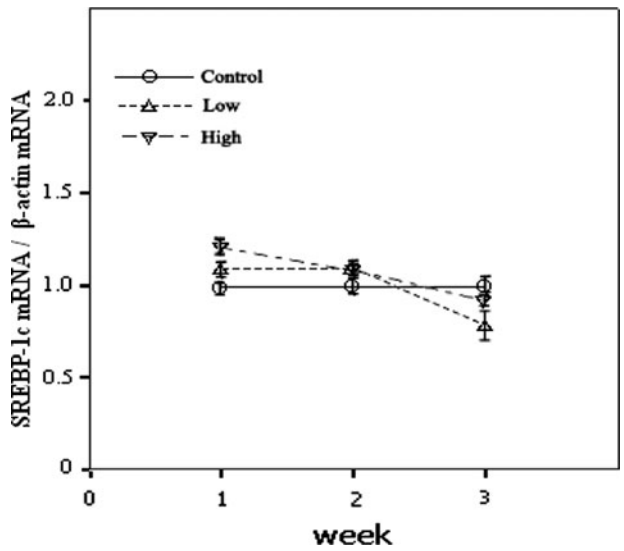

Fig. 3 Effect of DHA on *SREBP-1c* expression in mice adipose for 3 weeks. Real-time analysis of the expression level of *SREBP-1c*. *β-actin* was used as an internal control. Values are means ± SEM of experiments from 15 mice, each has five repetition

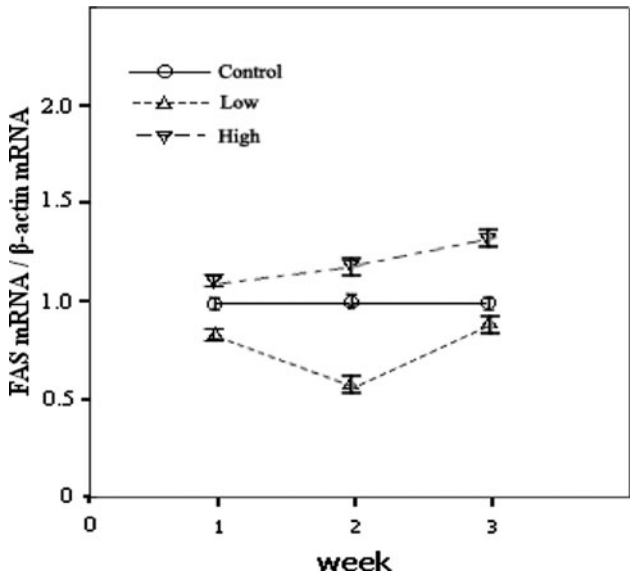

Fig. 4 Effect of DHA on *FAS* expression in mice adipose for 3 weeks. Real-time analysis of the expression level of *FAS*. *β-actin* was used as an internal control. Values are means ± SEM of experiments from 15 mice, each sample has five repetition

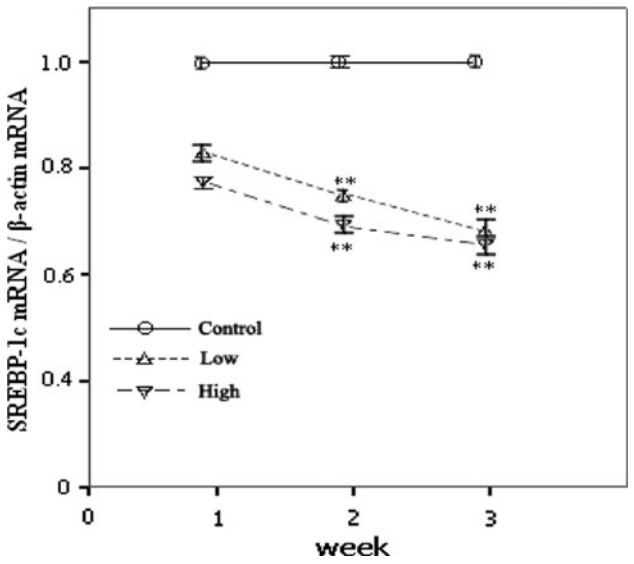

Fig. 6 Effect of DHA on *SREBP-1c* expression in mice liver for 3 weeks. Expression level of *SREBP-1c* in mice liver was analyzed by using quantitative PCR. *β-actin* was used as an internal control. Values are means ± SEM of experiments from 15 mice, each sample has five repetition. ** $P < 0.01$

