Fatty Acid Regulation of Hepatic Gene Transcription[1,2]

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ABSTRACT Dietary fat regulates gene expression by controlling the activity or abundance of key transcription factors. In vitro binding and cell culture studies have identified many transcription factors as prospective targets for fatty acid regulation, including peroxisome proliferator-activated receptors (PPARα, β, γ1, and γ2), sterol regulatory element binding protein-1c (SREBP-1c), hepatic nuclear factors (HNF-4α and γ), retinoid X receptor (RXRα), liver X receptor (LXRα), and others. In vivo studies established that PPARα- and SREBP-1c–regulated genes are key targets for PUFA control of hepatic gene expression. PUFA activate PPARα by direct binding, leading to the induction of hepatic fatty acid oxidation. PUFA inhibit hepatic fatty acid synthesis by suppressing SREBP-1c nuclear abundance through several mechanisms, including suppression of SREBP-1c gene transcription and enhancement of proteasomal degradation and $mRNA_{SREBP1c}$ decay. Changes in intracellular nonesterified fatty acids (NEFA) correlate well with changes in PPARα activity and $mRNA_{SREBP\text{-}1c}$ abundance. Several mechanisms regulate intracellular NEFA composition, including fatty acid transport, acyl CoA synthetases and thioesterases, fatty acid elongases and desaturases, neutral and polar lipid lipases, and fatty acid oxidation. Many of these mechanisms are regulated by PPARα or SREBP-1c. Together, these mechanisms control hepatic lipid composition and affect whole-body lipid composition. J. Nutr. 135: 2503–2506, 2005.

KEY WORDS: • gene transcription • hepatic fatty acid metabolism

Dietary fat is an important macronutrient for growth and development of all organisms. It provides substrates for energy metabolism, membranes, and signaling molecules and regulates gene expression. Since the original description of dietary fat as a regulator of gene expression over a decade ago, many transcription factors were identified as prospective targets for fatty acid regulation, including peroxisome proliferator-activated receptors (PPARα, β, γ1, and γ2),[4] sterol regulatory element binding protein-1c (SREBP-1c), hepatic nuclear factors (HNF-4α and γ), retinoid X receptor (RXRα), liver X receptor (LXRα), and others (1,2). Nonesterified fatty acids (NEFA) bind PPAR (3), HNF4 (4,5), RXRα (6), and LXRα (7). In this fashion, fatty acids act like hydrophobic hormones to control gene expression. However, fatty acids regulate other transcription factors, such as SREBP-1c and nuclear factor κB, through indirect mechanisms. Fatty acid control of these transcription factors is less clear.

This review focuses on the (n-3) PUFA control of hepatic PPARα and SREBP-1c. In vivo studies established that multiple PPARα and SREBP-1c target genes are regulated by changes in dietary fat composition. PPARα induces fatty acid oxidation, whereas SREBP-1c induces fatty acid synthesis. This mechanism controls hepatic lipid composition as well as the type and quantity of lipids available for VLDL synthesis and secretion (**Fig. 1**). Because the liver plays a central role in whole-body lipid metabolism, such regulatory schemes affect whole-body lipid composition and likely contribute to the onset and progression of several chronic diseases, including atherosclerosis, diabetes, and obesity (1).

Overview of Fatty Acid Effects on Hepatic Gene Expression. An underlying assumption regarding fatty acid effects on gene expression has been that fatty acids enter cells and control the activity or abundance of transcription factors (Fig. 1). However, fatty acids also regulate G-protein–linked membrane receptors (8). The tissue distribution and ligand specificity of these membrane receptors cannot explain fatty acid effects on hepatic gene expression. Moreover, these receptors are likely involved in acute effects of fatty acids on cells. Our focus is on intracellular lipids, their metabolism, and control of gene transcription.

