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Fatty acid regulation of hepatic lipid metabolism

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Abstract

Purpose of review—To discuss transcriptional mechanisms regulating hepatic lipid metabolism.

Recent findings—Humans who are obese or have diabetes (NIDDM) or metabolic syndrome (MetS) have low blood and tissue levels of C_{20–22} polyunsaturated fatty acids (PUFAs). Although the impact of low C_{20–22} PUFAs on disease progression in humans is not fully understood, studies with mice have provided clues suggesting that impaired PUFA metabolism may contribute to the severity of risk factors associated with NIDDM and MetS. High fat diets promote hyperglycemia, insulin resistance and fatty liver in C57BL/6J mice, an effect that correlates with suppressed expression of enzymes involved in PUFA synthesis and decreased hepatic C_{20–22} PUFA content. A/J mice, in contrast, are resistant to diet-induced obesity and diabetes; these mice have elevated expression of hepatic enzymes involved in PUFA synthesis and C_{20–22} PUFA content. Moreover, loss-of-function and gain-of-function studies have identified fatty acid elongase (Elovl5), a key enzyme involved in PUFA synthesis, as a regulator of hepatic lipid and carbohydrate metabolism. Elovl5 activity regulates hepatic C_{20–22} PUFA content, signaling pathways (Akt and PP2A) and transcription factors (SREBP-1, PPARα, FoxO1 and PGC1α) that control fatty acid synthesis and gluconeogenesis.

Summary—These studies may help define novel strategies to control fatty liver and hyperglycemia associated with NIDDM and MetS.

Keywords

fatty acid elongation; fatty acid synthesis and oxidation; fatty liver; FoxO1; gluconeogenesis; VLDL metabolism

Introduction

Dietary fat is an essential component in the human diet, but too much fat or an imbalance of the type of fat can have negative effects on health and well-being [1•]. Chronic consumption of excessive calories coupled with physical inactivity promotes obesity, diabetes and metabolic syndrome [2•]. Obesity is associated with excessive ectopic deposition of fat in tissues, such as heart, β-cell, liver and adipose, leading to lipotoxicity and inflammation [3]. The accumulation of lipid in liver, that is, hepatosteatosis, leads to nonalcoholic fatty liver disease, a growing health problem in the obese population and more severe liver diseases such as nonalcoholic steatohepatitis, fibrosis, cirrhosis and cancer [4•]. Although excessive saturated fat (SFA) consumption promotes lipid storage and

inflammation, dietary polyunsaturated fatty acids (PUFAs) play a protective role by controlling synthesis and oxidation of SFA and monounsaturated fatty acid (MUFA), lower hepatic fat content [5] and improve blood lipid profiles associated with risk of cardiovascular disease [1•,6]. The goal of this article is to highlight recent studies implicating fatty acid synthesis as a target for controlling the severity of risk factors associated with diabetes (NIDDM) and metabolic syndrome (MetS).

Dietary fat regulates *de-novo* lipogenesis and monounsaturated fatty acid synthesis

Expression of the enzymes involved in *de novo* lipogenesis (DNL) (ACC1, FASN) and MUFA synthesis (SCD1 and Elovl6) synthesis are coordinately controlled during fasting and refeeding, and by insulin, dietary carbohydrate and dietary fat (Fig. 1) [7,8]. This coordinate regulation is due, at least in part, to the hormonal and nutrient control of key transcription factors regulating the expression of these enzymes. These transcription factors include SREBP-1 and the ChREBP/MLX, LXR/RXR and PPAR α /RXR heterodimers (Table 1) [5]. Insulin induces SREBP-1 nuclear abundance through several mechanisms, including increased transcription of the *SREBP-1c* gene, stabilization of SREBP-1 mRNA and protection of nuclear (mature) SREBP-1 from 26S proteasomal degradation. Feeding mice high fat diets containing predominately saturated fat for a short duration (24–28 h) induces SREBP-1 nuclear abundance and its co-activation by PGC1 β . Elevated nuclear content of SREBP-1 induces DNL, MUFA and triglyceride synthesis and storage [2•]. Long-term feeding (3 months) of high fat (lard) diets, however, has the opposite effect on SREBP-1 nuclear abundance and its target genes [8,9•]. This differential response can be linked to hepatic insulin resistance and elevated blood leptin and represents an adaption to the high fat diet [10]. Leptin suppresses SREBP-1 nuclear abundance and the expression of SREBP-1 target genes. Leptin also induces the phosphorylation of AMP-kinase (AMPK), which in turn phosphorylates acetyl CoA carboxylase (ACC) and lowers hepatic malonyl CoA (Table 2) [2•]. Malonyl CoA is a substrate for DNL and fatty acid elongation as well as an inhibitor of carnitine palmitoyl transferase-1 and β -oxidation [11].

