

Roles of vitamin A in the regulation of fatty acid synthesis

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Abstract

Dietary macronutrients and micronutrients play important roles in human health. On the other hand, the excessive energy derived from food is stored in the form of triacylglycerol. A variety of dietary and hormonal factors affect this process through the regulation of the activities and expression levels of those key player enzymes involved in fatty acid biosynthesis such as acetyl-CoA carboxylase, fatty acid synthase, fatty acid elongases, and desaturases. As a micronutrient, vitamin A is essential for the health of humans. Recently, vitamin A has been shown to play a role in the regulation of glucose and lipid metabolism. This review summarizes recent research progresses about the roles of vitamin A in fatty acid synthesis. It focuses on the effects of vitamin A on the activities and expression levels of mRNA and proteins of key enzymes for fatty acid synthesis *in vitro* and *in vivo*. It appears that vitamin A status and its signaling pathway regulate the expression levels of enzymes involved in fatty acid synthesis. Future research directions are also discussed.

Key Words: Vitamin A; Acetyl-CoA carboxylase; Fatty acid synthase; Fatty acid elongase; Stearoyl-CoA desaturase; Fatty acid synthesis

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Core Tip: Recent studies have shown that vitamin A plays a role in the regulation of glucose and fatty acid metabolism. Vitamin A status, its supplementation, and the treatment with its metabolite, retinoic acid, have been shown to regulate the activities,

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and the expression levels of protein and mRNA of acetyl-CoA carboxylase, fatty acid synthase, fatty acid elongases, and fatty acid desaturases in the animal tissues and cells. Systematic evaluations of the roles of vitamin A in the fatty acid metabolism are needed for the treatment and prevention of metabolic diseases such as obesity and type 2 diabetes.

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INTRODUCTION

Excessive accumulation of fat leads to obesity. Currently, human obesity has become a global concern of public health[1]. It is one of the main risk factors affecting human health and causes many chronic diseases such as diabetes and cardiovascular diseases [2]. Both dietary and *de novo* synthesized fatty acids (either saturated or unsaturated) are esterified to a glycerol to make a triacylglycerol (TAG)[3], which is stored in adipocytes that increase in sizes and number with the obesity development. In addition to a place for TAG deposition, the adipose tissue also acts as an endocrine organ and secretes adipokines with a variety of physiological functions[4]. Alterations of adipose tissue functions occur with the development of obesity and other chronic metabolic diseases[5].

Fatty acids are also components of other molecules such as phospholipids, sphingolipids, and esters. Furthermore, they also participate in mediating signal transduction in cells[6]. Dietary linoleic acid and alpha-linolenic acid are the two essential fatty acids for human health. Intracellular fatty acids synthesized can be further elongated and desaturated through multiple enzymes responsible for desaturation and elongation reactions[7,8].

Vitamin A (retinol), a micronutrient, regulates a variety of physiological functions [9]. Retinol molecule contains a β -ionone ring with a polyunsaturated chain and an alcohol group[10]. Its derivatives function in the vision cycle, and regulate cell growth and differentiation, *etc.* Dietary molecules with vitamin A activities are preformed vitamin A retinyl esters and provitamin A carotenoids, which are from animal and plant sources, respectively. Provitamin A molecules can be converted into vitamin A [9].

Recently, it has become clear that vitamin A plays a role in the regulation of glucose and fatty acid metabolism[11,12]. This is achieved through the regulation of gene expression by retinoic acid (RA), a product of retinol metabolism[13-15]. How RA regulates the expression of genes involved in lipid metabolism and their signaling pathways is something worth being investigated. Here, we try to summarize the effects of vitamin A status and its metabolites on the regulation of genes involved in fatty acid synthesis, desaturation, and elongation pathways. In July 2020, key words such as vitamin A, retinol, acetyl-CoA carboxylase (ACC), fatty acid synthase (FAS), fatty acid elongases, and desaturases were used to search PubMed and retrieve the relevant articles for further reading.

OVERVIEW OF FATTY ACID SYNTHESIS IN MAMMALIAN CELLS

Understanding the regulation of the hepatic fatty acid metabolism pathways has both theoretical and clinical significance for health. The liver plays a major role in the *de novo* lipogenesis[16,17]. After the formation of TAG, hepatocytes secrete very low-density lipoprotein containing the newly synthesized TAG to be stored or used in other tissues[18-20]. The synthesis of fatty acids occurs in the cytosol and uses acetyl-CoA as the building block. Acetyl-CoA comes from three sources, product of pyruvate dehydrogenase, β -oxidation of fatty acids, and catabolism of amino acids. It is mainly produced in the mitochondrion, and is first converted into citrate, which enters into cytosol using the citric acid transport system. After that, ATP citrate lyase in the cytosol hydrolyzes citrate into oxaloacetate and acetyl-CoA which is used in

lipogenesis[16].

