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Retinoic acid treatment for a week induced plasma triglyceride and hepatic SREBP-1c, FAS and SCD1 levels in rats regardless of vitamin A status

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Abstract

Background: Vitamin A (VA, retinol) is essential for maintaining hepatic homeostasis. Here, we investigated whether VA status and retinoic acid (RA) treatment affected hepatic lipogenesis.

Methods: Sprague-Dawley rats were divided into 4 groups, VA deficient (VAD), sufficient VA (VAS), VAD or VAS treated with RA for a week (VAD+RA or VAS+RA, respectively). Plasma levels of high-density lipoprotein, low-density lipoprotein, triglyceride (TG), and cholesterol were measured. Real-time PCR and Western-Blot were respectively performed to determine the mRNA and protein levels of sterol regulatory element-binding protein 1c (Srebp-1c), stearoyl CoA desaturase 1 (Scda) and fatty acid synthase (Fasn).

Results: The body and liver weights of VAD and VAD+RA groups were significantly lower than that of VAS and VAS+RA groups. The plasma TG levels, and mRNA and protein expressions of hepatic Srebp-1c, Fasn and Scda in the VAS and VAS+RA groups were respectively higher than that in the VAD and VAD+RA groups. RA treatment increased the mRNA levels of Fasn and Srebp-1c in the VAD and VAS groups, and Scda in the VAD group; and protein levels of all three of them in both VAD and VAS groups $P<0.05$.

Conclusions: RA treatment increases the hepatic lipogenesis regardless of VA status

Keywords: Vitamin A; Retinoic acid; Triglyceride; Sterol regulatory element-binding protein 1c (Srebp-1c); Fatty acid synthase (Fasn); Stearoyl CoA desaturase 1 (Scd1)

Introduction

As a lipophilic micronutrient, vitamin A (VA, retinol) is essential for human health. Active compounds derived from VA contribute to a variety of physiological activities such as vision, growth, and immunity [1,2]. Retinol is reversibly oxidized into retinal by (retinol) alcohol dehydrogenases and short-chain dehydrogenases/ reductases. Retinal is further converted into retinoic acid (RA) through an irreversible process mediated by (retinal) aldehyde dehydrogenases. RA exists in multiple isomeric forms, such as all-trans RA and 9-cis RA. RA's role in the regulation of gene expression has been attributed to two families of nuclear receptors, retinoic acid receptors (RARα, β, and γ), and retinoid X receptors (RXRα, β, and γ). However, additional nuclear receptors such as hepatocyte nuclear factor 4α and chicken ovalbumin upstream transcription factor II have also been shown to regulate RA signals. These transcriptional factors mediate VA signaling through retinoic acid responsive elements on the targeted gene promoters [3-5].

Metabolic abnormalities, such as obesity and diabetes, are often associated with profound changes in the hepatic glucose and lipid metabolism [6,7]. The body fat, but not cholesterol, is reduced when rats fed a VA deficient (VAD) diet [8]. In humans, subjects with acne treated with isotretinoin (13-cis RA) developed the isotretinoin-induced hypertriglyceridemia [9]. In healthy human subjects, isotretinoin treatment led to a rise of plasma apo C-III level, which was attributed to the activation of RXR [10]. The treatment with all-trans RA resulted in body

weight (BW) gain, and hyperlipidemia in patients with acute promyelocytic leukemia [11,12]. The treatments with all-trans and 13-cis RA induced hypertriglyceridemia in rats [13]. RXR specific agonist (LG100268) rapidly and constantly induced the plasma triglyceride (TG) level in rats [14].