High carbohydrate–low fat diets induce DNL and MUFA synthesis but diets supplemented with PUFAs (ω 3 or ω 6 PUFAs) suppress SREBP-1 nuclear abundance and the expression of genes involved in DNL and MUFA synthesis. Of the PUFAs examined, docosahexaenoic acid (C22 : 6, ω 3, DHA) is amongst the most robust suppressors of nuclear SREBP-1; DHA counters many of the effects of insulin on SREBP-1 but does not induce insulin resistance. This is achieved through effects on *SREBP-1c* gene transcription, SREBP-1 mRNA turnover and a 26S proteasome-dependent and Erk-dependent mechanism that accelerate the degradation of the mature form of SREBP-1 [5].

High carbohydrate–low fat diets also induce the accumulation of carbohydrate response element binding protein (ChREBP) in the nucleus. ChREBP along with its heterodimer partner max-like factor-X (MLX) control the expression of multiple genes (*Glut2*, *L-PK*, *ACC*, *FASN*, *SCD1* and *Elovl6*) involved in DNL and MUFA synthesis [12]. ChREBP binding to DNA requires MLX as a heterodimer partner. Dietary PUFAs suppress the nuclear content of both ChREBP and MLX nuclear abundance leading to a decline in expression of *ChREBP/MLX* target genes [5].

The LXR/RXR heterodimer is a major regulator of lipogenic gene expression through direct interaction with the promoters of these genes as well as inducing *SREBP-1c* gene transcription. Activation of LXR by high dietary cholesterol, oxysterols or other agonists elevates nuclear content of SREBP-1 and increases DNL and MUFA synthesis leading to hyperlipidemia [13]. Some investigators have reported effects of fatty acids on LXR

function [14], whereas others have found little effect of dietary PUFAs on LXR target genes (*ABCA1*, *ABCG5*, *ABCG8* and *CYP7A*) *in vivo* [5].

PPAR α , PPAR β/δ , PPAR γ 1 and PPAR γ 2 are fatty acid-activated nuclear receptors that respond to changes in intracellular fatty acid content [15]. In primary hepatocytes, however, the response of PPAR α to various fatty acids is not uniform. Eicosapentaenoic acid (C20 : 5, ω 3, EPA) is a robust activator of PPAR α , whereas SFA, MUFA and other ω 3 and ω 6 PUFAs are weak regulators of PPAR α [5]. PPAR α is a major regulator of genes involved in mitochondrial, peroxisomal and microsomal fatty acid oxidation as well as genes involved in gluconeogenesis through its regulation of PGC1 α and FGF21 [16,17]. Moreover, PPAR α is a major drug target for treating severe hyperlipidemia. When compared to pharmaceutical agonists, however, EPA is a weak activator of PPAR α [5].

Elevated DNL and esterification of fatty acids into triglycerides contributes to the elevation of plasma triglycerides seen in MetS. Elevated plasma triglycerides are an independent risk factor for cardiovascular disease [18–20]. Hepatic production of VLDL is governed by availability of substrate (TAG) and apolipoproteins required for VLDL assembly, such as apoB. Dietary C_{20–22} ω 3 PUFAs inhibit VLDL secretion by inhibiting DNL, enhancing fatty acid oxidation, and promoting apoB degradation [21,22,23,24].