The steps of mammalian fatty acid synthesis are shown in Figure 1. Acetyl-CoA is first converted to malonyl-CoA by ACC. Both acetyl-CoA and malonyl-CoA are loaded onto acyl carrier protein (ACP) domains of FAS to form acetyl-ACP and malonyl-ACP, respectively[21,22]. Mammalian FAS is a polypeptide containing multi-functional subdomains with seven enzymatic activities, which are acetyl-CoA-ACP transacylase, malonyl-CoA-ACP transacylase, β -ketoacyl-ACP condensase, β -ketoacyl-ACP reductase, β -hydroxyacyl-ACP dehydratase, enoyl-ACP reductase, and palmitoyl-ACP thioesterase. FAS repetitively catalyzes condensation, reduction, dehydration, and reduction reactions to add two carbons each time until a 16-carbon acyl chain is formed. The final product of FAS is palmitic acid, a saturated fatty acid.

Fatty acids with longer chain length and double bonds can be produced from palmitic acid *via* other enzymes[23,24]. Elongases (ELOVLs) add two carbons each time to create a longer chain fatty acid. Desaturases introduce double bonds to the saturated and unsaturated fatty acids, which results in the production of monounsaturated fatty acids (MUFAs) and polyunsaturated fatty acids (PUFAs), respectively. Desaturases are specific for double bond formation in specific positions on a fatty acid molecule. The formation of each double bond requires an oxygen molecule and two electrons to participate. The first desaturation reaction is catalyzed by stearoyl-CoA desaturase 1 (SCD1), which introduces the first double bond in palmitic acid and stearic acid[25,26]. Saturated fatty acids and unsaturated fatty acids can be used to form TAG, phospholipids, and other lipids. The impacts of nutritional factors on the expression and activities of these lipogenic enzymes have been the interests of nutritional sciences.

OVERVIEW OF VITAMIN A METABOLISM

Humans and other mammals are unable to synthesize vitamin A in the body. Dietary preformed vitamin A and provitamin A are from animal and plant foods, respectively. Vitamin A is mainly stored as retinyl esters such as retinyl palmitate in the liver[27-30]. Figure 2 shows the digestion, absorption, transport, and storage of vitamin A in the body. Dietary retinyl esters and carotenoids form micelles with other lipids in the digestion and absorption processes[10,27]. The released retinol and carotenoids are absorbed into the enterocytes after crossing the unstirred water layer. Within the enterocytes, β -carotene is hydrolyzed to retinal by 15,15'-dioxygenase, and retinal is reduced to retinol by retinal reductase[28]. Retinol is re-esterified to form retinyl esters again by lecithin retinol acyltransferase or acyl-CoA retinol acyltransferase and then incorporated into chylomicrons, the lipoprotein for the transport of dietary lipids, which enter the lymph circulation and then the blood circulation[29].

The retinol released from retinyl esters in chylomicron remnants is catabolized into retinal and then RA (*all trans* RA unless defined otherwise) in the liver. The excessive retinol is re-esterified into retinyl esters, which are stored in the hepatic stellate cells [29]. A cellular retinol-binding protein binds to free retinol in the cells and is responsible to modulate the intracellular free retinol concentration. Retinol is secreted back from the liver in a complex containing retinol-binding protein 4, transthyretin, and thyroxine in the blood. Peripheral cells uptake retinol, and convert it into retinal and then RA to exert physiological responses. Other metabolites derived from retinol and RA can be excreted in the urine and the bile. Extrahepatic tissues, retina, adipose tissues, skeletal muscle, bone marrow, blood cells, spleen, heart, lungs, and kidneys can also uptake retinyl esters and metabolize retinol as the liver.

RA enters the nucleus, and binds to RA receptors (RARs) and retinoid X receptors (RXRs) interacting with the RA response elements (RAREs) in the promoter of the targeted genes[30-32]. Retinoids regulate gene expression through the RAREs in the promoters of their targeted genes. Some of those genes are involved in the regulation of glucose and fatty acid metabolism as reviewed[11,12]. Our lab has shown that the vitamin A metabolism participates in the regulation of hepatic lipogenic gene expressions during the cycle of fasting and refeeding in rats[33]. Therefore, understanding the role of vitamin A in fatty acid synthesis helps to clarify the regulation of lipogenesis for the prevention and treatment of chronic metabolic diseases such as obesity.