NEFA enter cells through transporters [fatty acid transport protein (FATP) or fatty acid transporter CD36 (FAT)] or diffusion (Fig. 1). NEFA are rapidly converted to fatty acyl CoA (FACoA) by FATP (9) or fatty acyl CoA synthetases (10). NEFA and FACoA are bound to fatty acid binding protein (FABP) and acyl CoA binding protein (ACBP), proteins that transport fatty acids to intracellular compartments for metabolism (11) or to the nucleus to interact with transcription factors (12). Cells challenged with exogenous fatty acids rapidly assimilate the fatty acids into neutral and polar lipids; some will be oxidized. These metabolic pathways keep intracellular NEFA and FACoA very low. However, intracellular NEFA can also arise from the hydrolysis of complex lipids by lipases (13) or the hydrolysis of FACoA by thioesterases

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[4] Abbreviations used: ABCA1, ATP-binding cassette, sub-family A (ABC1), member 1; ACBP, acyl CoA binding protein; ER, endoplasmic reticulum; FABP, fatty acid binding protein; FACoA, fatty acyl CoA; FAT, fatty acid transporter (CD36); FATP, fatty acid transport protein; HNF-4, hepatic nuclear factor-4; LXR, liver X-receptor; LXRE, LXR response element; MUFA, monounsaturated fatty acid; NEFA, nonesterified fatty acid; PI3 kinase, phosphoinositide 3 kinase; PPAR, peroxisome proliferator-activated receptor; RXRα, retinoid X receptor; SCAP, SREBP-cleavage activating protein; SREBP, sterol regulatory element binding protein.

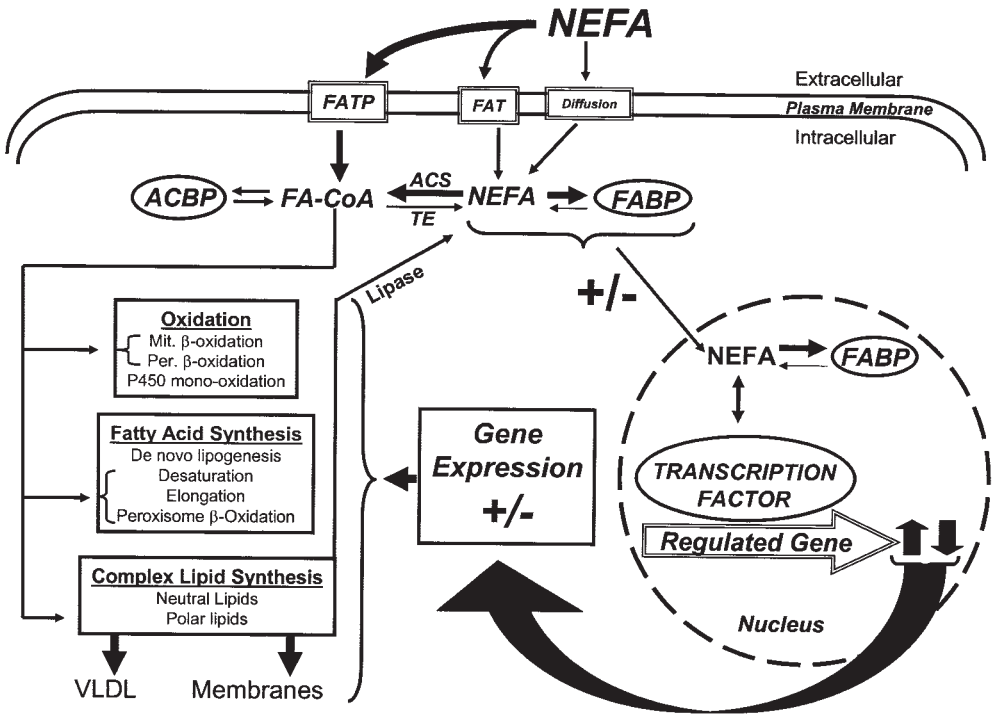

FIGURE 1 Schematic of fatty acid effects on hepatic metabolism and gene expression.

(14). As discussed below, these pathways play an important role in controlling the availability of lipid mediators regulating transcription factors.

