



Review

Regulation of energy metabolism by long-chain fatty acids



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ABSTRACT

In mammals, excess energy is stored primarily as triglycerides, which are mobilized when energy demands arise. This review mainly focuses on the role of long chain fatty acids (LCFAs) in regulating energy metabolism as ligands of peroxisome proliferator-activated receptors (PPARs). PPAR- α expressed primarily in liver is essential for metabolic adaptation to starvation by inducing genes for beta-oxidation and ketogenesis and by downregulating energy expenditure through fibroblast growth factor 21. PPAR- δ is highly expressed in skeletal muscle and induces genes for LCFA oxidation during fasting and endurance exercise. PPAR- δ also regulates glucose metabolism and mitochondrial biogenesis by inducing FOXO1 and PGC1- α . Genes targeted by PPAR- γ in adipocytes suggest that PPAR- γ senses incoming non-esterified LCFAs and induces the pathways to store LCFAs as triglycerides. Adiponectin, another important target of PPAR- γ may act as a spacer between adipocytes to maintain their metabolic activity and insulin sensitivity. Another topic of this review is effects of skin LCFAs on energy metabolism. Specific LCFAs are required for the synthesis of skin lipids, which are essential for water barrier and thermal insulation functions of the skin. Disturbance of skin lipid metabolism often causes apparent resistance to developing obesity at the expense of normal skin function.

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Contents

1. Introduction	125
1.1. LCFAs as endogenous ligands of PPARs	126
1.1.1. Discovery of PPARs	126
1.1.2. Binding kinetics of LCFAs to PPARs	126
1.1.3. Structural basis of PPAR activation by ligands and their specificity	126
1.2. Other nuclear receptors that bind to or are inhibited by LCFAs	127
1.2.1. RXR	127
1.2.2. HNF4	127
1.2.3. LXR	127

Abbreviations: ACAA2, 3-oxoacyl-CoA thiolase; ADIPOR, adiponectin receptor; AF12, activation function 1,2; AMPK, AMP-activated protein kinase; ATF4, activating transcription factor 4; ATGL, adipose triglyceride lipase; CaMK, calcium/calmodulin-dependent kinase; CD36, fatty acid translocase; CPT1A, carnitine palmitoyltransferase 1A (liver type); CPT1B, carnitine palmitoyltransferase 1B (muscle type); CREB, cAMP responsive element binding protein 1; D6D, delta-6 desaturase (also called FADS2); DBD, DNA binding domain; DGAT, diacylglycerol acyltransferase; EFA, essential fatty acid; ELOVL, elongation of very-long chain; ETFDH, electron-transferring flavoprotein dehydrogenase; FABP, fatty acid binding protein; FAS, fatty acid synthase; FATP, fatty acid transfer protein; FFAR, free fatty acid receptor; FGF21, fibroblast growth factor 21; FOXO1, forkhead box O1; FXR, farnesoid-X receptor; G3P, glycerol-3-phosphate; GH, growth hormone; GK, glucokinase; GLUT4, glucose transporter 4; GPR, G protein-coupled receptor; HADHA, trifunctional protein α subunit; HMGCS2, 3-hydroxy-3-methylglutaryl-CoA synthase 2; HMW adiponectin, high molecular weight adiponectin (up to 18mer); HNF4, hepatocyte nuclear factor 4; HSL, hormone sensitive lipase; IGF1, insulin-like growth factor 1; IGF1BP, IGF1 binding protein; Kd, dissociation constant; KO, gene knockout; LACS, long chain acyl-CoA synthase; LBD, ligand binding domain; LCAD, long chain acyl-CoA dehydrogenase; LCFA, long chain fatty acid ($C = 14-20$); LPL, lipoprotein lipase; LXR, liver-X receptor; MCDL, malonyl-CoA decarboxylase; MEF2, myocyte enhancer factor 2; PDH, pyruvate dehydrogenase; PDK, pyruvate dehydrogenase kinase; PEPCCK, phosphoenolpyruvate carboxykinase; PFK, phosphofructokinase; PFKFB3, 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3; PKA, protein kinase A; PPAR, peroxisome proliferator-activated receptor; PGC1 α , peroxisome proliferator-activated receptor gamma coactivator 1 α ; PPARE, peroxisome proliferator response element; PUFA, polyunsaturated fatty acid; RAR, retinoic acid receptor; RXR, retinoid-X receptor; SCD1, stearoyl-CoA desaturase 1; SOCS2, suppressor of cytokine signaling 2; STAT5, signal transducer and activator of transcription 5; TNF α , tumor necrosis factor alpha; TR, thyroid hormone receptor; TRB3, tribbles homolog 3; TZD, thiazolidinedione; UCP, uncoupling protein; VDR, vitamin D receptor; VLCAD, very long chain acyl-CoA dehydrogenase; VLDL, very low density lipoprotein.