When we tried to find the hepatic lipophilic molecules modulating insulin-mediated transcription, we found an activity that can modulate insulin-regulated expressions of the cytosolic form of phosphoenolpyruvate carboxyl kinase gene (Pck1) [15] and glucokinase gene (Gck) [16] in primary rat hepatocytes. The molecules responsible for this activity were identified as retinoids [16]. Furthermore, RA synergizes with insulin to induce the expression of sterol regulatory element-binding protein 1c gene (Srebp-1c), which is a master regulator of the expressions of genes responsible for hepatic lipogenesis [17]. All these demonstrate the role of VA signaling in the regulation of the expression levels of genes for the hepatic lipid metabolism. Here, Sprague-Dawley (SD) rats at weaning were fed a VAD or a VA sufficient (VAS) diet for 8 weeks before a group of them were treated with RA for 7 more days. We found that the RA treatment was able to increase TG level and partially restore the expression levels of hepatic genes involved in lipogenesis in VAD rats.

Materials and Methods

Animals and diet manipulations

SD rats at weaning (3 weeks old) were fed a VAS (Xiaoshu Youtai Biotechnology Co., Ltd) or an isocaloric VAD (Xiaoshu Youtai Biotechnology Co., Ltd) diet for 8 weeks. Both diets contained the same number of calories and other nutrients except for VA. The synthetic basal diet with 22.1 IU/g of VA is sufficient to support the normal growth of laboratory rodents. Its total energy content is 4.05 kcal/g (1 cal =4.184 J) which includes 0.745 (18.3%), 0.900 (22.1%), and 2.424 (59.6%) kcal/g from protein, fat (ether extract), and carbohydrate, respectively. Both diets have 10% fat, in which the contents of total saturated, monounsaturated, and polyunsaturated fatty acids are 2.72%, 3.31%, and 3.42%, respectively. After the treatment with the VAS or VAD diet for 8 weeks, RA (Sigma, NO R2625) was administrated intragastrically to a group of VAD or VAS animals daily for additional one week, when they were maintained on their respective diet. All procedures and animal care were done in accordance with the Guide to the Care and Use of Experimental Animals [18]. The protocol was approved by the Institutional Animal Care and Use Committee at Wuhan Puren Hospital (NO:WHPR10231).

Preparations of plasma and tissue samples

After the animals were fed the VAD or VAS diet for 8 weeks, or treated with RA for additional 1 week, they were fasted for 6 hours and euthanized for the collection of vena cava blood and tissue samples. Accumulated venous blood was collected using the K3 EDTA coated vacuum blood collection tube and saved on ice before being further processed. The whole blood samples in the tubes were centrifuged at 1600×g and 4°C for 30 min. The supernatant formed after centrifugation was named plasma, which was transferred to 1.5 ml microcentrifuge tubes for storage at -80°C until being used. The liver was collected after the blood drainage. Both epididymal white adipose tissue (WAT) pads were removed carefully from sides. The weights of liver, WAT and brown fat (BAT) samples were recorded before they were frozen in liquid nitrogen for storage at -80°C. Plasma levels of glucose, high-density lipoprotein (HDL), low-density lipoprotein (LDL), TG, and cholesterol were determined using colorimetry assay kits (Nanjing Jiancheng Bioengineering Institute, NO A043-1-1) and insulin level was measured using ELISA kit (Camilo biological, NO KMLJr30973.).

RNA extraction and quantitative real-time PCR

Total RNA was extracted using the TRIZOL reagent (Invitrogen, NO10296028). Reagents for complementary DNA (cDNA) synthesis and real-time PCR were obtained from ABI-Invitrogen. Methods for analysis of RNA were described previously [16]. The primer sets for actin (forward 5′-CTGAACG TGAAATTGTCCGAGA-3′ and reverse 5′-TTGCCAATGGTGATGACCTG-3′); Srebp-1c (forward 5′-TGTCTGACCTGCAACCCAT-3′ and reverse 5′-CAGCA ACCA CT GGGTCCAA-3′); Fasn (forward 5′-CGAGTTAAATGTTCGAATGC-3′ and reverse 5′-GCCCACTTGATATAACCCT-3′) and Scda (forward 5′-TCTCCAG TTCCTACACGACCAC-3′ and reverse 5′-CTCATTTCAGGACGGATG TCT-3′) were designed using the Primer Express software (Applied Biosystems). Data were presented as the difference of the cycle threshold (Ct) numbers of actin and the indicated gene (–Δ Ct).