Studies with PPARα null mice, SREBP-1c, and LXRα overexpression revealed 3 pathways for (n-3) PUFA control of hepatic gene expression: *1*) n-3 PUFA induction of mono- and β-oxidation requires PPARα; *2*) (n-3) PUFA suppression of de novo lipogenesis and monounsaturated fatty acid (MUFA) synthesis requires SREBP-1c; *3*) (n-3) PUFA suppression of the glycolytic enzyme, L-pyruvate kinase, does not involve PPARα, SREBP-1c, or LXR (15–18). The (n-3) PUFA function as feed-forward activators of fatty acid oxidation and feedback inhibitors to prevent the production of new fatty acids, including PUFA. This regulatory scheme not only reduces overall hepatic lipid content and VLDL secretion, but also eliminates excessive very long-chain PUFA that may promote oxidant stress or impair membrane integrity.

Fatty Acid Regulation of Hepatic PPARα. PPARα binds (n-3) PUFA (3) and (n-3) PUFA regulate multiple PPARα target genes in cell culture and in vivo (1,17). If PPARs are sensors of intracellular lipid, then intracellular NEFA should parallel changes in PPARα activity and the abundance of target gene transcripts. Indeed, when hepatocytes are challenged with 20:5(n-3), induction of PPARα target genes, such as cytochrome P_{450} 4A and cytosolic thioesterase I, correlates well with changes in nonesterified 20:5(n-3) (17,19). While challenging hepatocytes with 18:3(n-3) also significantly changes in intracellular non-esterified 18:3(n-3) and complex lipid composition, 18:3(n-3) weakly activates PPARα. Such studies suggest that merely perturbing intracellular NEFA is insufficient to activate PPARα. Several explanations can account for this difference: *1*) selective transport of fatty acids to the nucleus and interaction with PPARα; *2*) selective recruitment of coactivators by the fatty acid-PPARα/RXRα heterodimer; and *3*) differential fatty acid metabolism.

Although the first 2 possibilities were not tested, there is reasonable evidence for differential metabolism of 18:3(n-3) and 20:5(n-3) in hepatocytes. C20 PUFA, but not C18 PUFA, are rapidly elongated to C22 PUFA in primary hepatocytes and other cell types (19,20). Elovl-2 and Elovl-5 are the fatty acid elongases that carry out this reaction. These enzymes are components of the pathway that converts dietary 18:2(n-6) and 18:3(n-3) to 20:4(n-6) and 22:6(n-3), the main C20–22 PUFA that accumulate in membranes. The fact that 18:3(n-3) is neither elongated nor desaturated in primary hepatocytes indicates either low Δ6 desaturase activity or channeling into other metabolic pathways (**Fig. 2**).

Although products of 20:5(n-3) elongation (C22 PUFA) are weak PPARα activators (19), the addition of C22 PUFA to hepatocytes yields a net gain of 20:5(n-3) in both the esterified and nonesterified lipid fraction of the cell (19). C22 PUFA-CoA are retroconverted to C20 PUFA-CoA in the peroxisome by β-oxidation (21). Most chain-shortened (β-oxidized) products are assimilated into neutral or polar lipids. However, lipases acting on complex lipids or thioesterases acting on FACoA generate 20:5(n-3) as a NEFA (Fig. 2). This cycle of fatty acid assimilation into complex lipid and release of NEFA reflects remodeling of membranes and neutral lipids (13) and is likely a sorting mechanism to control cellular lipid composition.

Strong PPARα agonists, such as WY14,643, induce several fatty acid elongases, desaturases, and peroxisomal enzymes, leading to changes in hepatic and blood lipid profiles (18,22,23). The expression of these enzymes is controlled by nutritional, hormonal, developmental, and tissue-specific factors. We anticipate that changes in the activity of these enzymes will affect complex lipid and intracellular NEFA composition, as well as the control of fatty acid–regulated transcription factors.

