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Review

Long-chain fatty acid uptake and FAT/CD36 translocation in heart and skeletal muscle

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Abstract

Cellular long-chain fatty acid (LCFA) uptake constitutes a process that is not yet fully understood. LCFA uptake likely involves both passive diffusion and protein-mediated transport. Several lines of evidence support the involvement of a number of plasma membrane-associated proteins, including fatty acid translocase (FAT)/CD36, plasma membrane-bound fatty acid binding protein (FABPpm), and fatty acid transport protein (FATP). In heart and skeletal muscle primary attention has been given to unravel the mechanisms by which FAT/CD36 expression and function are regulated. It appears that both insulin and contractions induce the translocation of intracellular stored FAT/CD36 to the plasma membrane to increase cellular LCFA uptake. This review focuses on this novel mechanism of regulation of LCFA uptake in heart and skeletal muscle in health and disease. The distinct signaling pathways underlying insulin-induced and contraction-induced FAT/CD36 translocation will be discussed and a comparison will be made with the well-defined glucose transport system involving the glucose transporter GLUT4. Finally, it is hypothesized that malfunctioning of recycling of these transporters may lead to intracellular triacylglycerol (TAG) accumulation and cellular insulin resistance. Current data indicate a pivotal role for FAT/CD36 in the regulation of LCFA utilization in heart and skeletal muscle under normal conditions as well as during the altered LCFA utilization observed in obesity and insulin resistance. Hence, FAT/CD36 might provide a useful therapeutic target for the prevention or treatment of insulin resistance.

Keywords: Long-chain fatty acid uptake; FAT/CD36; Insulin; PI(3)K; Contraction; GLUT4

1. Introduction

In skeletal muscle and heart, the oxidation of long-chain fatty acids (LCFA) provides much of the energy needed for proper function. Since intramuscular storage sites are a limited source, these tissues rely heavily on the continuous supply of exogenous LCFA mainly derived from adipose tissue. Although the single-pass extraction of albumin-bound LCFA from the circulation is very efficient in both heart [1] and muscle [2,3], LCFA uptake into these tissues involves the passage of LCFA across many barriers, as reviewed previously [1,4,5]. The plasma membrane is the final barrier to be crossed before LCFA reach the interior of the muscle cells (i.e., the cytoplasm), where LCFA transfer between intracellular membranes is facilitated by binding to soluble fatty acid-binding proteins (FABPc) [6,7]. Specifically, the predominant FABP isoform in muscle tissues, heart-type FABPc (H-FABPc) is

Abbreviations: ACC, acetyl-CoA carboxylase; AICAR, 5′-aminoimidazole-4-carboxamide 1-β-D-ribofuranoside; AMPK, adenosine monophosphate (AMP)-activated protein kinase; Akt/PKB, protein kinase B; cAMP, adenosine 3′:5′-cyclic monophosphate; DAG, diacylglycerol; FABPc, cytoplasmic fatty acid-binding protein; FABPpm, plasmalemmal fatty acid-binding protein; FAT/CD36, fatty acid translocase; FATP, fatty acid transport protein; IBMX, 3-isobutyl-1-methylxanthine; LCFA, long-chain fatty acid; MAPK, mitogen-activated protein kinase; PDE, phosphodiesterase; PKA, protein kinase A; PKC, protein kinase C; PL, phospholipids; PI(3)K, phosphatidylinositol-3-OH-kinase; TAG, triacylglycerol; TfR, transferrin receptor; VLACS, very long-chain acyl-CoA synthethase

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responsible for delivery of LCFA from the sarcolemma through the cytoplasm to the outer mitochondrial membrane, the site of acyl-CoA synthetase. This enzyme converts LCFA into acyl-CoA to make it available for (i) triacylglycerol synthesis or (ii) mitochondrial β-oxidation. When destined for β-oxidation, acyl-CoA will cross the mitochondrial outer and inner membranes by virtue of the carnitine shuttle, in which the first step, i.e., the conversion of acyl-CoA into acyl-carnitine as mediated by carnitine palmitoyl-transferase I (CPT I), is an important control step in cellular energy metabolism [8,9].

Several factors have been suggested to control the level of LCFA utilization both at rest and during exercise. There is sufficient evidence to suggest that LCFA utilization is regulated at the level of adipose tissue by control of the rate of lipolysis, export of LCFA from adipose tissue, and their subsequent transport by the vascular system to the heart and skeletal muscle [10,11]. In addition, alterations in lipoprotein lipase activity will also contribute to the regulation of LCFA supply to the muscle [12]. On the other hand, there is evidence to indicate that LCFA utilization is regulated at the level of the myocytes themselves. Generally, it is believed that LCFA transport into the mitochondria by the rate-limiting enzyme CPT I is the most regulated step in the muscular control of LCFA utilization. For extended overviews of the potential regulators of CPT I activity and LCFA oxidation, the reader is referred to recent reviews by Lopaschuk [8,13] on heart and Jeukendrup [14] on skeletal muscle.

