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N-3 polyunsaturated fatty acid regulation of hepatic gene transcription

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Abstract

Purpose of review—The liver plays a central role in whole body lipid metabolism and adapts rapidly to changes in dietary fat composition. This adaption involves changes in the expression of genes involved in glycolysis, de-novo lipogenesis, fatty acid elongation, desaturation and oxidation. This review brings together metabolic and molecular studies that help explain n-3 (omega-3) polyunsaturated fatty acid regulation of hepatic gene transcription.

Recent findings—Dietary n-3 polyunsaturated fatty acid regulates hepatic gene expression by targeting three major transcriptional regulatory networks: peroxisome proliferator-activated receptor α, sterol regulatory element binding protein-1 and the carbohydrate regulatory element binding protein/Max-like factor X heterodimer. 22 : 6,n-3, the most prominent n-3 polyunsaturated fatty acid in tissues, is a weak activator of peroxisome proliferator-activated receptor α. Hepatic metabolism of 22 : 6,n-3, however, generates 20 : 5,n-3, a strong peroxisome proliferator-activated receptor α activator. In contrast to peroxisome proliferator-activated receptor α, 22 : 6,n-3 is the most potent fatty acid regulator of hepatic sterol regulatory element binding protein-1. 22 : 6,n-3 suppresses sterol regulatory element binding protein-1 gene expression while enhancing degradation of nuclear sterol regulatory element binding protein-1 through 26S proteasome and Erk1/2-dependent mechanisms. Both n-3 and n-6 polyunsaturated fatty acid suppress carbohydrate regulatory element binding protein and Max-like factor X nuclear abundance and interfere with glucose-regulated hepatic metabolism.

Summary—These studies have revealed unique mechanisms by which specific polyunsaturated fatty acids control peroxisome proliferator activated receptor α, sterol regulatory element binding protein-1 and carbohydrate regulatory element binding protein/Max-like factor X function. As such, specific metabolic and signal transduction pathways contribute significantly to the fatty acid regulation of these transcription factors and their corresponding regulatory networks.

Keywords

carbohydrate regulatory element binding protein; hepatic fatty acid metabolism; Max-like factor X; peroxisome proliferator activated receptor; polyunsaturated fatty acid α; sterol regulatory element binding protein-1

Introduction

The type and quantity of fat ingested regulates hepatic lipid composition and gene expression [1]. Key targets for this control include glycolysis, de-novo lipogenesis (DNL), fatty acid elongation, desaturation and oxidation (Fig. 1 and Table 1) [2,3]. Other targets of fatty acid

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control have been identified by microarray analyses [4,5]. Although dietary fat has effects on mRNA turnover and processing [6], this review will focus on mechanisms by which n-3 polyunsaturated fatty acids (PUFAs) regulate key transcription factors controlling hepatic carbohydrate and lipid metabolism. Of the three n-3 PUFAs commonly encountered in the diet, α-linolenic acid (18 : 3,n-3) is a weak regulator of hepatic gene expression, while eicosapentaenoic acid (20 : 5,n-3) and docosahexaenoic acid (22 : 6,n-3) are strong regulators of hepatic gene expression [3,7].

Overview of polyunsaturated fatty acid-regulated hepatic gene transcription

Several transcription factors have been identified as prospective targets for fatty acid regulation, including nuclear receptors: peroxisome proliferator-activated receptor (PPAR) family α, β, γ1 and γ2, retinoid X receptor (RXR) α, liver X receptor (LXR) α and hepatic nuclear factor (HNF-4) α and γ; and basic helix–loop–helix leucine-zipper transcription factors (bHLH-LZ): sterol regulatory element binding protein-1 (SREBP-1), carbohydrate regulatory element binding protein (ChREBP) and Max-like factor X (MLX)] [1,8–11]. Two general mechanisms characterize fatty acid control of these transcription factors. Fatty acids bind to and control the activity of specific nuclear receptors. In this fashion, fatty acids act like hydrophobic hormones regulating nuclear receptor function. Nonesterified fatty acids bind to PPAR (α, β, γ1 and γ2), HNF-4 (α and γ), RXRα and LXRα. Of these, PPAR subtypes are well recognized as fatty acid-regulated transcription factors *in vivo* [1]. Fatty acids control the nuclear abundance of SREBP-1, NFκB, ChREBP and MLX [8–10]. The mechanisms controlling these transcription factors are less clear, but likely involve changes in phosphorylation status of the transcription factor, which in turn controls transcription factor nuclear abundance and activity.