Are Other Hepatic Nuclear Receptors Regulated by PUFA? LXR. LXRα, but not LXRβ, is a target of fatty acid regulation in established cell lines (7,20,24). Although some LXR-regulated gene products such as ATP-binding cassette, sub-family A (ABC1), member 1(ABCA1) and SREBP-1c are downregulated by fatty acids, the mechanisms for control cannot be attributed to fatty acid interference with oxysterol activation of LXRα. MUFAs destabilize ABCA1 in cell mem-

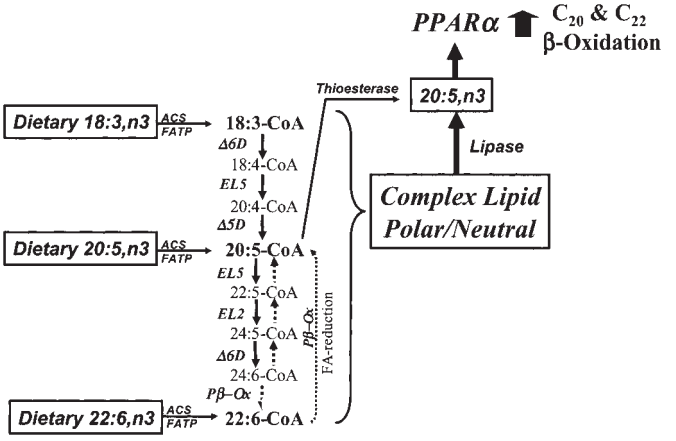

FIGURE 2 Pathway for (n-3) PUFA metabolism and the production of ligands regulating nuclear receptors. Nonesterified 18:3(n-3), 20:5(n-3), and 22:6(n-3) enter cells, are rapidly converted to FACoA by ACS or FATP and assimilated into complex lipids. At the FACoA stage, 18:3(n-3) and 20:5(n-3) are desaturated (Δ5 and Δ6 desaturase) and elongated (Elovl-2 and Elovl-5) to the end product of the pathway, 22:6-CoA; 22:6 is assimilated into complex lipids. Excessive cellular 22:6 is converted to 22:6-CoA, retroconverted in the peroxisome (β-oxidation/reduced) to 20:5(n-3)-CoA and reassimilated into complex lipids. Complex lipid turnover (lipase) or hydrolysis of 20:5(n-3)-CoA by thioesterase releases 20:5(n-3) as NEFA, a PPARα ligand.

branes (25,26), and promoter analyses indicate that the LXR response element (LXRE) in the SREBP-1c promoter is not required for PUFA suppression of SREBP-1c gene transcription (27). These observations, coupled with the absence of PUFA suppression of many LXR-regulated genes in vivo (17) argue against LXRα as a target for PUFA control of gene transcription in vivo.

HNF-4. HNF-4α and γ bind FACoA, and fatty acids (4,5), and HNF-4α has fatty acyl thioesterase activity (28). HNF-4α controls an extensive network of genes in the liver and other tissues. Of these, few are regulated by dietary PUFA in vivo; exceptions include L-pyruvate kinase, glucose 6-phosphatase, and apolipoproteins A1 and CIII. Our studies suggest that fatty acid control of HNF-4 target genes is promoter specific (unpublished data). As such, factors other than HNF-4 are likely involved in the PUFA control of these genes. Additional studies are required to evaluate the role that fatty acids, fatty acyl CoA, and the newly described thioesterase activity play in the control of HNF-4 and its regulatory network in vivo.

SREBP-1c is a Target for Fatty Acid Control in Liver.

Worgall et al. (29) reported that SREBP-1 and SREBP-2 were targets of fatty acid control in established cell lines. Subsequent reports established that only SREBP-1c was a major target of PUFA control in liver (1). SREBP-1c is one of 3 helix loop-helix-basic leucine zipper protein transcription factors (SREBP-1a, SREBP-1c, and SREBP-2) that play a central role in the control of cholesterol and fatty acid synthesis, VLDL assembly, and gluconeogenesis (30,31).

The principal mechanism for SREBP regulation of gene transcription involves control of its nuclear abundance (nSREBP). nSREBP is regulated by 2 post-translational mechanisms, proteolytic processing (31) and proteasomal degradation (32). All SREBPs are synthesized as precursors (pSREBP, ~125 kDa) tethered to the endoplasmic reticulum (ER) and escorted to the Golgi complex by SREBP-cleavage activating protein (SCAP) for proteolytic processing. nSREBP is transported to the nucleus, via importin-β (33), where it binds sterol regulatory elements in promoters of specific genes, recruits coactivators to the promoter, and stimulates gene transcription (34). Phosphorylation and ubiquitination of nSREBP targets nSREBP for proteasomal degradation (35). Sterols regulate nSREBP levels by controlling the proteolytic processing step, not proteasomal degradation. Sterols induce the ER-resident proteins, Insig-1 and Insig-2, to bind SCAP; this retains the SCAP-SREBP complex in the ER and prevents its cleavage to nSREBP (36). This is the molecular basis for cholesterol suppression of nuclear SREBP-2 abundance and the suppression of endogenous cholesterol synthesis.