Protein extraction and Western Blot (immuno-blotting)

To prepare total protein extract, around 100 mg of liver sample was homogenized in 1 ml of tissue lysis buffer (1% Triton X-100, 10 % glycerol, 1% IGEPAL CA-630, 50 mM Hepes, 100 mM NaF, 10 mM EDTA, 1 mM sodium molybdate, 1 mM sodium β-glycerophsphate, 5 mM sodium orthovanadate, 1.9 mg/ml aprotinin, 5 μg/ml leupeptin, 1 mM benzamide, 2.5 mM PMSF, pH 8.0) using a tissue homogenizer (MDL, NO MDL91201). The lysates were placed on ice for at least 20 min and centrifugated at 12,000×g for 15 min. The supernatant was named total protein lysate. The protein content was measured using the BCA protein assay kit (MDL, NO MD913053). For the protein separation, 50 μg of total protein in the lysates was loaded onto each lane and proteins in it were separated on 8% or 10%SDS-PAGE gels. The separated proteins were transferred to the Immuno-Blot PVDF membranes (Millipore, NO ISEQ00010), and detected using primary antibodies to the indicated proteins at appropriate dilutions. The ratio of the density of the detected protein to that of the β-actin in the same sample were calculated and used for quantification.

Statistics

SPSS 23.0 software was used for statistical analysis. One-way ANOVA with least significance difference post-hoc analysis tests were performed to compare two and more than two groups,

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respectively. If needed, natural log transformation was performed before analysis. Data were presented as means ± S.E.M. The p-value less than 0.05 (P<0.05) was considered significantly different.

Results

VAS status resulted in higher body and liver weights than VAD status in SD rats

The BW and liver weights of rats in the VAD+RA group were not significantly different from that in the VAD group. The weights of BAT (0.62±0.08 VS 0.57±0.05) and WAT (12.02±1.02 VS 10.10±1.85) of rats in the VAD groups seemed to be slightly reduced after the RA administration for 1 week. Rats in the VAS group, however, had significantly higher liver weight than those in the VAD and VAD+RA groups (14.99±2.46,15.08±2.81 VS 17.36±2.68, P<0.05). The highest BW and liver weight were in VAS+RA rats (532.17±30.43 VS 557.33±40.19, 14.99±2.46 VS 18.15±1.49, 12.02±1.02 VS 13.25±4.40), which demonstrated the synergistic effects of VA sufficiency and RA treatment on promoting body growth in rats (Table 1). Although there is a trend of higher WAT in VAS and VAS+RA groups (13.25±4.4) compared with that in the VAD group (12.02±1.02), it did not reach statistical significance (P<0.05) (Table 1).

Table 1: Weights of body, liver and fat tissue in SD rats of VAD, VAS, VAD+RA and VAS+RA groups

	Body weight (BW, g)	Liver weight (LW, g)	Brown adipose tissue (BAT, g)	White adipose tissue (WAT, g)
VAD	532.17±30.43*	14.99±2.46a*	0.62±0.08	12.02±1.02
VAD+RA	532.17±49.43*	15.08±2.81a*	0.57±0.05	10.10±1.85
VAS	542.67±73.92	17.36±2.68	0.64±0.17	12.22±7.84
VAS+RA	557.33±40.19	18.15±1.49	0.62±0.11	13.25±4.40

*for comparing with VAS+RA, a for comparing with VAS, P<0.05.