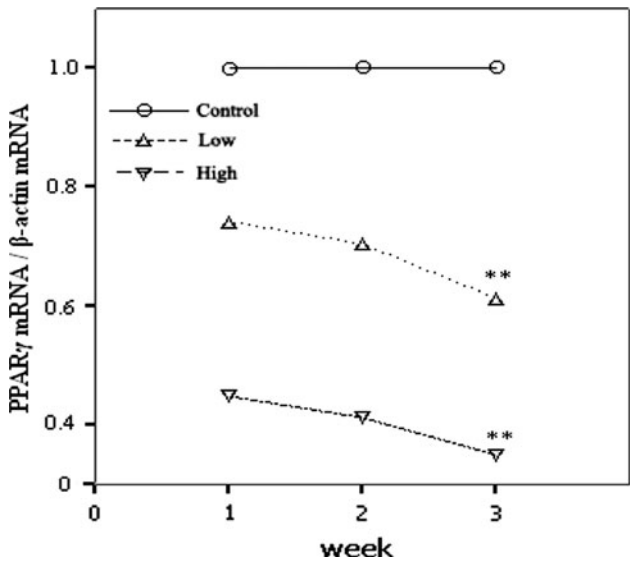

Fig. 5 Effect of DHA on *PPARγ* expression in mice liver for 3 weeks. Expression level of *PPARγ* in mice liver was analyzed by using quantitative PCR. *β-actin* was used as an internal control. Values are means ± SEM of experiments from 15 mice, each sample has five repetition. ** $P < 0.01$

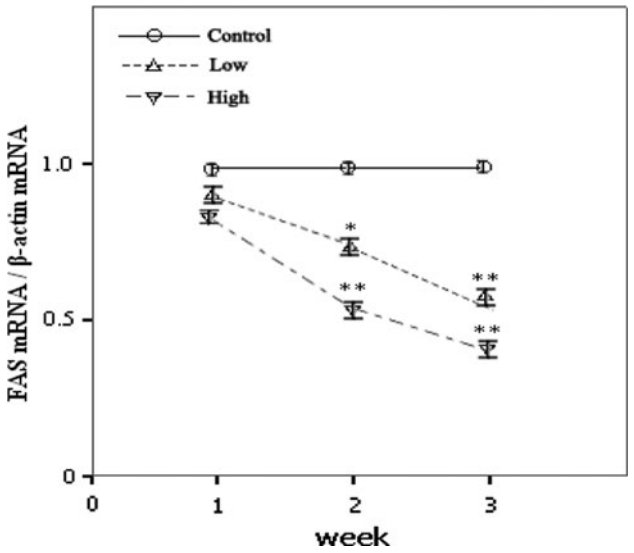

Fig. 7 Effect of DHA on *FAS* expression in mice liver for 3 weeks. Real-time PCR analysis of the expression level of *FAS* in mice liver. *β-actin* was used as an internal control. Values are means ± SEM of experiments from 15 mice, each sample has five repetition. ** $P < 0.01$. * $P < 0.05$

compared with control for every week) in liver after the treatment of DHA ($P < 0.01$) (Fig. 10).These findings indicated that DHA can up-regulate the expression of *HSL* both in adipose tissue and liver. However, *TGH* expressed no difference in liver among groups and weeks ($P > 0.05$) (Fig. 11).