Another site that more recently has been suggested to play a role in the regulation of LCFA utilization by heart and skeletal muscle is the initial step in cellular uptake of LCFA, namely their trapping and passage across the plasma membrane. It is well documented that the transfer of LCFA through the plasma membrane barrier is facilitated by membrane-associated LCFA binding proteins (reviewed by [15,16]). In addition to their facilitory role in LCFA transport, a number of recent studies have suggested a regulatory role for these LCFA transport proteins in LCFA metabolism as well [3,17–19]. Although it is not known whether LCFA transport across the plasma membrane may become rate-limiting under specific conditions, it has been demonstrated that regulation of LCFA uptake in response to acute stimuli, such as insulin and muscular contractions, involves the translocation of one of the proteins involved, i.e., fatty acid translocase (FAT)/CD36, from intracellular storage compartments towards to plasma membrane [20,21]. Moreover, long-term regulation of LCFA uptake in trained men has also been observed to involve an upregulation of the muscular expression of this and other putative LCFA membrane transporters [19,22,23]. Therefore, currently much effort is being made to define the signaling pathways involved in the expression and translocation of FAT/CD36 in heart and skeletal muscle in response to insulin and exercise. Full understanding of the significance of LCFA transport proteins to overall LCFA utilization in health and disease will contribute to developing alternative approaches to manipulate substrate utilization by heart and skeletal muscle.

The outline of this review is, therefore, first to give a brief background into the mechanism of cellular LCFA uptake, then to describe the underlying mechanism and signaling pathways involved in the acute regulation of LCFA uptake by recycling of FAT/CD36 between intracellular storage compartments and the plasma membrane. Finally, the attention will be drawn on the impact of physiological stimuli (chronic exercise, aging, dietary interventions) and selected pathophysiological conditions (diabetes, obesity) on this novel regulatory mechanism of LCFA transport across the plasma membrane.

The data presented in this review are primarily derived from studies performed in rodent cardiac and skeletal muscle. However, where available, the results of human studies will be included.

2. Transmembrane transport of LCFA

2.1. Putative transport proteins involved in transmembrane transport of LCFA in heart and skeletal muscle

The plasma membrane of most tissue cells contains a sophisticated set of substrate specific transporter proteins, including glucose transporter isoforms (GLUTs), monocarboxylate transporters (MCTs), and multiple transport systems for the cellular exchange of amino acids [24–29]. Likewise, several plasma membrane-associated proteins have been identified as candidate LCFA transport proteins according to their ‘putative’ role in protein-mediated LCFA transport [16,30–32]. Substantial evidence for a prominent role in the transmembrane movement of LCFA in heart and skeletal muscle is now available for fatty acid translocase (FAT)/CD36, plasmalemmal fatty acid binding protein (FABPpm), fatty acid transport protein (FATP) 1 and the heart-specific FATP6 [3,23,33–40]. For an extended review on this topic, see [15].

Notably, all of the putative LCFA membrane transporters have other established functions, either related (FATP1, FAT/CD36) or unrelated (FABPpm, FAT/CD36) to fatty acid metabolism. FABPpm is identical to mitochondrial aspartate aminotransferase (mAspAT) [41,42]. The reason why FABPpm is a bifunctional protein with two unrelated and entirely different functions is, however, still unknown. FATP1 has been found to exhibit intrinsic acyl-CoA synthetase activity with a broad specificity for both LCFA and very long-chain fatty acids [43–46]. Hence, FATP1 has been proposed to be a bifunctional protein, but it remains to be investigated whether LCFA import is driven by this intrinsic acyl-CoA synthethase activity or whether transport and activation are indeed two distinct functions [46]. FAT/CD36 is the rat homolog of human platelet CD36, also known as glycoprotein (GP) IIIb, GPIV, and PASIV [47,48]. CD36 has been first described as a platelet membrane component and was later shown to act as a receptor for thrombospondin-1 and a class B scavenger receptor B involved in the binding of modified and native lipoproteins and anionic phospholipids [47–49]. Apart from these functions unrelated to fatty acid metabolism, a recent report by Campbell et al. [50] suggested a role for FAT/CD36 in mitochondrial acyl-CoA uptake, revealing a novel role of FAT/CD36 in overall LCFA metabolism.