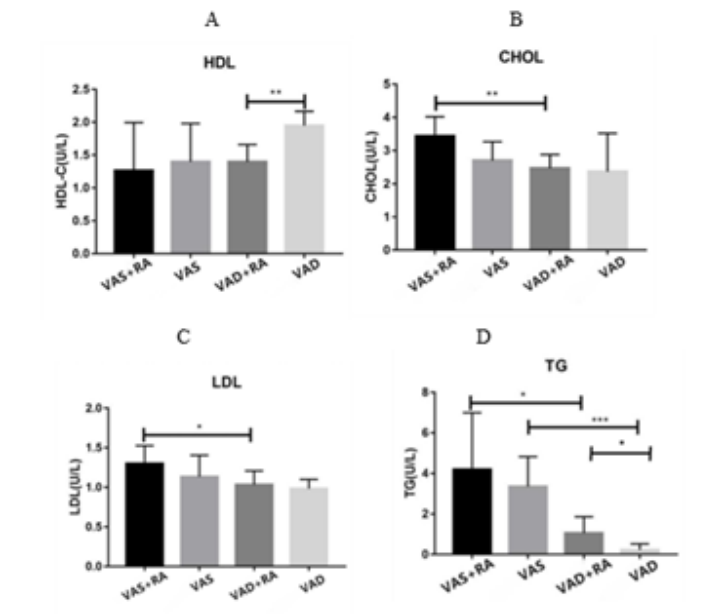

Figure 1: The plasma levels of high-density lipoprotein (HDL) (A), cholesterol (CHOL) (B), low-density lipoprotein (LDL) (C) and triglyceride (TG) (D) in VAD, VAS, VAD+RA and VAS+RA rats. After SD rats were fed the VAD or VAS diet for 8 weeks, or treated with RA for additional 1 week (n=5 in each group), they were fasted for six hours and then euthanized for the collection of the plasma tissue samples. Results were presented as means±SD. *P<0.05, **P<0.01,***P<0.001.

RA treatment significantly increased plasma lipids levels in the VAD rats

As RA treatment promoted body growth, we examined whether VA status and RA administration impacted the plasma lipid levels in different groups. As seen in Figure 1, RA treatment for 1 week in the VAD group obviously lowered the HDL level as compared with that in the VAD group (P<0.01) Figure 1(A). In terms of total cholesterol Figure 1(B) and LDL Figure 1(C), VAS+RA group had higher levels of LDL and cholesterol than those in the VAD+RA group (P<0.05). The plasma TG level of VAD rats, on the other hand, was significantly increased after rats were

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treated with RA for 1 week (P<0.05). Rats in the VAS+RA group had the highest TG level. It is worthy to mention that even though the RA treatment significantly increased the TG level in the VAD rats, the TG level still could not return to that of rats in the VAS group (VAD+RA vs VAS) (P<0.05) Figure 1(D).

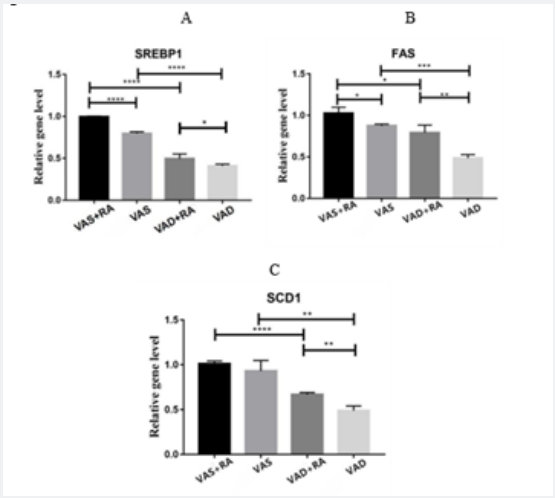

Figure 2: : The mRNA levels of Srebp-1c (A), Fasn (B), and Scda (C) in VAD, VAS, VAD+RA and VAS+RA rats. After SD rats were fed the VAD or VAS diet for 8 weeks, or treated with RA for additional 1 week (n=5 in each group), they were fasted for six hours and then euthanized for the collection of the plasma tissue samples. The total RNA was extracted and subjected to real-time PCR analysis. Results were presented as means±SD of–Δ Ct (against actin). *P<0.05, **P<0.01,***P<0.001.Sterol regulatory element-binding protein 1c (Srebp-1c), fatty acid synthase (Fasn), stearoyl CoA desaturase 1 (Scda).

