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Fatty acid transport across the cell membrane: Regulation by fatty acid transporters

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A B S T R A C T

Transport of long-chain fatty acids across the cell membrane has long been thought to occur by passive diffusion. However, in recent years there has been a fundamental shift in understanding, and it is now generally recognized that fatty acids cross the cell membrane via a protein-mediated mechanism. Membrane-associated fatty acid-binding proteins ('fatty acid transporters') not only facilitate but also regulate cellular fatty acid uptake, for instance through their inducible rapid (and reversible) translocation from intracellular storage pools to the cell membrane. A number of fatty acid transporters have been identified, including CD36, plasma membrane-associated fatty acid-binding protein ($FABP_{pm}$), and a family of fatty acid transport proteins (FATP1–6). Fatty acid transporters are also implicated in metabolic disease, such as insulin resistance and type-2 diabetes. In this report we briefly review current understanding of the mechanism of transmembrane fatty acid transport, and the function of fatty acid transporters in healthy cardiac and skeletal muscle, and in insulin resistance/type-2 diabetes. Fatty acid transporters hold promise as a future target to rectify lipid fluxes in the body and regain metabolic homeostasis.

1. Introduction

The solubility of long-chain fatty acids in aqueous solutions is extremely low, i.e., in the range of 1–10 nM [1]. The presence of proteins with the ability to bind fatty acids (for convenience used to designate 'long-chain fatty acids') dramatically increases the total amount of fatty acids that can be present in the aqueous phase. For instance, albumin occurs in plasma and interstitium at a concentration of 300–600 μM and can accommodate up to 1–2 mM fatty acids [2]. Likewise, cytoplasmic fatty acid-binding protein ($FABP_c$) is abundantly present in the soluble cytoplasm of cells with an active fatty acid metabolism and can accommodate up to 150–300 μM fatty acids [3,4]. As a result, albumin and $FABP_c$ act as extracellular and intracellular buffers, respectively, for fatty acids (Fig. 1). Consistent with this, the average concentration of (non-protein bound) fatty acids in plasma from healthy subjects was found to be 7.5 ± 2.5 nM [5], indicating that of the total amount of fatty acids in plasma only < 1 part in 10^5 is present in the aqueous phase.

The above data also indicate that under normal physiological conditions, with a total plasma fatty acid concentration of 100–400 μM and a total cytosolic fatty acid concentration < 50 μM, both albumin and $FABP_c$ are in such abundance that fluctuations in their presence will hardly affect their fatty acid buffering function. Thus, studies on fatty acid uptake by hindlimb muscle from mice lacking (heart-type) $FABP_c$ showed that a 65% reduction in $FABP_c$ in heterozygous mice did not affect the rate of muscle fatty acid uptake while the full ablation of $FABP_c$ (homozygous null mice) decreased fatty acid uptake markedly [6]. This latter study illustrates that $FABP_c$ inside the cell functions as a sink for incoming fatty acids, yet plays a merely permissive action in cellular fatty acid uptake.

2. Mechanism of transmembrane fatty acid transport

During the preceding two decades there has been considerable discussion on the mechanism by which fatty acids enter cells, particularly whether fatty acid transport across the plasma membrane occurs by simple ('passive') diffusion, or whether fatty acid uptake is facilitated by (one or more) membrane-associated proteins (for review see [7,8]). While the various experimental

Abbreviations: $FABP_c$, cytoplasmic fatty acid-binding protein; $FABP_{pm}$, plasma membrane fatty acid-binding protein; FATP, fatty acid transport protein; GLUT4, glucose transporter-4; ACS, acyl-CoA synthetase; CPT, carnitine palmitoyltransferase; AMPK, AMP-activated kinase

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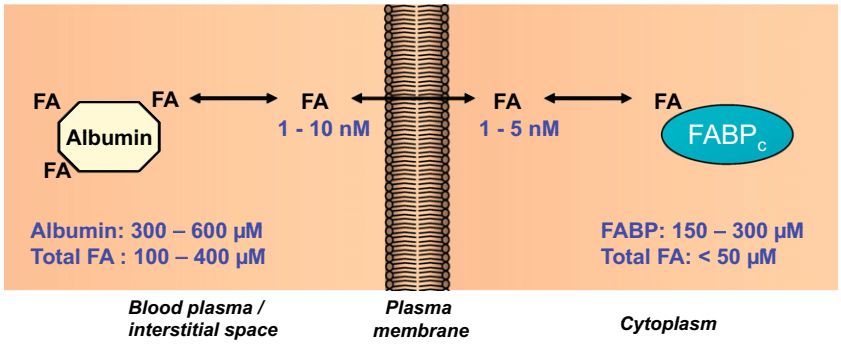

Fig. 1. Quantitative comparison of the presence of albumin in the extracellular space, cytoplasmic fatty acid-binding protein ($FABP_c$) inside cells, and fatty acid concentrations under normal physiological conditions. Albumin and $FABP_c$ provide a buffer for the extremely low aqueous concentration of (long-chain) fatty acids. Albumin has 3–6 binding sites for fatty acids. $FABP_c$ occurs in 9 distinct types of which liver-type $FABP_c$ has two ligand binding sites while all other types have only a single ligand binding site [58,59].

studies provide support for both of these possibilities, evidence in support of a protein-mediated fatty acid uptake system is now believed to be the dominant means by which fatty acids are taken up by metabolically important tissues.