Targeting fatty acid synthesis as a means to control risk factors associated with NIDDM and metabolic syndrome

Ablation or overexpression of enzymes involved in DNL, that is, acetyl CoA carboxylase (ACC1 and ACC2) [25], fatty acid synthase (FASN) [26] or MUFA synthesis, that is, stearoyl CoA desaturase-1 (SCD1) [27] or fatty acid elongase-6 (Elovl6) [28], significantly affects the severity of diet-induced hyperglycemia, dyslipidemia and fatty liver. Ntambi's group [27] was the first to report that mice lacking SCD1 are protected against diet-induced and genetically induced obesity, fatty liver, hypertriglyceridemia and insulin resistance. More recently, Brown *et al.* [29] used an antisense oligonucleotide approach to suppress SCD1 expression in LDLR^{-/-}, ApoB^{100/100} mice, a model of hyperlipidemia and atherosclerosis. Although suppression of SCD1 protects mice from diet-induced obesity, insulin resistance and fatty liver, this treatment induced aortic atherosclerosis. In a subsequent report, Rudel's group combined the SCD1 antisense oligonucleotide approach with dietary ω 3 PUFAs and prevented the symptoms of both MetS and atherosclerosis [30]. Although these studies reveal the complexities associated with targeting a specific enzyme to manage risk factors associated with metabolic disease, they also offer a remedy by including dietary ω 3 PUFA supplementation in the therapy regime.

Control of hepatic polyunsaturated fatty acid synthesis

Dietary PUFAs and in particular the C_{20–22} ω 3 PUFAs are beneficial to human health and well-being by controlling lipid metabolism, blood lipids and inflammation [1,31–34]. Obese humans or patients with NIDDM or MetS, however, have low blood and tissue levels of C_{20–22} PUFAs; an effect usually attributed to impaired PUFA synthesis [4,35–38]. The metabolic basis and physiological consequences of low circulating and tissue levels of PUFAs in humans remain unclear. Studies on essential fatty acid deficiency and fatty acid desaturase-2 (FADS2, Δ^6 desaturase) null mice make clear the necessity for dietary PUFAs and its conversion to ARA and DHA for the maintenance of multiple physiological processes and well-being [39,40,41].

The conversion of dietary precursors, linoleic acid and α -linolenic acids, to ARA and DHA requires fatty acid desaturases (FADS1, FADS2), fatty acid elongases (Elovl2 and Elovl5)

and peroxisomal β -oxidation (Fig. 1) [5]. SREBP-1, PPAR α , and HNF4 α , but not ChREBP/MLX or LXR/RXR control the expression levels of these enzymes (Table 1). When compared with enzymes involved in DNL and MUFA synthesis, expression of these enzymes is less responsive to changes in blood insulin, fasting or refeeding (Table 2) [7,8]. Recent studies in mice have provided some clues as to the significance of changes in PUFA synthesis in the control of metabolic disease. In contrast to C57BL/6J mice, A/J mice are resistant to high fat diet-induced obesity, atherosclerotic lesions and fatty liver. Microarray analysis reveals elevated expression of enzymes involved in lipid metabolism, including those involved in peroxisome biogenesis and β -oxidation, fatty acid elongation (*Elovl5*) and desaturation (*FADS1* and *FADS2*) [42•] in livers of A/J mice. Hall *et al.* [42•] linked the increased hepatic expression of these enzymes to elevated ARA levels in lysophosphatidylcholine and 2-arachidonylglycerol. These complex lipids are PPAR α and cannabinoid receptor agonists, respectively. Moreover, proinflammatory cytokines (IL-1 β and GSF) were lower in livers of A/J mice.

Livers of obese C57BL/6J mice fed high fat diets, however, have impaired PUFA synthesis as reflected by a low ratio of C20 : 4, ω 6 to C18 : 2, ω 6 and suppressed expression and activity of *Elovl5*. Interestingly, the expression of *FADS1* or *FADS2* was not affected by high fat (lard) diets [8]. Global ablation of *Elovl5* lowers hepatic ARA and promotes fatty liver; an effect linked to the induction of nuclear SREBP-1 but not ChREBP [43]. In contrast, induction of hepatic *Elovl5* activity, using a recombinant adenovirus approach, essentially abolished fatty liver in obese-diabetic mice [9•,44]. Although induction of hepatic *Elovl5* activity did not elevate hepatic C20 : 4, ω 6 levels, di-homo- γ -linolenic acid (C20 : 3, ω 6) and adrenic acid (C22 : 4, ω 6) were increased in livers of these mice [9•].