Although SREBP-1c and SREBP-2 are structurally similar, their regulation in the liver by nutrients, hormones, and during postnatal development is quite different (**Fig. 3**). Unlike SREBP-2, SREBP-1c nuclear abundance is controlled by several mechanisms (Fig. 3). Insulin and oxysterols (LXR agonists) induce SREBP-1c gene transcription, elevate nSREBP-1c, and induce de novo lipogenesis (31). Insulin regulates SREBP-1c gene transcription through phosphoinositide 3 kinase (PI3 kinase) and Akt (37) as well as changes in Insig-1 and -2 expression (38). The SREBP-1c promoter contains regulatory elements for LXR, SREBP, NFY, and Sp1. Both LXR agonists and elevated nSREBP stimulate SREBP-1c promoter activity.

PUFA effects on insulin regulation of PI3 kinase, AKT activity, or Insig expression have not been reported. PUFA suppression of SREBP-1c promoter activity does not require the LXRE (27), but may depend on antecedent mechanisms that

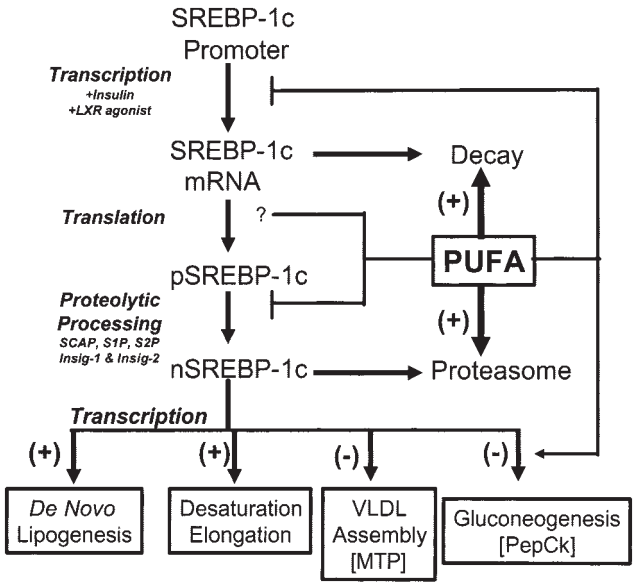

FIGURE 3 (n-3) PUFA affect multiple mechanisms to control SREBP-1c nuclear abundance. The diagram illustrates the production of SREBP-1c from the gene to the nuclear form (nSREBP-1c), the form that regulates gene transcription by binding sterol regulatory elements in promoters of key genes. Insulin and oxysterols induce nSREBP-1c, which in turn, stimulates transcription of genes involved in de novo lipogenesis, fatty acid desaturases and elongases, and suppresses expression of microsomal transfer protein (MTP) and phosphoenolpyruvate carboxykinase (PepCk). The diagram also includes key factors involved in proteolytic processing of SREBP-1c to the nuclear form, SCAP, site 1 and site 2 protease [S1P and S2P], Insig-1 and -2. (n-3) PUFA suppress nSREBP-1c through multiple mechanisms including suppression of SREBP-1c gene transcription and proteolytic processing, and enhanced $mRNA_{SREBP\text{-}1c}$ decay and nSREBP-1c degradation in the proteasome. A decline in nSREBP-1c results in reduced de novo lipogenesis, fatty acid desaturation and elongation, and elevated expression of MTP and PepCk.

suppress nSREBP-1c. (n-3) PUFA enhance $mRNA_{SREBP1c}$ decay (39) and stimulate proteasomal degradation (unpublished data); 20:5(n-3) and 22:6(n-3) induce a prompt decline in $mRNA_{SREBP1c}$. How (n-3) PUFA promote transient changes in $mRNA_{SREBP1c}$ or augments proteasomal degradation remains to be clarified.