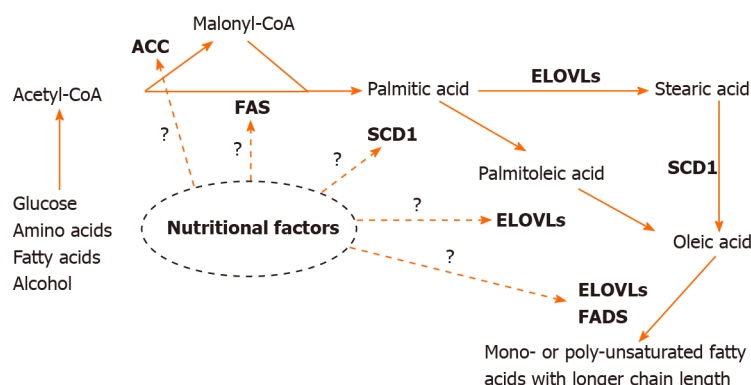


Figure 1 Fatty acid synthesis process in a mammalian cell. Dietary nutrients are metabolized into acetyl-CoA, which is converted into malonyl-CoA by acetyl-CoA carboxylase. Malonyl-CoA and acetyl-CoA are used by fatty acid synthase to generate palmitic acid, which can be either elongated into stearic acids by elongases (ELOVLs) or desaturated into palmitoleic acid, a monounsaturated fatty acid (MUFA), by stearoyl-CoA desaturase 1 (SCD1). Oleic acid (an MUFA) can be created either via elongation of palmitoleic acid by ELOVLs or desaturation of stearic acid by SCD1. Additional fatty acid with longer chain length or more double bonds can be generated from oleic acid through the activities of ELOVLs and fatty acid desaturases. ACC: Acetyl-CoA carboxylase; FAS: Fatty acid synthase; SCD1: Stearoyl-CoA desaturase 1; FADS: Fatty acid desaturases.

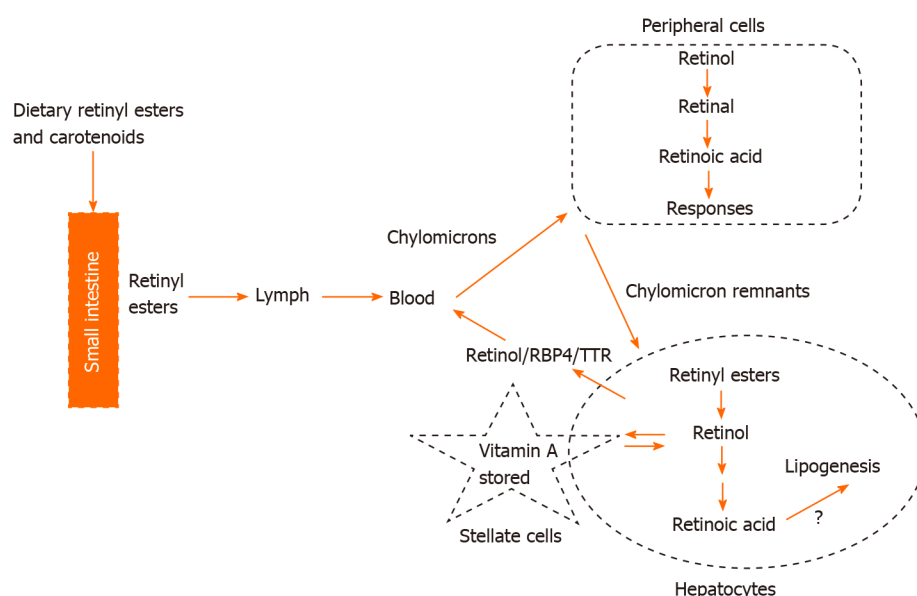


Figure 2 Overview of vitamin A metabolism in the body. Vitamin A (retinol) is in the forms of preformed vitamin A, retinyl esters, and provitamin A, carotenoids, in our diets. After digestion and absorption, resynthesized retinyl esters are packed as chylomicrons and released into the lymph circulation and then blood circulation to be delivered to the peripheral tissues first. The chylomicron remnants are taken up by the hepatocytes, which will hydrolyze retinyl esters to retinol, which is used for the productions of retinoic acid, stored again in the form of retinyl ester in stellate cells, or a complex containing retinol, retinol binding protein, and transthyretin, which is released into the blood circulation again. Retinol in the circulation is taken up by cells and oxidized into retinal, and then retinoic acid, which participates into the regulation of gene expression, and in turn cellular responses.

EFFECTS OF VITAMIN A STATUS AND RA TREATMENT ON ACC

ACC catalyzes the conversion of acetyl-CoA to malonyl-CoA, and plays an important role in the control of fatty acid metabolism[34,35]. Two isoforms of ACC have been identified, ACC α and ACC β . The malonyl-CoA produced by ACC is located in the cytoplasm and can be used for fatty acid synthesis, and suppression of fatty acid oxidation through the inhibition of carnitine palmitoyl transferase I (CPT1) activity [36]. Vitamin A can regulate ACC activity and gene expression levels, thereby affecting fatty acid synthesis.

Reports have shown that vitamin A signaling system regulates the activity and expression of ACC. The effect of vitamin A deficiency (VAD) on myocardial lipid metabolism has been studied in rats. VAD causes changes of lipid synthesis and composition, and reduces the ACC activity significantly[37]. In the heart, the VAD rats have reductions of ACC activity (but not *Accb* mRNA), mRNA levels of *Rxrs*, and

cardiolipin content, and increases in CPT1 activity and its mRNA level, and phosphatidic acid levels compared with those fed the same diet supplemented with 8 mg of retinyl palmitate/kg diet. The incorporations of [1-¹⁴C]-acetate into cholesterol and [methyl-¹⁴C]-choline into phosphatidylcholine are increased in the VAD animals. All these changes returned to their original levels after the VAD rats were fed a vitamin A sufficient (VAS) diet for 15 d, demonstrating the significant alterations of lipid metabolism in the heart of VAD rats[37].