Discussion

The PPARs were the nuclear receptors family, eicosanoids and fatty acids can regulate gene transcription through PPARs. *PPARγ* is one member of this family, and plays important roles in regulating lipogenesis and some diseases

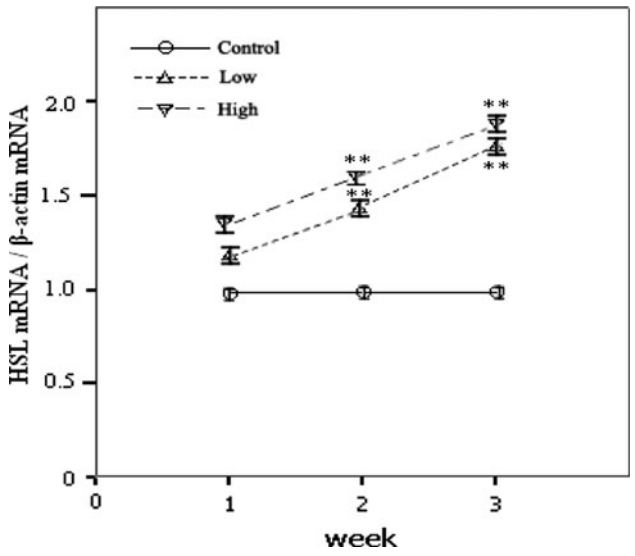

Fig. 8 Effect of DHA on *HSL* expression in mice adipose for 3 weeks. Real-time PCR analysis of the expression level of *HSL* in mice adipose. *β-actin* was used as an internal control. Values are means ± SEM of experiments from 15 mice, each sample has five repetition. ** $P < 0.01$

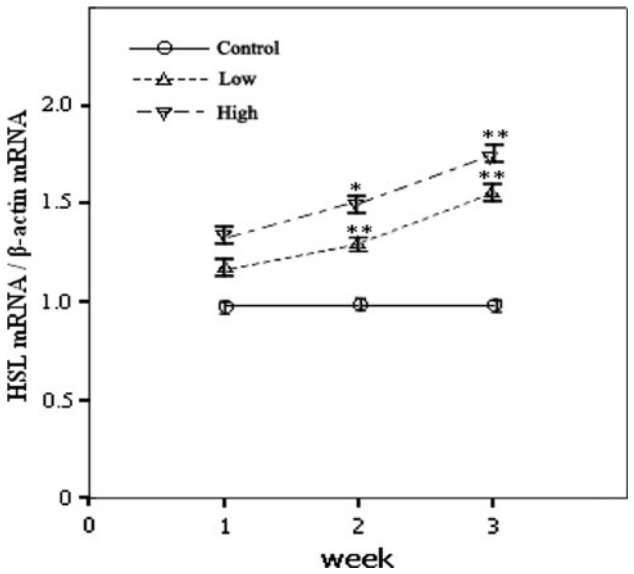

Fig. 10 Effect of DHA on *HSL* expression in mice liver for 3 weeks. The expression level of *HSL* in mice liver was analyzed by using real-time PCR, and *β-actin* was used as an internal control. Values are means ± SEM of experiments from 15 mice, each sample has five repetition. ** $P < 0.01$. * $P < 0.05$