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1.3.	Other transcription factors regulated by PUFAs but not by LCFAs in general	127
1.3.1.	SREBP1c	127
1.3.2.	ChREBP	127
1.3.3.	Implications	127
1.4.	Free fatty acid receptors (FFARs)	128
2.	Adaptation to fasting mediated by LCFAs	128
2.1.	Essential role of PPAR α in adaptation to fasting	128
2.2.	Genes induced by PPAR α in liver during fasting	128
2.2.1.	Induction of fatty acid oxidation and ketogenesis in mitochondria	128
2.2.2.	Induction of fibroblast growth factor 21	129
2.3.	Altered glucose and amino acid metabolism in PPAR α KO mice	129
2.4.	Species differences in the response to peroxisome proliferators	130
3.	Regulation of fatty acid oxidation by PPAR δ in skeletal muscle	130
3.1.	Skeletal muscle metabolism and PPAR δ	130
3.1.1.	Adaptation of energy metabolism in skeletal muscle	130
3.1.2.	Biological roles of PPAR δ	130
3.1.3.	Indispensable role of PPAR δ in skeletal muscle	131
3.2.	PPAR δ in response to fasting	131
3.2.1.	Induction of FOXO1 and PDK4 by PPAR δ	131
3.2.2.	PPAR γ coactivator 1 α (PGC1 α) amplifies the adaptive response of muscle to fasting	131
3.3.	Role of PPAR δ in response to exercise	131
3.3.1.	Induction of PPAR δ and its target genes by endurance exercise	131
3.3.2.	Role of NRF, ERR α and PPAR δ in mitochondrial biogenesis	132
3.3.3.	MEF2 and fiber type change	132
3.3.4.	A central role of PGC1 α in the adaptation of muscle to endurance exercise	133
4.	Role of LCFA in adipocyte metabolism	133
4.1.	PPAR γ target genes in adipose tissue	133
4.2.	Role of adiponectin in regulation of adipocyte metabolism	133
4.2.1.	Structure and oligomerization	134
4.2.2.	Adiposity and plasma adiponectin	134
4.2.3.	Proposed function of adiponectin-T-cadherin complex as an inter-cellular spacer	134
4.2.4.	Endocrine function of adiponectin	134
4.2.5.	Physiological significance of adiponectin induction by PPAR γ in adipose	135
4.2.6.	Induction of adiponectin by FGF21 in adipose in fed and fasted conditions	135
5.	Effects of skin LCFAs on energy metabolism	135
5.1.	Skin lipids	135
5.1.1.	Keratinocytes and ceramides	135
5.1.2.	Sebaceous gland and wax esters	135
5.2.	Animal models with a skin lipid impairment	136
5.2.1.	Linoleic acid deficiency	136
5.2.2.	ELOVL4 mutation, KO mice	136
5.2.3.	ELOVL3 KO mice	136
5.2.4.	Asebia, SCD1 KO mice	137
5.2.5.	DGAT1 KO mice	137
5.2.6.	DGAT2 KO mice	138
5.3.	Apparent resistance to development of metabolic syndrome in the animals with impaired skin function	138
6.	Concluding remarks and future directions	138
	Acknowledgments	139
	References	139

1. Introduction

From single-cell organisms to humans, it is essential for survival to adjust macronutrient metabolism to physiological conditions and nutrient availability. In mammals, excess energy is stored primarily as triglycerides, which are mobilized when demand for energy arises. Hormones sense physiological conditions and accordingly coordinate energy metabolism among organs. For example, pancreatic beta-cells sense abundance of nutrients and secrete insulin, which then activates a multitude of metabolic pathways including glycogen synthesis, glycolysis, glucose oxidation, *de novo* lipogenesis and protein synthesis, whereas norepinephrine secreted from the adrenal medulla mobilizes stored energy when there is an acute increase in energy demand. In the past decades, it has become increasingly clear that all macronutrients, carbohydrates, proteins and lipids, also play an important role in the regulation of energy metabolism. The discovery of regulation

of energy metabolism by long-chain fatty acids (LCFAs) is a fairly recent event and is still emerging. Thus, the objective of this review is to summarize recent findings in this area, place them in physiological contexts, and provide likely regulatory schemes whenever possible. LCFAs refer to saturated and unsaturated fatty acids with 14–20 carbons. The primary focus of this review is on the regulation of energy metabolism by LCFAs irrespective to the degree of unsaturation. Polyunsaturated fatty acid (PUFA) specific effects are mentioned only briefly in the SREBP1 and ChREBP sections because the topic has been reviewed elsewhere [1–3]. In this review, we focus on five topics. The first, as part of the introduction, is a review of binding kinetics of peroxisome proliferator-activated receptors (PPARs) and the evidence for LCFAs as primary endogenous ligands of PPARs. Also, in the introduction, mediators of LCFA regulation other than PPARs are briefly reviewed to highlight why we are focusing on PPARs in the subsequent sections. The second topic deals with the role of LCFAs in adaptation to fasting and

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