Changes of the hepatic ACC activity and its mRNA expression levels in VAD status are observed. Male Wistar rats at weaning (3 wk of age) fed a VAD diet for 3 mo have lower body weight gain, liver and plasma retinol levels, and plasma TAG and cholesterol levels than those fed a VAS diet or those refed the control diet for 15 d[38]. The incorporations of [1-¹⁴C]-acetate into cholesterol and [methyl-¹⁴C]-choline into phosphatidylcholine are lowered due to the VAD status. The activity of hepatic ACC in the VAD male Wistar rat is significantly lower than that in the control group[38]. Similarly, the hepatic expression of *Acc* mRNA in the VAD group is significantly lower than that in the control group and the refed group. When the VAD animals were refed a VAS diet, the expression of *Acc* mRNA returned to that of the control value[38].

NMRI male mice at 12-wk-old age have been treated with RA at 10, 50, or 100 mg/kg body weight/d for 4 d. Levels of *Pparδ*, *Accb*, *Rxra*, and *Cpt1* mRNA in the skeletal muscle tissue are induced by the RA treatment. The proteins levels of PPARδ and RXRα are elevated in the group of mice treated with the 50 mg/kg body weight/d RA[39].

The effect of RA on fatty acid synthesis in bovine mammary alveolar cells (MAC-T) have been studied[40]. MAC-T cells after being differentiated for 4 d have been treated with 0, 1.0, 1.5, and 2.0 μmol/L RA for additional 3 d. RA treatment increases the amounts of short-chain and medium-chain, saturated and monosaturated fatty acids, and reduces the amounts of long-chain and PUFAs in the cells. Interestingly, the mRNA level of *Acca* is reduced by 1 μmol/L RA, but induced by 2 μmol/L RA[40].

In H9C2 myotube, a rat heart muscle cell line, RA treatment significantly induces the expression of *Accb* gene expression through the RXRα-mediated activation of muscle regulatory factor 4, which interacts with the *Accb* gene promoter[41]. In HL-60 promyelocytic leukemia cells treated with RA for 24 h and 7 d, the activity of ACC decreased by 44.9% and 99.7%, respectively[42].

Table 1 summarizes the effects of vitamin A status and RA treatment on the ACC activity and its mRNA and protein expression levels in animals and cells. It seems that the enzymatic activity and mRNA expression levels of ACC have been studied to certain extent. However, more protein data appear to be needed.

EFFECTS OF VITAMIN A STATUS AND RA TREATMENT ON FAS

As one of the key enzymes of *de novo* lipogenesis, FAS in the cytosol uses acetyl-CoA and malonyl-CoA to produce the 16-carbon palmitic acid[22]. The expression level of *Fas* mRNA changes in response to nutritional states[43].

In the male lambs, supplementation of VA at 500000 IU/animal twice per week from birth to 100 d of age does not affect body weight and lipid content during growth. However, this treatment increases the number of adipocytes in the perirenal depot, but reduces the sizes of adipocytes in the omental and perirenal depots, which is associated with the reduction of FAS activity in the perirenal fat depot[44]. On the other hand, a vitamin A supplementation study did not show any change of the marbling scores and lipogenic enzyme activities including the FAS activity in the adipose tissues of yearling beef steer[45]. Glucocorticoids can stimulate fatty acid biosynthesis and increase the activity of FAS protein and *Fas* mRNA levels. However, studies of the *Fas* gene in the lungs of rat fetuses in late pregnancy indicate that glucocorticoid-stimulated *Fas* gene expression is antagonized by the RA treatment[46].

Doses of RA at 10 or 100 mg/kg body weight have been injected daily subcutaneously for 4 d to 13-wk-old NMRI male mice[47]. The 100 mg/kg body weight, but not 10 mg/kg body weight, dose reduces the epididymal white adipose tissue weight. However, both doses of RA reduce hepatic *Srebp-1c* and *Fas* mRNA levels[47]. Our lab has shown that the VAD status leads to the reduction of hepatic expression levels of FAS protein in the refeeding of a VAS diet in the VAD rat liver[33]. In addition, vitamin A status regulates the *Fas* mRNA levels in both Zucker lean (ZL) and Zucker fat (ZF) rats. The VAD ZL and ZF rats have lower hepatic *Fas* mRNA levels than their respective VAS controls[48].