PPARα, SREBP-1c and ChREBP/MLX regulate multiple pathways involved in hepatic carbohydrate and lipid metabolism (Fig. 1 and Table 1). PUFA activation of PPARα enhances fatty acid oxidation, while PUFA suppression of SREBP-1 and ChREBP/MLX results in the inhibition of DNL and PUFA synthesis. As such, PUFAs promote a shift in metabolism toward fatty acid oxidation and away from fatty acid synthesis and storage. This shift in metabolism will alter hepatic VLDL composition, which in turn affects extrahepatic lipid composition (Fig. 1) [2,9,10,12,13•]. PUFA effects on lipid synthesis are seen in liver, but not necessarily in other tissues, like brain [14,15].

Fatty acid regulation of hepatic PPAR*α*

PPARs bind saturated, monounstaurated and polyunsaturated fatty acids. In cells and *in vivo*, hepatic PPARα responds to changes in both exogenous (dietary) fat and newly synthesized fat (de-novo lipogenesis; DNL) [1,16]. This response is marked by changes in the expression of multiple enzymes involved in fatty acyl CoA formation and hydrolysis, fatty acid elongation and desaturation, and fatty acid oxidation (Table 1) [3,17,18]. Intracellular fatty acid ligands for PPAR, that is, nonesterified fatty acids (NEFAs), are maintained at low levels representing under 0.1% of the total cellular lipid [7]. In primary hepatocytes certain fatty acids are more effective activators of PPARα than others. Challenging cells with a fatty acid that is normally abundant in cells, such as 18 : 1,n-9, has little effect on intracellular NEFA mass and does not induce PPARα activity. In contrast, challenging cells with a fatty acid that is typically a minor component of the cell, such as 20 : 5,n-3, not only perturbs the NEFA fraction but also significantly activates PPARα and induces its target genes, for example cytochrome P450-4A (CYP4A) and cytosolic fatty acyl thioesterase-1 (CTE1) [3,7].

Rodents fed fish oil-containing diets (at <20% calories as fat) have multiple hepatic genes induced through PPARα (Table 1) [2,3,12]. Although fish oil contains nearly equivalent amounts of 20 : 5,n-3 and 22 : 6,n-3, liver, plasma and extrahepatic tissues accumulate 22 :

6,n-3. Surprisingly, 22 : 6,n-3 is a weak activator of hepatic PPARα. When hepatocytes are treated with 22 : 6,n-3, a small fraction of 22 : 6,n-3 is metabolized to 20 : 5,n-3 through a pathway called retroconversion [7,19] (Fig. 2).

Retroconverted fatty acids accumulate as esterified and nonesterified lipids. The generation of a preferred PPARα ligand, such as 20 : 5,n-3, through retroconversion may be a mechanism to control hepatic 22-carbon PUFA content. Enzymes involved in PUFA synthesis (elongases, desaturases and peroxisomal β-oxidation) are regulated by dietary fat, PPARα and SREBP-1 (Table 1) [12,20]. The expression of these enzymes is altered during postnatal development [2] and in chronic metabolic diseases like obesity and diabetes [2,12,21,22]. Since these enzymes affect cellular abundance of PPARα ligands, an important unanswered question is whether changes in the activity of these enzymes plays any role in controlling PPARα activity or the progression of chronic metabolic disease.