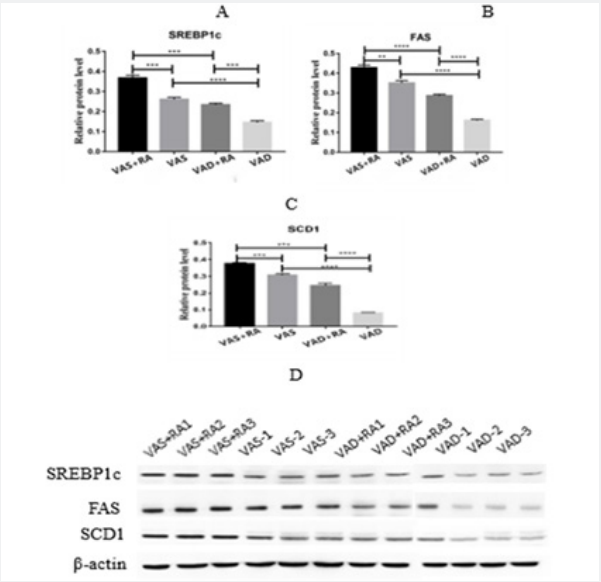

Figure 3: Relative protein levels of SREBP1c (A), FAS (B) and SCD1 (C) and blot graphs of these proteins and the internal control beta actin (D) in VAD, VAS, VAD+RA and VAS+RA rats. After SD rats were fed the VAD or VAS diet for 8 weeks, or treated with RA for additional 1 week (n=5 in each group), they were fasted for six hours and then euthanized for the collection of the plasma tissue samples. The whole protein of 4 groups rats (n=5/group) were extracted and then subjected to WB assay. A, B and C represent the means ± SD of the ratios of the indicated protein to beta actin. D. shows the Western blot graphs of the indicated proteins (SREBP1c, FAS and SCD1) and internal control beta actin.***P<0.001,****P<0.0001. Sterol regulatory element-binding protein 1c (SREBP1c), fatty acid synthase (FAS), stearoyl CoA desaturase 1 (SCD1).

The hepatic expression levels of Srebp-1c, Fasn, and Scda mRNA in the VAD and VAS rats treated with or without RA for one week were significantly upregulated

In order to determine the underlying molecular mechanisms by which the elevated plasma TG levels in RA treated rats, we measured the expression levels of Srebp-1c, Fasn, and Scda mRNA

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using real-time PCR. As shown in Figure 2A, the expression levels of Srebp-1c mRNA in the VAS groups were higher than that in the VAD groups, respectively (VAD vs VAS, and VAD+RA vs VAS+RA, P<0.001). The RA treatment for one week significantly increased the Srebp-1c mRNA expression levels in the VAD (VAD vs VAD+RA) and VAS (VAS vs VAS+RA) groups (P<0.05). Interestingly, the Srebp-1c mRNA level in the VAD+RA group was still lower than that in the VAS group, indicating other factors contributing to the Srebp-1c homeostasis..

As shown in Figure 2(B), the expression level of Fasn mRNA of rats in the VAD+RA group was significantly induced after the RA treatment for 1 week (P<0.01). The level of Fasn in rats fed the VAS diet for 8 weeks was significantly higher than those in the VAD groups (VAD VS VAS, P<0.001). The animals in the VAS+RA group had the highest expression of Fasn mRNA level compared with that in the VAD, VAD+RA and VAS groups (P<0.05). As for the Scda Mrna Figure 2(C), its level in the VAS and VAS+VA groups were similar, whereas RA treatment for 1 week significantly upregulated the Scda mRNA in the VAD group (P<0.01).