Post-translational mechanisms are the dominant means for controlling nSREBP-1c in neonatal liver (18,40). Suckling rats have ample hepatic nSREBP-2, but essentially no nSREBP-1c. The selective expression of SREBP-2 vs. SREBP-1c in liver nuclei during postnatal development leads to enhanced cholesterol synthesis and suppressed synthesis of saturated (de novo lipogenesis) and monounsaturated fatty acids (Δ9 desaturase and fatty acid elongase-6). The mechanism for the selective elimination of SREBP-1c from the nucleus is linked to low circulating insulin and the ingestion of a high-fat milk diet. Rat milk is deficient in very long-chain PUFA (18). The mechanisms controlling nSREBP-1c in neonatal liver differ from those of the adult. We speculate that diminished insulin stimulation of nSREBP-1c accumulation and enhanced nSREBP-1c proteasomal degradation account for the absence of nSREBP-1c in neonatal liver.

Perspective and Future Studies. Changes in intracellular NEFA correlate well with the control of both PPARα and SREBP-1c function. The capacity of cells to interconvert fatty acids (Fig. 2) and release these fatty acids as NEFA represents a novel mechanism for the generation of lipid mediators controlling transcription factors. It is reasonable to predict that manipulation of the metabolic pathways that control intracellular NEFA composition will affect fatty acid–regulated transcription factors and their regulatory networks. Pharmacological or genetic targeting of these enzymes is required to evaluate these possibilities. Such studies may reveal novel strategies for the management of hepatic and whole-body lipid composition.