Hepatic glycolysis and de-novo lipogenesis is regulated by dietary polyunsaturated fatty acids

Glycolysis and DNL are metabolic pathways for glucose utilization and fuel storage in the form of glycogen and triglycerides. Key transcription factors controlling glycolysis and DNL include SREBP-1, ChREBP, MLX and LXR (Fig. 1 and Table 1) [13•,23,24•,25]. PUFAs suppress at least one glycolytic enzyme, that is, L-pyruvate kinase (L-PK), and several enzymes involved in DNL and monounsaturated fatty acid synthesis, including ATP citrate lyase (ACL), acetyl CoA carboxylase (ACC), fatty acid synthase (FAS), SCD1 and Elovl-6 [1,8]. PUFAs, however, have no effect on the expression of enzymes involved in bile acid synthesis (CYP7A) or cholesterol efflux (ABCA1, ABCG5, ABCG8). As such, PUFA does not interfere with LXR (α or β)-regulated gene expression [3].

ChREBP and MLX

Glucose effects on hepatic carbohydrate and lipid metabolism are mediated by glucose control of insulin secretion from pancreatic β-cells and insulin-stimulated glucose metabolism [13•]. In a recent report, glucose was found to activate LXRα and β [24•]. Activated LXR targets the ChREBP promoter and induces ChREBP gene transcription and the accumulation of $mRNA_{ChREBP}$ [26•]. Although there is considerable pretranslational control of ChREBP, much of the acute control by glucose and PUFA involves posttranslational mechanisms regulating ChREBP nuclear abundance [8,13•,27,28•]. Glucose treatment of primary hepatocytes induces the accumulation of ChREBP in hepatocyte nuclei where ChREBP binds to carbohydrate regulatory elements (ChoRE) in promoters of responsive genes, including L-PK, ACC, FAS, and SCD1 (Table 1). Binding of ChREBP to ChoRE requires MLX [29]. Neither insulin nor glucose regulates MLX nuclear content [27,29].

Hormones that promote the accumulation of cAMP (glucagon or epinephrine) or metabolic states that activate AMP-kinase (starvation) induce ChREBP phosphorylation; phospho-ChREBP does not accumulate in nuclei or bind well to ChoRE [13•,28•]. Thus, the expression of genes involved in hepatic glycolysis and DNL are suppressed. In the well fed state, dietary glucose is in excess; glucose metabolism through the pentose phosphate pathway increases xylulose-5-phosphate production, a protein phosphatases 2A (PP2A) activator. PP2A dephosphorylates ChREBP allowing ChREBP to accumulate in nuclei [30]. The influx of ChREBP into nuclei triggers formation of ChREBP/MLX heterodimers on the ChoRE, as well as increased histone H3 and H4 acetylation and recruitment of RNA polymerase II to promoters of glucose responsive genes [8,13•,29].

Both n-3 and n-6 PUFA inhibit L-PK gene transcription by suppressing ChREBP [8,9] and MLX [8] nuclear abundance. PUFAs achieve this control through posttranslational

mechanisms; PUFAs have no effect on mRNAs encoding ChREBP or MLX [8,9]. Although some have reported that PUFAs increase AMPKα phosphorylation [31], others have found no evidence for PUFA regulation of AMPK phosphorylation status [8,9]. While PUFAs affect both ChREBP and MLX nuclear abundance, overexpressed MLX, but not over-expressed ChREBP, abrogates PUFA control of L-PK and FAS [8]. These studies provide a key missing link in our understanding of how PUFAs control glycolysis (L-pyruvate kinase) and DNL (ACL, ACC, FAS, SCD1 and Elovl6). Unfortunately, the molecular basis for PUFA control of ChREBP and MLX nuclear abundance remains unresolved.