Hepatic steatosis is associated with low β -oxidation [4•] and low fasting blood levels of β -hydroxybutyrate [9•]. Increasing hepatic *Elovl5* activity in obese mice restored β -hydroxybutyrate to normal levels suggesting that *Elovl5* induced β -oxidation and ketogenesis. Because several targets of PPAR α action were suppressed in livers of obese mice with elevated hepatic *Elovl5* activity, *Elovl5* may induce β -oxidation and ketogenesis through mechanisms independent of PPAR α . The outcome of these studies establishes that: fatty acid elongases are regulated by diet; endogenous PUFA synthesis controls hepatic triglyceride content; and a change in elongase activity alone is sufficient to impact PUFA synthesis and hepatic triglyceride content. Similar studies using the *FADS2* null mouse have not been reported but it is anticipated that *FADS1* and *FADS2* play equally important roles in controlling hepatic lipid metabolism and the onset of fatty liver and dyslipidemia.

Fatty acid control of hepatic glucose metabolism

Mice fed high fat (saturated) diets have fasting hyperglycemia due to increased hepatic glucose production and insulin resistance [45,46]. Hepatic glucose production during fasting is due to the induction of glycogenolysis and gluconeogenesis as well as the availability of gluconeogenic substrates [47•,48•]. Expression of enzymes involved in gluconeogenesis, that is, phosphoenolpyruvate carboxykinase (*Pck1*), pyruvate carboxylase (*Pcx*) and glucose-6 phosphatase catalytic unit (*G6Pc*), is controlled by several transcription factors (*FoxO1*, *CREB*, *HNF4 α* , *c/EBP* and *PPAR α*) and regulatory proteins (*PGC1 α* , *CBP*, *CRTC2*, *TRB3* and *SIRT1*) [46,49•,50,51]. *CREB*, *CRTC2*, *FoxO1* and *PGC1 α* have been identified as major regulators of *Pck1* and *G6Pc* expression in fasting induced gluconeogenesis [46,52,53].

C57BL/6J mice fed high-fat diets develop fasting hyperglycemia, hyperinsulinemia and glucose intolerance [8,9•,45]. Hepatic nuclei of these mice have elevated levels of *FoxO1*, *CRTC2* and *PGC1 α* which induces expression of *Pck1* and *G6Pc*. Livers of these obese

diabetic mice have a low ratio of C20 : 4, ω 6 to C18 : 2, ω 6 and low activity of Elovl5 reflecting problems with PUFA synthesis. Inducing hepatic Elovl5 activity elevated hepatic C_{20–22} PUFAs and abrogates fasting hyperglycemia, hyperinsulinemia and glucose intolerance in these obese mice [9•]. Elevated Elovl5 activity attenuated Pck1 and G6Pc expression and suppressed nuclear content of FoxO1 and PGC1 α but had no effect on the nuclear content of CREB, CRT2, PPAR α or HNF4 α .

Nuclear levels of FoxO1 are regulated by controlling its phosphorylation and acetylation status [54•]. The serine–threonine kinase, Akt and the phosphatases, PP2A and MKP-3, control the phosphorylation status of FoxO1 [55–57,58•]. Transcriptional co-activators with histone acetyl transferase activity, for example CREB-binding protein (CBP) and protein deacetylase activity, for example, sirtuins 1 (SIRT1), control the acetylation status of FoxO1 and PGC1 α [54•,59]. The Elovl5-mediated decline in nuclear FoxO1 content was correlated with increased FoxO1 phosphorylation; phospho-FoxO1 is excluded from nuclei and degraded in the proteasome. Increased hepatic phospho-FoxO1 was correlated with elevated phosphorylation of Akt and the catalytic unit of PP2A. Phospho-Akt is an active kinase, whereas phosphorylation of PP2A catalytic unit inactivates PP2A phosphatase activity. Moreover, elevated Elovl5 activity suppressed hepatic levels of the Akt inhibitor, TRB3, but did not stimulate the phosphorylation of IRS2 or PDK1/2. The outcome of these studies indicates that elevation of hepatic Elovl5 activity maintains the phosphorylated form of FoxO1 during fasting, an event that lowers nuclear FoxO1 and suppresses expression of enzymes involved in gluconeogenesis. Similar studies investigating the effects of Elovl5 on the acetylation status of FoxO1 and PGC1 α have not been reported. The outcome of these studies identified a novel link between hepatic carbohydrate metabolism and PUFA metabolism not seen with dietary C_{20–22} PUFAs.