LITERATURE CITED

1. Jump, D. B. (2004) Fatty acid regulation of gene transcription. Crit. Rev. Clin. Lab. Sci. 41: 41–78.
2. Pegorier, J. P., Le May, C. & Girard, J. (2004) Control of gene expression by fatty acids. J. Nutr. 134: 2444S–2449S.
3. Xu, H. E., Lambert, M. H., Montana, V. G., Parks, D. J., Blanchard, S. G., Brown, P. J., Sternbach, D. D., Lehmann, J. M., Wisely, G. B., et al. (1999) Molecular recognition of fatty acids by PPAR. Mol. Cell. 3: 397–403.
4. Wisely, G. B., Miller, A. B., Davis, R. G., Thornquest, A. D., Jr., Johnson, R., Spitzer, T., Sefler, A., Shearer, B., Moore, J. T., et al. (2002) HNF-4γ is a transcription factor that constitutively binds fatty acids. Structure 10: 1225–1234.
5. Dhe-Paganon, S., Duda, K., Iwamoto, M., Chi, Y. I. & Shoelson, S. E. (2002) Crystal structure of the HNF-4α ligand binding domain in complex with endogenous fatty acid ligand. J. Biol. Chem. 277: 37973–37976.
6. de Urquiza, M. A., Liu, S., Sjoberg, M., Zetterstrom, R.H., Griffiths, W., Sjovall, J. & Perlmann, T. (2000) Docosahexaenoic acid, a ligand for RXR in mouse brain. Science (Washington, DC) 290: 2140–2144.
7. Ou, J., Tu, H., Shan, B., Luk, A., DeBose-Boyd, R. A., Bashmakov, Y., Goldstein, J. L. & Brown, M. S. (2001) Unsaturated fatty acids inhibit transcription of the SREBP-1c gene by antagonizing ligand-dependent activation of the LXR. Proc. Natl. Acad. Sci. U.S.A. 98: 6027–6032.
8. Kostenis, E. (2004) A glance at G-protein-coupled receptors for lipid mediators: a growing receptor family with remarkably diverse ligands. Pharmacol. Ther. 102: 243–257.
9. DiRusso, C. C., Li, H., Darwis, D., Watkins, P. A., Berger, J. & Black, P. N. (2005) Comparative biochemical studies of the murine FATP expressed in yeast. J. Biol. Chem. 280: 16829–16837.
10. Coleman, R. A., Lewin, T. M., Van Horn, C. G. & Gonzalez-Baró, M. R. (2002) Do long-chain acyl-CoA synthetases regulate fatty acid entry into synthetic versus degradative pathways? J. Nutr. 132: 2123–2126.
11. Hertzel, A. V. & Bernlohr, D. A. (2000) The mammalian fatty acid-binding protein multigene family: molecular and genetic insights into function. Trends Endocrinol. Metab. 11: 175–180.
12. Wolfrum, C., Borrmann, C. M., Borchers, T. & Spener, F. (2001) Fatty acids and hypolipidemic drugs regulate PPARα- and γ-mediated gene transcription via liver fatty acid binding protein: a signaling path to the nucleus. Proc. Natl. Acad. Sci. U.S.A. 98: 2323–2328.
13. Patton, G. M., Fasulo, J. M. & Robins, S. J. (1994) Hepatic phosphatidylcholines: evidence for synthesis in the rat by extensive reutilization of endogenous acylglycerides. J. Lipid Res. 35: 1211–1221.
14. Hunt, M. C. & Alexson, S. E. (2002) The role Acyl-CoA thioesterases play in mediating intracellular lipid metabolism. Prog. Lipid Res. 41: 99–130.
15. Ren, B., Thelen, A. P., Peters, J. M., Gonzalez, F. J. & Jump, D. B. (1997) Polyunsaturated fatty acid suppression of hepatic fatty acid synthase and S14 gene expression does not require PPARα. J. Biol. Chem. 272: 26827–26832.
16. Pan, D. A., Mater, M. K., Thelen, A. P., Peters, J. M., Gonzalez, F. J. & Jump, D. B. (2000) Evidence against the PPARα as the mediator for PUFA suppression of hepatic L-pyruvate kinase gene transcription. J. Lipid Res. 41: 742–751.
17. Pawar, A., Botolin, D., Mangelsdorf, D. J. & Jump, D. B. (2003) The role of LXR-α in the fatty acid regulation of hepatic gene expression. J. Biol. Chem. 278: 40736–40743.
18. Wang, Y., Botolin, D., Christian, B., Busik, C., Xu, J. & Jump, D. B. (2005) Tissue-specific, nutritional and developmental regulation of rat fatty acid elongases. J. Lipid Res. 46: 706–715.
19. Pawar, A. & Jump, D. B. (2003) Unsaturated fatty acid regulation of PPARα activity in primary rat hepatocytes. J. Biol. Chem. 278: 35931–35939.
20. Pawar, A., Xu, J., Jerks, E., Mangelsdorf, D. J. & Jump, D. B. (2002) Fatty acid regulation of LXR and PPARα in HEK293 cells. J. Biol. Chem. 277: 39243–39250.
21. Sprecher, H. (2000) Metabolism of highly unsaturated n-3 and n-6 fatty acids. Biochim. Biophys. Acta 1486: 219–231.