SREBP-1

SREBP-1c is one of three bHLH-LZ transcription factors (SREBP-1a, SREBP-1c and SREBP-2) controlling hepatic and whole body cholesterol and fatty acid synthesis. SREBP-1 regulates multiple pathways for fatty acid synthesis (Table 1) and VLDL assembly [23], while SREBP-2 controls cholesterol synthesis and uptake [23]. Mechanisms controlling SREBP nuclear abundance play a major role in determining the impact of SREBP on gene transcription. These posttranslational mechanisms include proteolytic processing [32] and 26S proteasomal degradation [33]. All SREBPs are synthesized as precursors (pSREBP, approximately 125 kDa) tethered to the endoplasmic reticulum. Precursor SREBPs are escorted from the endoplasmic reticulum to the Golgi by SREBP-cleavage activating protein for proteolytic processing. Site 1 and site 2 proteases in the Golgi cleave the SREBP precursor to generate mature SREBP [32]. Mature SREBP is transported to the nucleus as a dimer, via importin-β [34] where SREBP dimers bind sterol regulatory elements in promoters of target genes. Once bound, SREBPs recruit co-activators to promoters and stimulate gene transcription [23].

While sterols (cholesterol) suppress nuclear SREBP-2 levels by controlling the proteolytic processing step [35,36], PUFAs utilize multiple mechanisms to suppress SREBP-1 nuclear abundance [1]. Oxysterols (LXR agonists) and insulin induce SREBP-1 nuclear abundance [25]. While PUFAs do not interfere with LXR-regulated gene expression in hepatocytes or *in vivo* [3], PUFAs interfere with insulin control of SREBP-1 (Table 2) [11]. Insulin induces SREBP1c gene transcription through phosphoinositol-3 kinase and Akt-dependent pathways [37]. PUFAs transiently suppress insulin-stimulated Akt phosphorylation. Yet, overexpressed constitutively active Akt fails to abrogate PUFA suppression of SREBP-1 nuclear abundance [11]. Insulin induces hepatic $mRNA_{SREBP\text{-}1c}$, while PUFA enhances the turnover of mRNAs encoding both SREBP-1a and 1c [38]. Insig 1 and 2 are resident endoplasmic reticulum proteins involved in SREBP processing [32]. PUFAs, like insulin, suppress Insig-2 expression [11]. Insulin inhibits the 26S proteasomal degradation of nuclear SREBP-1 [11,33]. The PUFA 22 : 6,n-3, but not other PUFAs, lowers SREBP-1 nuclear content through a 26S proteasome-dependent mechanism [11]. While n-3 and n-6 PUFAs control SREBP-1 function by regulating SREBP-1c gene transcription and $mRNA_{SREBP\text{-}1}$ turnover, only 22 : 6, n-3 regulates SREBP-1 through a 26S proteasome-dependent mechanism.

These posttranslational mechanisms play a major role in controlling SREBP-1 nuclear abundance *in vivo*, particularly during the early postnatal period [11,39]. The very low levels of hepatic nuclear SREBP-1 in suckling rat pups [39] correlate with low blood insulin levels [40]. Injection of 12-day-old rats with insulin induces a prompt, but transient, rise in nuclear SREBP-1. Co-injection with insulin and a 26S proteasome inhibitor sustains elevated SREBP-1 levels in hepatic nuclei of suckling animals (unpublished observation). In primary rat hepatocytes, removal of insulin leads to a decline in SREBP-1 nuclear content ($t_{1/2}$ approximately 10 h); inhibitors of 26S proteasomal degradation block this decline [11]. Treatment of primary hepatocytes with 22 : 6,n-3 accelerates the loss of nuclear SREBP-1 ($t_{1/2}$ approximately 4 h); 26S proteasome inhibitors completely block the 22 : 6-mediated suppression of nuclear SREBP-1. Regulating the 26S proteasomal degradation appears to be

a major mechanism controlling SREBP-1 nuclear abundance during early postnatal development and in adult animals. In contrast to SREBP-1, the 26S proteasome is not involved in the PUFA regulation of ChREBP or MLX nuclear abundance (unpublished observation).