Table 1 Effects of vitamin A status and retinoic acid treatment on acetyl-CoA carboxylase enzymatic activity and its mRNA and protein expression levels in cells and tissues

Treatment	Tissue/cells	ACC activity	mRNA levels	Protein levels	Ref.
Vitamin A deficiency	Rat heart	Reduced	No change of <i>Accb</i>	ND	Vega <i>et al</i> [37]
	Rat liver	Reduced	Reduced <i>Acc</i>	ND	Oliveros <i>et al</i> [38]
	Rat liver	ND	ND	Reduced in <i>ad libitum</i>	Li <i>et al</i> [33]
RA treatment	NMRI mouse muscle	ND	Increased <i>Accb</i>	ND	Amengual <i>et al</i> [39]
	MAC-T cells		<i>Acca</i> reduced by 1 $\mu\text{mol/L}$ and induced by 2 $\mu\text{mol/L}$		Liao <i>et al</i> [40]
	H9C2 myotube		Increased <i>Accb</i>		Kim <i>et al</i> [41]
	HL-60 PL cells	Reduced	ND	ND	Fischkoff <i>et al</i> [42]

ACC: Acetyl-CoA carboxylase; HL-60 PL: HL-60 promyelocytic leukemia cells; MAC-T: Bovine mammary alveolar cells; ND: Not determined; RA: Retinoic acid; VAD: Vitamin A deficiency.

The effect of glucose on the RA-induced lipogenesis has been investigated in 3T3L1 adipocytes cells. RA has been shown to induce or suppress lipid accumulation when medium glucose concentrations are 25 and 5.5 mmol/L, respectively. These RA effects are associated with inductions and reductions of *Ap2* and *Fas* mRNA expression at 25 mmol/L and 5.5 mmol/L medium glucose concentrations, respectively[49]. On the other hand, 0.5, 5, or 50 $\mu\text{mol/L}$ RA treatment increases the expression levels of *ob* mRNA[49]. Other studies from the same group show that RA at 1 $\mu\text{mol/L}$ inhibits the mRNA levels of *Srebp-1a* and *Fas*, which is associated with the reduction of lipid accumulation in 3T3-L1 cells[50]. Interestingly, RA at 1 $\mu\text{mol/L}$ is able to inhibit the differentiation of 3T3-L1 cells and suppress the FAS activity[51]. In human AML-I preadipocytes, the treatment with 50 $\mu\text{mol/L}$ RA or 9-*cis* RA induces the cell growth arrest and cell death[52]. The 50 $\mu\text{mol/L}$ RA treatment for 4 to 5 d results in the elevation of *Fas* mRNA[52].

In primary rat hepatocytes, RA synergizes with insulin to induce the *Srebp-1c* and *Fas* expression, which is mediated by the two liver X responsive elements in the *Srebp-1c* promoter[14]. In HepG2 cells, RA treatment induces the activation of *FAS* promoter in a transient reporter gene assay[53]. The responsive element is attributed to an E-box region that is considered a place for multiple hormonal effects[54]. The mechanism of the RA-induced expression of *FAS* mRNA and protein is thought to be mediated by SREBP-1c[55]. RXR, but not RAR, is thought to be responsible for this phenomenon[55]. Interestingly, in HepG2 cells, 1 $\mu\text{mol/L}$ RA treatment for 24 h induces the mRNA levels of *CPT1*, *SREBP-1c*, and *FAS*, which is associated with the elevation of the fatty acid oxidation based on the authors' conclusions[56]. Farnesol treatment significantly down-regulates the mRNA level of *FAS* in the clone-9 cultured rat hepatocytes, which involves a 9-*cis* RA mediated mechanism[57]. Stimulatory proteins 1 and 3, nuclear factor Y, upstream stimulatory factor, and SREBP-1 have cognate binding sites in the *FAS* promoter, which may contribute to the RA-regulated *FAS* expression in HepG2 cells[58]. The region of the rat *Fas* promoter contains specific cis-elements responsible for the RA responses, which might not be RAREs. It is possible that RA induces SREBP-1c expression in hepatocytes, and in turn, SREBP-1c mediates the RA signal to activate the *FAS* promoter[59].

In LNCaP prostate cells, 1 $\mu\text{mol/L}$ RA treatment for 24 or 72 h is sufficient to induce *FAS* mRNA expression, which is accompanied by the incorporation of [2- ^{14}C] acetate into lipids, especially TAG, indicating the elevation of lipid synthesis and accumulation[60]. Retinol in human glioblastoma cells affects fatty acid biosynthetic pathways. *FAS* protein expression is down-regulated after the treatment with retinol[61].

Table 2 summarizes the effects of vitamin A status and RA treatment on the *FAS* protein and mRNA expression levels in different cells and organs. It appears that vitamin A status affects the *Fas* mRNA levels in rat hepatocytes. In addition, RA treatments also regulate *FAS* protein and mRNA expression levels. The outcomes depend on the cell types and glucose content in the culture media.