22. Matsuzaka, T., Shimano, H., Yahagi, N., Amemiya-Kudo, M., Yoshikawa, T., Hasty, A. H., Tamura, Y., Osuga, J., Okazaki, H. et al. (2002) Dual regulation of mouse Δ5- and Δ6-desaturase gene expression by SREBP-1 and PPARα. J. Lipid Res. 43: 107–114.
23. Reddy, J. K. & Mannaerts, G. P. (1994) Peroxisomal lipid metabolism. Annu. Rev. Nutr. 14: 343–370.
24. Murthy, S., Born, E., Mathur, S. N. & Field, F. J. (2004) LXR-mediated increase in ATP-binding cassette transporter A1 expression is attenuated by fatty acids in CaCo-2 cells: effect on cholesterol efflux to high-density lipoprotein. Biochem. J. 377: 545–552.
25. Wang, Y., Kurdi-Haidar, B. & Oram, J. F. (2004) LXR-mediated activation of macrophage stearoyl-CoA desaturase generates unsaturated fatty acids that destabilize ABCA1. J. Lipid Res. 45: 972–980.
26. Sun, Y., Hao, M., Luo, Y., Liang, C. P., Silver, D. L., Cheng, C., Maxfield, F. R. & Tall, A. R. (2003) Stearoyl-CoA desaturase inhibits ATP-binding cassette transporter A1-mediated cholesterol efflux and modulates membrane domain structure. J. Biol. Chem. 278: 5813–5820.
27. Deng, X., Cagen, L. M., Wilcox, H. G., Park, E. A., Raghow, R. & Elam, M. B. (2002) Regulation of the rat SREBP-1c promoter in primary rat hepatocytes. Biochem. Biophys. Res. Commun. 290: 256–262.
28. Hertz, R., Kalderon, B., Byk, T., Berman, I., Za'tara, G., Mayer, R. & Bar-Tana, J. (2005) Thioesterase activity and acyl-CoA/fatty acid cross talk of HNF-4α. J. Biol. Chem.
29. Worgall, T. S., Sturley, S. L., Seo, T., Osborne, T. F. & Deckelbaum, R. J. (1998) PUFA decrease expression of promoters with sterol regulatory elements by decreasing levels of mature SREBP. J. Biol. Chem. 273: 25537–25540.
30. Horton, J. D., Shah, N. A., Warrington, J. A., Anderson, N. N., Park, S. W., Brown, M. S. & Goldstein, J. L. (2003) Combined analysis of oligonucleotide microarray data from transgenic and knockout mice identifies direct SREBP target genes. Proc. Natl. Acad. Sci. U.S.A. 100: 12027–12032.
31. Horton, J. D., Goldstein, J. L. & Brown, M. S. (2002) SREBPs: activators of the complete program of cholesterol and fatty acid synthesis in the liver. J. Clin. Investig. 109: 1125–1131.
32. Sundqvist, A., Bengoechea-Alonso, M. T., Ye, X., Lukiyanchuk, Jin, J., Harper, J. W. & Ericsson, J. (2005) Control of lipid metabolism by phosphorylation-dependent degradation of the SREBP family of transcription factors by SCGFBW7. Cell Metab. 1: 379–391.
33. Nagoshi, E., Imamoto, N., Sato, R. & Yoneda, Y. (1999) Nuclear import of SREBP-2, a basic helix-loop-helix-leucine zipper (bHLH-Zip)-containing transcription factor, occurs through the direct interaction of importin-β with HLH-Zip. Mol. Biol. Cell. 10: 2221–2233.
34. Bennett, M. K., Toth, J. I. & Osborne, T. F. (2004) Selective association of SREBP isoforms with target promoters in vivo. J. Biol. Chem. 279: 37360–37367.
35. Hirano, Y., Yoshida, M., Shimizu, M. & Sato, R. (2001) Direct demonstration of rapid degradation of nuclear SREBP by the ubiquitin-proteasome pathway. J. Biol. Chem. 276: 36431–36437.
36. Adams, C. M., Reitz, J., De Brabander, J. K., Feramisco, J. D., Li, L., Brown, M. S. & Goldstein, J. L. (2004) Cholesterol and 25-hydroxycholesterol inhibit activation of SREBPs by different mechanisms, both involving SCAP and Insigs. J. Biol. Chem. 279: 52772–52780.
37. Ribaux, P. G. & Iynedjian, P. B. (2003) Analysis of the role of protein kinase B (cAKT) in insulin-dependent induction of glucokinase and sterol regulatory element-binding protein 1 (SREBP1) mRNAs in hepatocytes. Biochem. J. 376: 697–705.
38. Yabe, D., Komuro, R., Liang, G., Goldstein, J. L. & Brown, M. S. (2003) Liver-specific mRNA for Insig-2 down-regulated by insulin: implications for fatty acid synthesis. Proc. Natl. Acad. Sci. U.S.A. 100: 3155–3160.
39. Xu, J., Teran-Garcia, M., Park, J. H., Nakamura, M. T. & Clarke, S. D. (2001) PUFA suppress hepatic SREBP-1 expression by accelerating transcript decay. J. Biol. Chem. 276: 9800–9807.
40. Botolin, D. & Jump, D. B. (2003) Selective proteolytic processing of rat hepatic sterol regulatory SREBP-1 and SREBP-2 during postnatal development. J. Biol. Chem. 278: 6959–6962.