SREBPs are phosphoproteins and their phosphorylation status controls their capacity to transactivate genes. cAMP-activated protein kinase A phosphorylates SREBPs within the DNA binding domain inhibiting SREBP binding to sterol regulatory elements [41]. SREBPs are phosphorylated by active (dephosphorylated) Gsk3 [33,42]. Phosphorylation of SREBP promotes ubiquitin ligase SCF^{Fbw7} binding, SREBP ubiquitination and 26S proteasome degradation [33]. Insulin inhibits Gsk3 activity by stimulating Gsk3 phosphorylation through Akt [43]. Our preliminary studies indicate that 22 : 6,n-3, like insulin, induces Gsk3β phosphorylation. If these studies are confirmed, Gsk3 may not be the mediator of 22 : 6,n-3 control of SREBP-1 proteasomal degradation.

SREBPs are targets of Erk1/2 phosphorylation; Erk-phosphorylation of SREBP-1 impairs its regulation of LDL-receptor expression [44]. Treatment of primary hepatocytes with 22 : 6,n-3 [11] or feeding rats fish oil (unpublished observation) induces hepatic Erk1/2 phosphorylation. Erk1/2 is a target of insulin action [45]. Insulin typically induces a rapid, but transient, increase in Erk1/2 phosphorylation in primary hepatocytes. Inclusion of 22 : 6,n-3 does not impair the rapid insulin-stimulated increase in Erk1/2 phosphorylation. Instead, 22 : 6,n-3 prolongs elevated levels of Erk1/2 phosphorylation (Table 2). MEK inhibitors rapidly attenuate both 22 : 6-induced Erk1/2 phosphorylation and 22 : 6,n-3 suppression of SREBP-1 nuclear content implicating the MEK/Erk pathway in controlling SREBP-1 nuclear abundance [11]. The connections between the Erk1/2 pathway, the 26S proteasome and 22 : 6,n-3 control of SREBP-1 nuclear abundance remains unresolved.

Despite the apparent interference of n-3 PUFA with some facets of insulin action, n-3 PUFA, and in particular 22 : 6,n-3, mimics many insulin actions (Table 2). Moreover, in-vivo studies have established that n-3 PUFAs do not promote insulin resistance [46,47]. The basis for the selective control of insulin-regulated pathways by n-3 PUFA requires more study.

Conclusion

The central role of the liver in whole body lipid metabolism places it in a critical position to affect body fat composition. Dietary fat alters hepatic carbohydrate and lipid metabolism through changes in gene expression (Fig. 1 and Table 1). Several metabolic pathways are controlled by the PUFA-regulated transcription factors, PPARα, SREBP-1, ChREBP and MLX. Identification of these transcription factors as targets of PUFA control was a major advance in our understanding of how dietary fat controlled gene expression. Interestingly, these transcription factors display a differential response to PUFA. 20 : 5,n-3, but not 22 : 6,n-3, is a potent activator of PPARα. 22 : 6,n-3, but not 20 : 5,n-3, controls SREBP-1 nuclear abundance through 26S proteasome and Erk-dependent mechanisms. Nuclear abundance of the ChREBP/MLX-heterodimer, however, appears equally responsive to a wide range of 18–22-carbon n-3 and n-6 PUFAs. The significance of these differences will be revealed through more studies. In this regard, more study is required to define the metabolic and molecular basis for PUFA control of ligand availability for PPAR as well as mechanisms controlling SREBP-1, ChREBP and MLX function. Once defined, these mechanisms may provide new insights into disorders of lipid metabolism associated with chronic metabolic diseases such as diabetes and obesity.

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 315–317).