After SD rats were fed the VAD or VAS diet for 8 weeks or treated with RA for additional 1 week (n=5 in each group), they were fasted for six hours and then euthanized for the collection of the plasma tissue samples. The whole protein of 4 groups rats (n=5/group) were extracted and then subjected to WB assay. A, B and C represent the means ± SD of the ratios of the indicated protein to beta actin. D. shows the Western blot graphs of the indicated proteins (SREBP1c, FAS and SCD1) and internal control beta actin.***P<0.001,****P<0.0001. Sterol regulatory element-binding protein 1c (SREBP1c), fatty acid synthase (FAS), stearoyl CoA desaturase 1 (SCD1).

The hepatic expression levels of SREBP1c, FAS and SCD1 proteins in the VAD and VAS rats treated with or without RA for one week were significantly induced after RA treatment.

As demonstrated in Figure 3, in addition to mRNA levels were expressed at higher levels after RA treatment, the expression levels of SREBP1c (A), FAS (B) and SCD1(C) proteins of SD rats in the VAS+RA and VAD+RA groups were also dramatically upregulated compared with the VAS and VAD groups, respectively (P<0.001). It appears that regardless of VA status, RA treatment significantly induced the expression levels of the key lipogenic proteins of rats in the VAD and VAS rats (P<0.001). These results clearly demonstrated the active roles of RA in regulating lipogenic process.

Discussion

Here, to determine the effects of VA signaling in the regulation of hepatic lipogenesis, we generated VA deficiency in SD rats after they were fed a VAD diet for 8 weeks, and then treated a group of them with RA for a week. We found that RA treatment for one additional week (total 9 weeks) significantly induced the plasma TG level in those VAD rats as shown in Figure 1(D). This is associated with RA-induced expressions of Srebp-1c, Fasn and Scda mRNA levels Figure 2, and SREBP-1c, FASN, and SCD1 protein levels Figure 3 in those VAD rats fed a VAD diet. All these results clearly demonstrate that RA can induce the hepatic expression levels of lipogenic genes, which can contribute to the elevated plasma TG level in the VAD rats.

VA deficiency has been associated with the reduced mRNA expression levels of lipogenic genes such as Srebp1c and Fasn [19] and Scda [20]. These are also associated with the corrections of obesity and hyperlipidemia in Zucker fatty rats. We reported that the reduced dietary VA status also prevented the development of hyperlipidemia, obesity, and type 2 diabetes in Zucker diabetic fatty rats [21]. These studies clearly demonstrated the impacts of reduced VA status on metabolism. However, the impacts of reintroduction of VA or it signaling system into the system in VAD rats were still not known. Recently, we have referred a VAS diet to VAD ZL rats for a week and observed that the feeding of a VAS diet for a week in VAD rats led to the gain of BW [22]. This is associated with an induction of the hepatic Fasn, but not Srebp-1c mRNA. Therefore, an interesting question is whether RA can completely mimic the VA effects on fatty acid metabolism in VAD animals, which is what we have tested here.

As a key transcriptional factor that stimulates the expression levels of hepatic lipogenic genes, Srebp-1c is specifically induced by insulin in hepatocytes [23]. This is responsible for the insulin-induced lipogenesis [24]. The feeding of a VAS diet in the VAD rats for a week did not restore the Srebp-1c mRNA level to that of the rats fed the VAS diet for 8 weeks, indicating that other factors might also be needed to maintain the Srebp-1c mRNA levels in the liver in VAS rats [22]. Here, we found that the RA treatment for one week induced the Srebp-1c mRNA in the liver of VAD rats Figure 2(A). The SREBP-1c protein level was also significantly induced after RA treatment Figure 3(A) in the VAD rats. On the other hand, the RA treatment for 1 week significantly induced the Srebp-1c mRNA and SREBP-1c protein levels in VAS rats. All these indicate that the RA's ability to stimulate Srebp-1c expression in the liver regardless of the VA status. The liver X receptor (LXR) elements on the promoter of Srebp-1c have been thought to be critical for mediating insulin-induced Srebp-1c expression [25]. However, LXRs need to form heterodimer with RXR to work [26], whereas RXR is thought to be activated by 9-cis RA, which was not used in our study. Whether RXR activation or production of 9-cis RA is needed for Srebp-1c expression in VAD rats remains to be investigated.