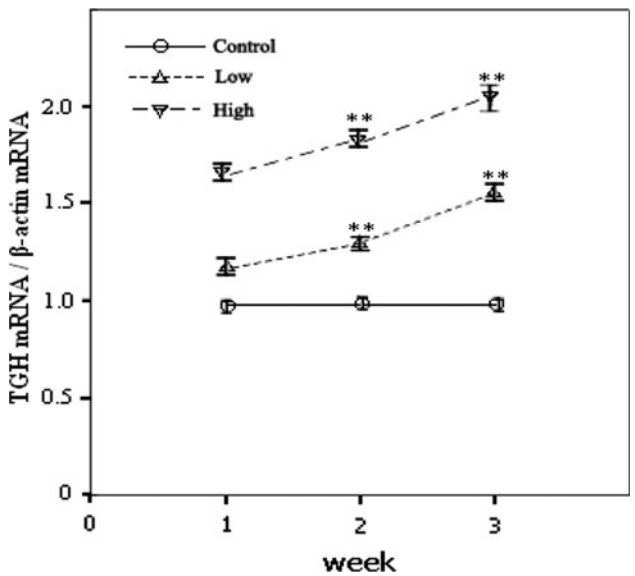

Fig. 9 Effect of DHA on *TGH* expression in mice adipose for 3 weeks. The expression level of *TGH* in mice adipose was analyzed by using real-time PCR, and *β-actin* was used as an internal control. Values are means ± SEM of experiments from 15 mice, each sample has five repetition. ** $P < 0.01$

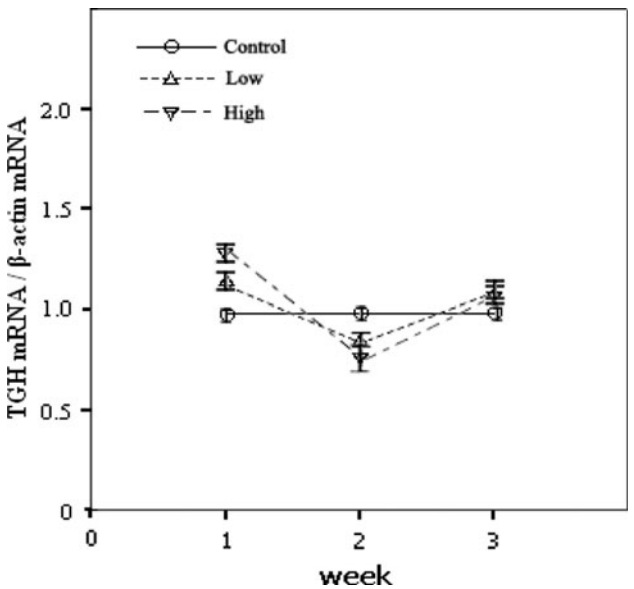

Fig. 11 Effect of DHA on *TGH* expression in mice liver for 3 weeks. Real-time analysis the expression level of *TGH* in mice liver, and *β-actin* was used as an internal control. Values are means ± SEM of experiments from 15 mice, each sample has five repetition. ($P > 0.05$)

relative with obesity [14]. Human isolated adipocytes were treated with eicosapentaenoic acid (EPA) and DHA for 6 h, a significant increase in *PPARγ* mRNA was observed in the presence of EPA, but DHA had no significant change [15]. Our data showed that when treated mice with DHA for 3 weeks, *PPARγ* expression increased significantly compared with control group in adipose. And the significant increase appeared in the third and the 2nd week in low and high concentration, respectively. These results indicated that there were different effects in treating concentrations, slow effect in the low treatment and quick effect in the high. Adipose tissue was obtained from pigs fed diet containing

10% safflower oil (SO) for 12 weeks, the abundance of *PPARγ* mRNA was increased fourfold by SO compared with the control diet [16]. Antonella Trombetta [17] found that A549 human lung-adenocarcinoma cells were treated with arachidonic (AA) and DHA, *PPARγ* expression was up-regulated at 48 h. Dietary n-3 PUFAs decreased adipose tissue mass and suppressed the development of obesity in rodents by targeting a set of key regulatory transcription factors involved in both adipogensis and lipid homeostasis in mature adipocytes [18]. We found that *PPARγ* expression was down-regulated by DHA in liver, it was possible to have close correlation with lipogenesis in liver. However, there was no difference in weeks in low group, in the high there was a significant decrease in the 3rd week. Maybe DHA would not produce a marked effect unless it accessed to a certain concentration.