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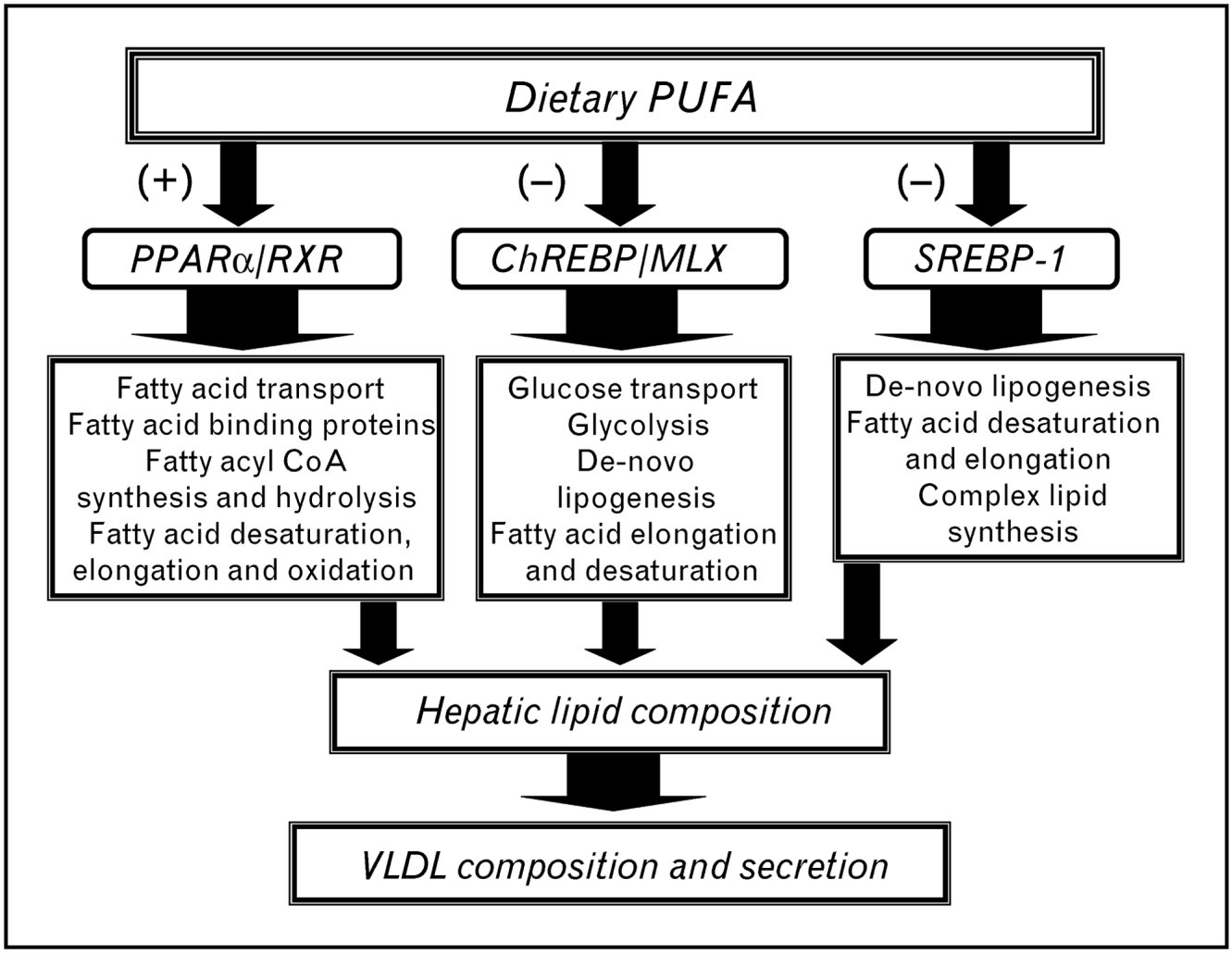

Figure 1. Impact of dietary polyunsaturated fatty acids (PUFAs) on hepatic gene transcription and lipid metabolism

Dietary polyunsaturated fatty acids (PUFAs) regulate three major transcriptional regulatory networks controlling multiple pathways involved in hepatic carbohydrate and lipid metabolism. PUFAs activate (+) peroxisome proliferator-activated receptor (PPAR)α/retinoid X receptor (RXR) and suppress (−) the nuclear abundance of carbohydrate regulatory element binding protein (ChREBP)/Max-like factor X (MLX) and sterol regulatory element binding protein (SREBP-1). Changes in hepatic lipid composition affect VLDL composition.