On the other hand, the RA treatment for a week induced the Fasn mRNA and FAS protein in VAD and VAS rats. FAS is a key enzyme for de novo lipogenesis and is located in the cytosol [27] . It uses acetyl-CoA and malonyl-CoA to produce palmitic acid. The expression of Fasn mRNA is regulated by the nutritional states

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[28]. However, the Fasn mRNA level in VAD rats treated with RA only reached the level of the VAS rats, which is still lower than that of VAS+RA rats. The Fasn mRNA levels matched FAS protein levels very well, showing the impacts of RA treatment can induce Fasn gene expression regardless of the VA status. These results also fit the Fasn mRNA levels in VAD rats treated with a VAS diet for a week [22]. All these indicate that RA treatment can induce the lipogenesis. This probably explain why isotretinoin as a medicine for the therapy of acne induces hyperlipidemia in humans [29].

However, RA treatment at 10 or 100 mg/kg body weight for 4 days was shown to reduce the hepatic Srebp-1c and Fasn mRNA levels in 13-week-old NMRI male mice [30]. This appears to be inconsistent with our observations in rats as described here. Whether this is due to the dosage used, length of the treatment or different responses between species (rats vs mice) to RA remains to be determined.

SCD1 catalyzes the conversion of saturated fatty acids to monounsaturated fatty acids by introducing the first double bond on a saturated fatty acid, which is a key step in the desaturation of fatty acids and regulation of lipogenesis [31]. When Wistar rats fed a VAD diet for 16 weeks, their hepatic expression levels of Scda mRNA, but not SCD1 protein levels were reduced, which was associated with the reduction of TG level [32]. In VAD rats, the replenishment of dietary VA restored the SCD1 activity to that in the VAS rats [33]. Our data clearly show that RA treatment for a week induced the expression levels of hepatic Scda mRNA and SCD1 proteins in VAD rats. However, the same treatment only induced the SCD1 protein, but not Scda mRNA, in the VAS rats. Clearly, RA promotes hepatic lipogenesis and desaturation, which promotes anabolism in animals.

Our results shown in this study demonstrate that RA as a metabolite of VA can stimulate the plasma TG levels in VAD animals, indicating the potency of RA in promoting lipogenesis. In the VAD state, this induction was clearly not enough to restore the plasma TG level to that of the VAS animals Figure 1(D). This suggests that other factors are needed for the complete return of plasma TG level of VAD rats to that of VAS rats. The mRNA and protein levels of those lipogenic genes in VAD+RA rats were not comparable to that in VAS or VAS+RA rats also support our conclusion. Whether it takes longer time (more than 1 week) for the TG level of VAD animals to reach that of VAS rats or whether the TG level of VAD+RA will ever be restored without any participation of retinol remains to be seen.

Nevertheless, we have shown that RA can induce the expression levels of lipogenic genes and in turn, the plasma TG level in VAD rats. However, other factors derived from retinol probably are also important for the complete restoration of the plasma TG and gene expressions in VAD rats to that in VAS rats. Clearly, more studies are needed to fully reveal the role of VA in the regulation of lipogenesis.

Conclusion

RA treatment increases the hepatic SREBP1c, FAS and SCD1 proteins regardless of VA status, which can be attributed to the increases of mRNA levels of those lipogenic genes. VAD+RA rats still had lower expressions of those lipogenic genes than VAS+RA rats, suggesting the involvement of other factors to completely restore lipogenic gene expressions in VAD rats.

Author Contributions

Conceptualization, Y.Z. and GX. C; methodology, Y.Z.; formal analysis, Y.Z; investigation, DR. OY and WB C; writing—original draft preparation, Y.Z and D.R OY.; writing—review and editing, GX. C and Y.Z; funding acquisition, Y.Z. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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