Table 2 Effects of vitamin A supplementation, vitamin A status, and retinoic acid treatment on the *Fas* mRNA and fatty acid synthase protein levels in cells and tissues

Treatment	Tissue/cells	FAS activity	<i>Fas</i> mRNA	Protein levels	Ref.
Vitamin A supplementation	Perirenal fat depot of lamb	Reduced	ND	ND	Arana <i>et al</i> [44]
	Adipose tissue of yearling beef steers	No change	ND	ND	Bryant <i>et al</i> [45]
Vitamin A deficiency	ZL rat liver	ND	Not changed in ad libitum	Reduced in the refeeding of a VAS diet	Li <i>et al</i> [33]
	ZL and ZF rat liver	ND	Reduced in 6 h-fasting	ND	Zhang <i>et al</i> [48]
RA treatments	Rat fetus lung	Reduce GC-induced activity	Reduced GC-induced <i>Fas</i>	ND	Xu <i>et al</i> [46]
	Mouse EWAT	ND	Reduces <i>Fas</i>	ND	Amengual <i>et al</i> [47]
	3T3-L1 cells	ND	Induced at 25 mmol/L glucose, and reduced at 5.5 mmol/L glucose	ND	Abd Eldaim <i>et al</i> [49]
	3T3-L1 cells	ND	Reduced		Abd Eldaim <i>et al</i> [50] and Murray <i>et al</i> [51]
	Human AML-I preadipocytes	ND	Induced	ND	Morikawa <i>et al</i> [52]
	Primary rat hepatocytes	ND	Synergized with insulin to induce <i>Fas</i>	ND	Li <i>et al</i> [14]
	HepG2 cells	ND	Induced <i>FAS</i>	Induced <i>FAS</i>	Roder <i>et al</i> [55] and Amengual <i>et al</i> [56]
	LNCaP prostate cells	ND	Induced <i>FAS</i>	ND	Duncan and Archer[60]

GC: Glucocorticoid; EWAT: Epididymal white adipose tissue; FAS: Fatty acid synthase; ND: Not determined; RA: Retinoic acid; VAD: Vitamin A deficiency; ZL: Zucker lean; ZF: Zucker fatty; VAS: Vitamin A sufficient.

EFFECTS OF VITAMIN A STATUS AND RA ON ELOVLs

Currently, seven isoforms of ELOVLs, ELOVL1 to 7, have been identified in mammalian cells. They participate in the elongation reactions for the synthesis of very long chain fatty acids. Each ELOVL isozyme has its preferred acyl-CoA with particular carbon chain length and saturation[7,62]. Few reports have shown the relationship between vitamin A and ELOVLs.

Both male and female C57BL/6J mice at 35 d of age have been fed a stock diet with 20% total energy from ground nut oil (10% w/w) or 54% total energy from beef tallow (high-fat diet, 33% w/w) for 26 wk[63]. The hepatic retinol content in mice fed the high-fat diet is much higher (more than 5-fold) than that of mice fed the stock diet. The hepatic content of docosahexaenoic acid (C22:6n-3) and expression levels of ELOVL2 protein in male and female mice fed the high-fat diet are higher than those of mice fed the stock diet, but the mRNA was not determined[63]. VA supplementation increases the ELOVL4 in the retina of WNIN/Ob obese rats[64].

EFFECTS OF VITAMIN A STATUS AND RA ON DESATURASES

Fatty acid desaturases introduce double bonds onto saturated and unsaturated fatty acids. For example, SCD1 is responsible for the formation of the first double bond to produce MUFAs and regulation of lipogenesis[25,26].

Vitamin A restriction in beef cattle has been shown to improve the marbling scores in Japanese Black cattle[65]. Changes in the expression of genes for lipid synthesis are observed in the muscle tissues of the Japanese Black steers with the vitamin A restriction, and associated with the marbling phenotype[66]. However, semi-quantitative polymerase chain reaction did not find any significant change of *Scd* mRNA in the vitamin A restriction group[66]. In Angus-based steers, vitamin A restriction does not affect the marbling scores, but induces MUFA amounts and desaturase index in adipose tissues[67]. However, the SCD activity was not measured

in the study[67].

Wistar rats fed a VAD diet for 16 wk have reduced plasma TAG and hepatic expression levels of *Scd1* mRNA, but not SCD protein levels, both of which are induced by feeding of a high fructose diet[68]. The mRNA expression levels of *Elovl6* and *Scd1* are reduced after female mice were fed a high-fat diet for 4 wk[69]. The vitamin A supplementation does not have any impact on the *Elovl6* and *Scd1* mRNA expression in this experimental setting[69]. In mice, feeding of a diet containing high retinyl palmitate (0.1% w/w) for 36 h induces the hepatic *Scd1* mRNA expression[70]. However, the SCD1 protein and its mRNA levels in the kidney are not affected by the vitamin A status even though VAD leads to the elevation of oleic (C18:1) and total MUFA levels in the same tissue[71]. The feeding of a VAD diet reduces the retinol content, and increases the MUFAs in the kidney probably due to the regulation of SCD1 activity[71]. In the pancreas of rats fed a VAD diet for 16 wk, the oleic acid content is reduced, which is associated with the reduction of SCD1 protein level[72].