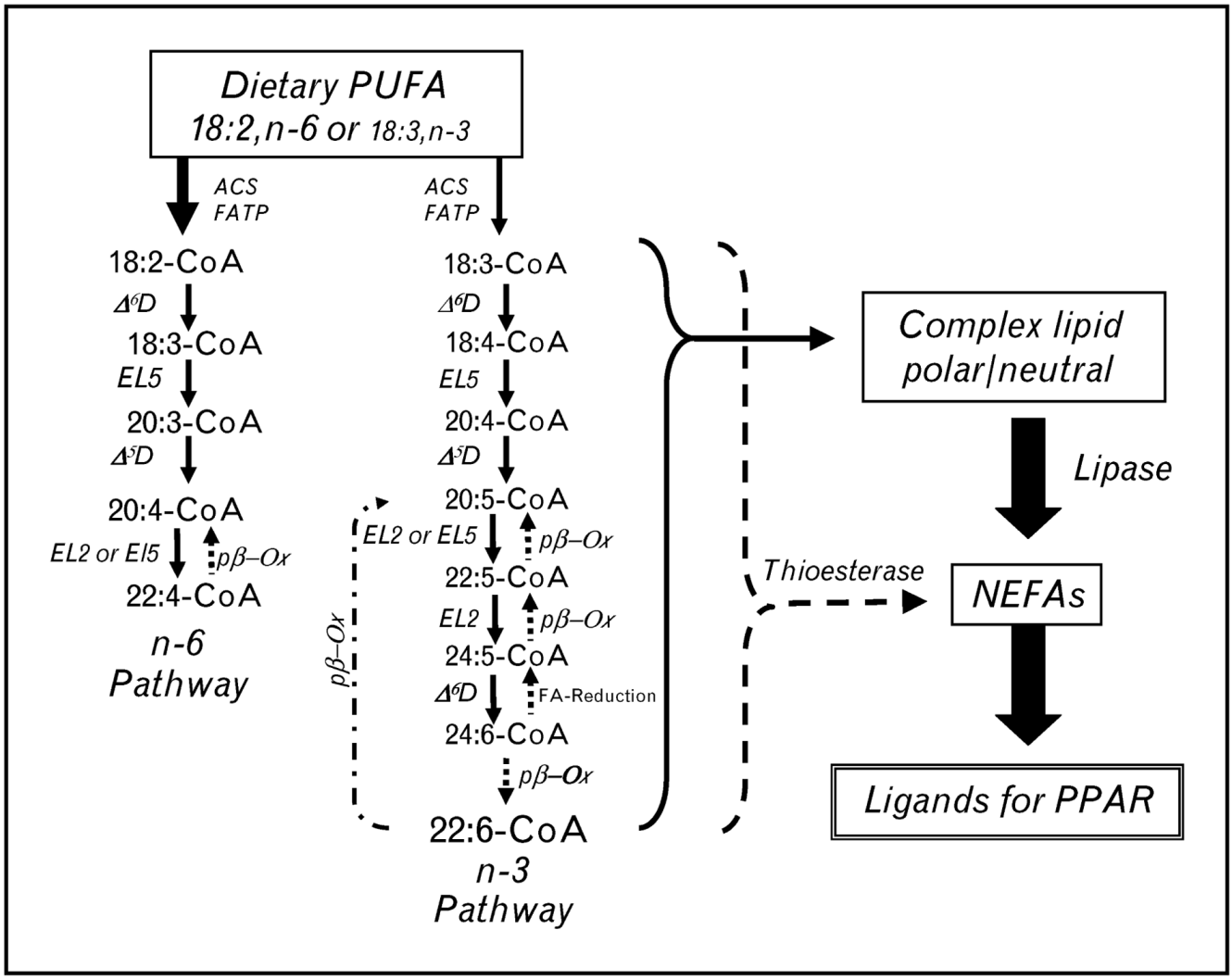

Figure 2. Metabolic pathways for n-3 and n-6 polyunsaturated fatty acid synthesis