Conclusion

Studies with genetically modified mice have established that enzymes involved in DNL and MUFA synthesis play an important role in controlling metabolism, gene expression and the onset and progression of diabetes and obesity. Recent studies with enzymes involved in PUFA synthesis indicate that these enzymes are equally important regulators of plasma and tissue fatty acid composition, signaling pathways controlling DNL, MUFA synthesis and gluconeogenesis. Although dietary PUFAs have well-established benefits to human health [1•], the studies discussed above indicate that controlling PUFA synthesis may provide additional health benefits not seen with dietary PUFAs alone.

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 213–214).

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Figure 1. Pathways for de-novo lipogenesis, monounsaturated and polyunsaturated fatty acid synthesis

(a) De-novo lipogenesis (DNL) and monounsaturated fatty acid (MUFA) synthesis. The pathway illustrates the conversion of dietary glucose and palmitate to 16-carbon and 18-carbon saturated and monounsaturated fatty acids by acetyl CoA carboxylase (ACC), fatty acid synthase (FASN), fatty acid elongase-5 and fatty acid elongase-6 (Elovl5 and Elovl6), and stearoyl CoA desaturase (SCD). (b) Polyunsaturated fatty acid (PUFA) synthesis. The pathway illustrates the conversion of dietary essential fatty acids, C18 : 2, ω6 and C18 : 3, ω3 to C₂₀₋₂₂ PUFAs by fatty acid desaturases (FADS1, FADS2), fatty acid elongases (Elovl2, Elovl5) and peroxisomal β-oxidation. Fatty acids in bold are the predominant PUFAs found in liver, that is, 18 : 2, ω6, 20 : 4, ω6, 22 : 6, ω3. *, precursors to bioactive eicosanoids and docosanoids; #, robust activator of PPARα; \$, robust suppressor of nuclear content of SREBP-1.

Table 1

Transcription factors inducing fatty acid synthesis, fatty acid elongation and desaturation

Pathways and enzymes	SREBP-1	LXR RXR	ChREBP MLX	PPAR α RXR
De-novo lipogenesis and MUFA synthesis				
Acetyl CoA carboxylase 1 and 2 (ACC1 and ACC2)	(++)	(++)	(++)	
Fatty acid synthase (FASN)	(++)	(++)	(++)	
Stearoyl CoA desaturase-1 (SCD1)	(++)	(++)	(++)	(+)
Fatty acid elongase-6 (Elovl6)	(++)	(++)	(++)	(+)
PUFA synthesis				
Δ^5 -desaturase (FADS1)	(+)			(+)
Δ^6 -desaturase (FADS2)	(+)			(+)
Fatty acid elongase-2 (Elovl2)	(+)			
Fatty acid elongase-5 (Elovl5)	(+)			(++)
Peroxisomal β -oxidation				(++)

++, strong induction; +, modest induction.

Table 2

Impact of obesity and diabetes on hepatic expression of enzymes involved in fatty acid synthesis, elongation and desaturation

Pathways and enzymes	Streptozotocin-induced diabetes	Leptin deficiency induced (<i>ob/ob</i>)	Diet-induced obesity and diabetes
De-novo lipogenesis and MUFA synthesis			
Acetyl CoA carboxylase 1 and 2 (ACC1 and ACC2)	(–)	(++)	(–)
Fatty acid synthase (FASN)	(–)	(++)	(–)
Stearoyl CoA desaturase-1 (SCD1)	(–)	(++)	(–)
Fatty acid elongase-6 (Elovl6)	(–)	(++)	(–)
PUFA synthesis			
Δ^5 -desaturase (FADS1)		(+)	
Δ^6 -desaturase (FADS2)		(+)	
Fatty acid elongase-2 (Elovl2)		(+)	
Fatty acid elongase-5 (Elovl5)		(++)	(–)

++, strong induction; +, modest induction; –, inhibition.