The restriction or deficiency of vitamin A in rats induces the hepatic mRNA levels of fatty acid delta-5 desaturase[73]. Interestingly, the liver of rats fed a VAD diet for 19 wk have higher microsomal activity of SCD1, but not delta 6-desaturase, than those fed a VAS diet[74]. The replenishment of vitamin A in the VAD rats restored the SCD1 activity to the level equal to that in the VAS rats[74]. In the skin of *Scd1* knockout mice, the retinoid metabolism is disturbed with the elevations of retinol and RA contents, and the expression levels of RA-induced genes such as *Rbp1*, *Crabp2*, and *Lcn2*, which is also associated with the elevations of *Il1b* and *Tnfa* mRNA levels[75].

In rat primary astrocytes pretreated with 10 μ mol/L retinol for 24 h, treatment with 50 μ mol/L docosahexaenoic acid for 24 h induces the mRNA expression of *Fads2* (delta 6-desaturase gene)[76]. In the initiation phase of 3T3-L1 adipocyte differentiation, the RA treatment prevents the lipid accumulation[77]. RA dose-dependently suppressed the *Scd1* and *Albp* mRNA expression, which is induced during the differentiation process[77]. In human retinal pigment epithelial cells, RA dose-dependently induces the SCD mRNA, which is mediated by the activation of both RAR and RXR [78].

Table 3 summarizes the effects of vitamin A status and RA treatments on the SCD1 activity, and the expression levels of its mRNA and protein in cells and tissues. In the liver, VAD reduces the SCD1 protein and mRNA expression levels. RA treatment affects the *Scd1* mRNA expression levels depending on the cells tested.

VITAMIN A AND NON-ALCOHOLIC FATTY LIVER DISEASE

Non-alcoholic fatty liver disease (NAFLD) has become a disease that challenges the public health systems in many countries[79,80]. NAFLD can develop to nonalcoholic steatohepatitis (NASH), cirrhosis, and then hepatocellular carcinoma in certain percent of the patients[81]. Elevation of fatty acid synthesis from acetyl CoA has been indicated as the major contribution to the development of NAFLD in humans[81].

The VA intakes, blood levels of retinol and RA, and the hepatic retinoid contents have been investigated in human subjects with NAFLD. The VA intakes of subjects with NAFLD have been shown to be lower than the control ones[82,83], higher than the control ones[84] or not different from the control groups[85]. The blood retinol is inversely associated with liver damages in patients with NAFLD[83,86]. Patients with a genetic variant of patatin-like phospholipase domain-containing 3 (I148M) that reduces its activity and is linked to NAFLD have reduced blood retinol levels[87]. In one study, the blood RA levels in patients with NAFLD and NASH are lower than that in the age-matched control group[88]. The hepatic levels of retinyl palmitate, RA, 13-*cis*-RA, and 4-*oxo*-atRA in NAFLD patients with simple steatosis and NASH are lower than that in the control subjects[89].

The hepatic genes involved in VA metabolism and signaling are also altered in the liver samples from patients with NAFLD. The expression level of *RXR α* mRNA in the liver biopsy samples of NAFLD patients is inversely correlated with hepatic steatosis [88]. The expression levels of retinaldehyde dehydrogenase 1 family, member A2 (ALDH1A2) and retinaldehyde dehydrogenase 1 family, member A3 (ALDH1A3), enzymes for RA synthesis, in NAFLD subjects are lower than those of the control subjects as well[85]. However, the mRNA levels of lecithin retinol acyltransferase (*LRAT*), *ALDH1A1*, *CYP26A1*, *RAR α* , and *RAR β* are not different between the control and NAFLD groups[89].

Animal studies have been done to determine the impacts of NAFLD on VA metabolism and VA signaling on the NAFLD development. Feeding a methionine and

Table 3 The effects of vitamin A supplement, vitamin A status and retinoic acid treatment on the stearoyl-CoA desaturase 1 activity, mRNA and protein levels in cells and tissues

Treatments	Tissue/cells	Activity	mRNA	Protein levels	Ref.
Vitamin A supplement	Mouse liver	ND	No change	ND	Weiss <i>et al</i> [69]
	Mouse liver	ND	Increased	ND	Miller <i>et al</i> [70]
Vitamin A restriction	Muscle tissues of the Japanese Black steers	ND	No change	ND	Hayashi <i>et al</i> [66]
Vitamin A deficiency	Rat liver	ND	Reduced	No change	Raja Gopal Reddy <i>et al</i> [68]
	Rat kidney	ND	No change	No change	Gopal Reddy <i>et al</i> [71]
	Rat pancreas	ND	ND	Reduced	Raja Gopal Reddy <i>et al</i> [72]
	Rat liver microsomal	Increased	ND	ND	Alam <i>et al</i> [74]
RA treatments	3T3-L1 cells	ND	ND	Reduced	Stone and Bernlohr[77]
	Human retinal cells	ND	Induced	ND	Samuel <i>et al</i> [78]

ND: Not determined; RA: Retinoic acid.