The metabolic pathway for n-3 and n-6 polyunsaturated fatty acid (PUFA) synthesis (solid line/arrows), retroconversion of 22 : 6,n-3 to 20 : 5,n-3 (stippled line/arrows) and the release of fatty acids from fatty acyl coenzyme A (CoA) or complex lipids by the action of fatty acyl thioesterases (dotted line/arrow) or lipases (solid line, arrow), respectively. 18 : 2,n-6, 20 : 4,n-6 and 22 : 6,n-3 are the predominant PUFAs accumulating in tissues as neutral and phospholipids. ACS, acyl CoA synthetase; FATP, fatty acid transport protein; Δ^5D, Δ^5-desaturase; Δ^6D, Δ^6-desaturase; EL2, fatty acid elongase-2; EL5, fatty acid elongase-5; pβ-Ox, peroxisomal β-oxidation; NEFAs, nonesterified fatty acids; PPAR; peroxisome proliferator-activated receptor.

Table 1

Transcription factors controlling hepatic glycolysis, fatty acid synthesis and oxidation

Protein	SREBP-1	ChREBP/MLX	PPARα
Glycolysis and gluconeogenesis			
Glucose transporter-2 (Glut2)		(+)	
L-Pyruvate kinase (L-PK)		(+)	(−)
Phosphoenolpyruvate carboxykinase (PepCk)	(−)		(+)
Fatty acyl synthetases and thioesterases			
Fatty acyl synthetase 1 (ACS1)			(+)
Cytosolic fatty acyl thioesterase (CTEI)			(+)
Mitochondrial fatty acyl thioesterase (MTEI)			(+)
Peroxisomal fatty acyl thioesterase (PTEI)			(+)
Fatty acid synthesis, desaturation and elongation			
ATP citrate lyase (ACL)	(+)	(+)	
Acetyl CoA carboxylase (ACC)	(+)	(+)	
Fatty acid synthase (FAS)	(+)	(+)	
Δ^5-desaturase (Δ^5D)	(+)		(+)
Δ^6-desaturase (Δ^6D)	(+)		(+)
Stearoyl CoA desaturase (Δ^9D)	(+)	(+)	(+)
Fatty acid elongase-5 (Elovl5)			(+)
Fatty acid elongase-6 (Elovl6)	(+)	(+)	(+)
Fatty acid oxidation			
Mitochondrial HMG CoA synthase (mtHMGCoASyn)			(+)
Peroxisomal acyl CoA oxidase (AOX)			(+)
Microsomal cytochrome P450-4A (Cyp4A)			(+)

(+), Transcription factor induces enzyme expression; (−), transcription factor represses enzyme expression.

Table 2

Comparison of insulin and n-3 polyunsaturated fatty acid effects on hepatic glycolysis, fatty acid synthesis and signaling mechanisms

	Insulin	n-3 PUFA
Genes		
Glucokinase	Increase	No effect
L-Pyruvate kinase	Increase	Decrease
Phosphoenolpyruvate carboxykinase	Decrease	No effect
Insig-2	Decrease	Decrease
Fatty acid synthesis		
De-novo lipogenesis	Increase	Decrease
PUFA synthesis	Increase	Decrease
Transcription factors		
Nuclear SREBP-1	Increase	Decrease
Nuclear ChREBP and MLX	Increase	Decrease
Cell signaling pathways		
Akt phosphorylation (Activates)	Increase	Decrease
AMPK phosphorylation (Activates)	Decrease	No effect
Erk1/2 phosphorylation (Activates)	Increase	Increase
Gsk-3β phosphorylation (Inhibits)	Increase	Increase

ChREBP, carbohydrate regulatory element binding protein; MLX, Max-like factor X; PUFA, polyunsaturated fatty acid; SREBP-1, sterol regulatory element binding protein.