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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-alpha 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-delta is highly expressed in skeletal muscle and induces genes for LCFA oxidation during fasting and endurance exercise. PPAR-delta also regulates glucose metabolism and mitochondrial biogenesis by inducing FOXO1 and PGC1-alpha. Genes targeted by PPAR-gamma in adipocytes suggest that PPAR-gamma senses incoming non-esterified LCFAs and induces the pathways to store LCFAs as triglycerides. Adiponectin, another important target of PPAR-gamma 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.

Contents

Abbreviations: ACAA2, 3-oxoacyl-CoA thiolase; ADIPOR, adiponectin receptor; AF1,2, 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; MCDC, malonyl-CoA decarboxylase; MEF2, myocyte enhancer factor 2; PDH, pyruvate dehydrogenase; PDK, pyruvate dehydrogenase kinase; PEPCK, phosphoenolpyruvate carboxykinase; PFK, phosphofructokinase; PFKFB3, 6-phosphofurcto-2-kinase/fructose-2,6-bisphosphatase 3; PKA, protein kinase A; PPAR, peroxisome proliferator-activated receptor; PGC1α, peroxisome proliferator-activated receptor gamma coactivator 1α; PPRE, 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; TNFα, 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. 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