choline deficient (MCD) diet, a diet that induces fatty liver in mice and rats, for 6 wk lowered plasma retinol level and increased hepatic retinol content in Wistar rats[90]. The expression levels of the hepatic *Lrat*, *Aldh1a1*, and *Aldh1a2* are also elevated in the rats fed the MCD diet[90]. The increased expression level of *Lrat* was also observed in mice fed a high-fat/cholesterol diet for 12 or 20 wk or in ob/ob mice, which is attributed to the increase in the formation of retinyl esters in hepatocytes, not hepatic stellate cells[91]. This is associated with the decrease of liver retinol and increase in retinyl palmitate contents[91]. The MCD diet also induces the expression level of platelet-type 12S-lipoxygenase in the hepatic stellate cells of mice, cells for VA storage and the development of hepatic fibrosis[92].

VA deficiency prevents the high-fructose diet-induced TAG in the liver and plasma in Wistar rats[68], and HFD-induced steatosis in mice[93]. On the other hand, treatment with RA has been shown to reduce lipid accumulation and steatosis in NAFLD mice[90,94-96]. Interestingly, RA improved insulin sensitivity and reduced blood glucose and liver damage in wild type, but not ob/ob mice[95]. M80 (an RAR α specific agonist) treatment reduces insulin and leptin resistance in KK-Ay mice and increases leptin receptor mRNA levels[95].

However, in another study, mice fed an HFD for 3 mo were treated with vehicle, and then treated with AM80 or AC261066 (an RAR β 2 specific agonist) for another month[97]. Mice in the AM80 group have higher degree of steatosis, TAG levels, inflammation, and blood glucose levels than those in the control and AC261066 groups [97]. The AC201066 group has higher hepatic TAG content than the control group as well[97].

Reduced RA production *via* heterozygous deletion of retinol dehydrogenase 10 (*Rdh10*) gene has been attributed to the increased adiposity and insulin resistance in mice fed an HFD for 16 wk, which can be corrected to certain extent by RA treatment *via* capsules for 3 wk[94]. On the other hand, altered location of retinyl ester formation from the stellate cells to hepatocytes is also considered a reason for fatty liver development in mice fed an HFD or ob/ob mice[91]. Furthermore, the Sirtuin pathway seems to be required for HFD-induced hyperglycemia, insulin resistance, and steatosis in mice fed an HFD, which can be attenuated if the HFD is supplemented with RA [96]. Additionally, the adenovirus-mediated overexpression of RXR α and RA treatment are shown to reduce the lipid accumulation in the liver and steatosis in mice [90].

It appears that VA metabolism is altered with the development of NAFLD based on the data of human and animal studies summarized here. Whether these alterations are the causes or consequences of the NAFLD remains to be determined. Interventional studies in rodents seem to yield conflict results. The VA deficiency status appears to reduce fatty liver in rats[68], and HFD-induced steatosis in mice[93]. The reduced RA production led to insulin resistance, and RA supplementation rescued the phenotype in mice[94]. It is interesting that extremely low VA availability in the body and exogenously derived RA both can reduce fatty liver phenotypes in rodents. Apparently, the role of VA in the lipid metabolism is more complicated than whether

there is enough RA produced or not. The VA metabolism probably should be considered more dynamically in the context of spatial and temporal manners, such as the transition of the cycle of fasting and refeeding[33].

Due to the lack of clear etiology and effective biomarkers for diagnosis (liver biopsy is the gold standard), the treatment methods for NAFLD are limited[98]. Nevertheless, given the roles of VA in the regulation of glucose and lipid metabolism, cautions must be given when supplementations of micronutrients are recommended in a clinical setting for the intervention of NAFLD. Another area that deserves more attention is the changes of VA and other micronutrients metabolism and their roles in the drug-induced hepatotoxicity that involves multiple mechanisms and pathways[99]. This is especially important as drugs are often used to treat comorbidities associated with NAFLD such as obesity and type 2 diabetes.

CONCLUSION

Fatty acid synthesis is closely related to the development of chronic metabolic diseases such as obesity, diabetes, and cardiovascular diseases. The key lipogenic enzymes and their genes seem to be regulated by the vitamin A statuses and its metabolite, RA. This has become more and more obvious with the accumulation of research data. As demonstrated in this review, this area is still in the preliminary stage, and more in-depth and systematic research is anticipated. The following areas are especially important in the future: (1) Systematic studies of the effects of vitamin A on the activities of key lipogenic genes in various mammalian cells should be conducted to establish the link between these two; (2) In the meantime, their mRNA and protein levels are also worth to be determined to indicate the potential mechanisms; (3) The interactions of vitamin A with insulin and other regulatory factors of lipogenesis should receive more attention; and (4) In addition to metabolism, since RA treatments affect tumor growth and cell apoptosis, the role of RA-regulated fatty acid synthesis is also worth to be investigated. Nevertheless, understanding the role of vitamin A in the regulation of lipogenesis will benefit not only metabolic studies but also interventions of human metabolic diseases.

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