Except *PPARγ*, *SREBP-1c* is another transcriptional factor which plays important role in adipose deposition. Teruyo Nakatani [19–21] found that feeding fish oil decreased mice body weight and fat mass in a dose-dependent manner, in parallel with *PPARα* activation and a decrease of *SREBP-1* mRNA in liver. When rat hepatocytes in monolayer culture were treated with albumin-bound 20:4(n-6) or 20:5(n-3) the half-life of total *SREBP-1* mRNA was reduced by 50%. And the decay of *SREBP-1c* mRNA was more sensitive to PUFA than that of *SREBP-1a* [22, 23]. In our research, the expression of *SREBP-1c* in liver had a decrease comparing with the control ($P < 0.01$), but it was not a dose-dependent manner. We also found a time-dependent manner of *SREBP-1c* in liver ($P < 0.01$). Another research reported that *SREBP-1c* level was suppressed by PUFA in liver and hepatocytes [24], however, in adipose and 3T3-L1 adipocytes there was no difference. This indicates that the effects of PUFA on *SREBP-1* gene expression are tissue-specific [25]. The same result was also found in pig by Hsu [6]. As the same, in our study DHA didn't affect *SREBP-1c* expression in adipose ($P > 0.05$). In the 3rd week it had a decrease in the low ($0.01 < P < 0.05$), perhaps it would have to reach an exact concentration and time to effect the gene expression. In corpulent JCR:LA-cp rats, both the olive oil and menhaden oil diets reduced expression of *SREBP-1c* and *FAS*, with concomitant reductions in hepatic triglyceride content, lipogenesis, and expression of enzymes related to lipid synthesis [10]. The nuclear concentrations of hepatic *SREBP-1* was 50% lower ($P < 0.05$) in rats that consumed a single PUFA-supplemented meal than the fat-free diet alone. This was paralleled by 63% reductions in the expression of *FAS*, which is the *SREBP-1* target gene [26]. In obese mice PUFA markedly decreased the mature form of SREBP-1 protein and thereby reduced the expression of *FAS* in the liver [27]. Our data indicated the same results, in liver *FAS* expressed a lower level than the control, and had a dose-independent manner from the 2nd week. FAS activity was markedly lower in the liver but not in the adipose tissues of rats fed containing fish oil diet [5]. Treating bovine mammary cells with 75 μmol/l *trans*-10, *cis*-12 CLA for 48 h resulted in reductions in mRNA abundance for acetyl CoA carboxylase, *FAS*, and stearoyl CoA desaturase, but there was no reduction in *SREBP-1* mRNA or precursor protein, whereas *cis*-9, *trans*-11 CLA had no effect on these genes [28]. This suggested that different PUFAs or cell type may have different effect. Therefore, it can explain our different result for *FAS* expression in adipose.

HSL is an intracellular neutral lipase that is capable of hydrolyzing triacylglycerols, diacylglycerols, monoacylglycerols, and cholesteryl esters, as well as other lipid and water soluble substrates. Its expression is highest in adipose tissue [29, 30]. In recent studies, TGH and ATGL are the two other enzymes in lipolysis besides HSL [31, 32]. Inhibiting TGH activity in primary rat hepatocytes could result in a dramatic decrease in secretion of TGs and secretion of cholesteryl ester and phosphatidylcholine was substantially decreased [33]. Mice were fed normal diet and high fat diet for 15 weeks, *TGH* and *HSL* expression had no difference in adipose between the two diets [34]. DHA can up-regulate *HSL* and *TGH* in adipose found in our study indicates that PUFA and normal fat has different effects on lipolysis. Feeding mice diets enriched in fatty acids for 3 weeks did not affect hepatic *TGH* expression, though a 3-week diet enriched in fatty acids and cholesterol increased hepatic *TGH* expression 2-fold [35]. This finding is coincidence with our conclusion in hepatic *TGH* expression. All these results suggest that *TGH* is not directly affected by DHA in liver, which pathway it influences is unknown. We also found DHA could up-regulate hepatic *HSL* in a dose-independent manner. It's supposed that DHA affects lipolysis through regulating *HSL* expression or activity and it needs further researches to elucidate the mechanisms.

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