The amphipathic nature of the fatty acid molecule, with a nonpolar chain and a polar head group, provides it with the biophysical properties for entry into the phospholipid bilayer of the cell membrane. Subsequent transfer of the fatty acid from the outer leaflet of the bilayer to the inner leaflet ('flip-flop') is hampered by the charge of the polar head group. However, in the vicinity of the membrane the apparent pK_a of the fatty acid shifts from about 4.5 in aqueous solutions to about 7.6 (independent of fatty acid type), as a result of which about half of the fatty acids are present in the un-ionized, i.e., protonated, form [9]. This uncharged species can then easily flip-flop to the inner leaflet of the membrane, whereafter a proton is donated to the interior solution and the fatty acid is available for desorption.

This mechanism suggests that biological membranes do not form a barrier for fatty acids. Indeed, Hamilton and co-workers have compared the permeabilities of various molecules and (long-chain) fatty acids in a phospholipid bilayer to conclude that the permeability of fatty acids is several orders of magnitude larger than that of water, glucose, and other small non-electrolytes [10]. In addition, measured values of desorption kinetics revealed half-times in the milliseconds to seconds time range for fatty acids, which is fast enough to support intracellular metabolism. Together, these data suggest that (i) fatty acids can rapidly pass phospholipid bilayers without the help of membrane proteins and (ii) membrane proteins are not needed for the purpose of releasing fatty acids into the cytosol [11].

If fatty acids could freely diffuse across biological membranes, the direction and rate of fatty acid movement would depend on fatty acid delivery to the tissue and on the transmembrane gradient of fatty acids. Such a mechanism would be difficult to control and, moreover, may not meet (changes in) metabolic demands in tissues, e.g., muscle upon the initiation of contraction. Thus, from a physiological perspective it would be highly desirable to regulate fatty acid entry into the cell, especially (i) to ensure fatty acid uptake when its extracellular concentration is low, (ii) to limit uptake when the extracellular concentration is high, (iii) to potentially select for specific fatty acid types, and (iv) to allow rapid adjustments in fatty acid provision to meet fluctuations in metabolic demands [12].

Since the early 1980s several investigators have searched for membrane-associated proteins able to bind fatty acids and that may function to facilitate and/or regulate transmembrane fatty acid transport. To date, various membrane proteins have been identified that facilitate the cellular uptake of fatty acids (Fig. 2).

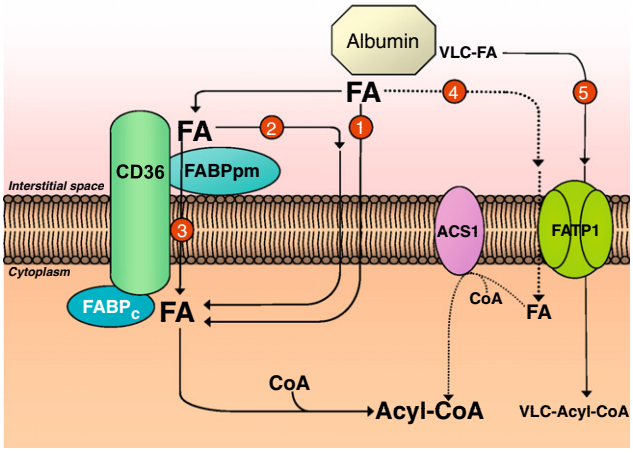

Fig. 2. Schematic representation of the current view of fatty acid transport across the cell membrane. Because the exact mechanism of transmembrane translocation of fatty acids is still unknown, different models have been suggested. (1) In view of their hydrophobic nature, fatty acids could cross the membrane by simple diffusion. (2) Alternatively, CD36 (88 kDa; also referred to as 'fatty acid translocase'), alone or together with the peripheral membrane protein $FABP_{pm}$ (plasma membrane-associated fatty acid-binding protein; 43 kDa) accepts fatty acids at the cell surface to increase their local concentration and thus increase the number of fatty acid diffusion events. (3) It is also possible that CD36 itself actively transports fatty acids across the membrane. Once at the inner side of the membrane fatty acids are bound by cytoplasmic FABP ($FABP_c$) before entering metabolic or signalling pathways. (4) Additionally, a minority of fatty acids are thought to be transported by fatty acid transport proteins and rapidly activated by plasma membrane acyl-CoA synthetase (ACS1) to form acyl-CoA esters. (5) Very-long-chain fatty acids (> C22) are preferentially transported by FATPs and by action of their synthetase activity directly converted into very-long-chain acyl-CoA esters (uptake by vectorial acylation).
Adapted from [27].

For convenience, these proteins are generally referred to as 'fatty acid transporters'. The prevalent view is that these fatty acid transporters act as acceptors for fatty acids whereafter the fatty acids make their way through the cell membrane by simple diffusion (route 2 in Fig. 2). At the inner side of the membrane, the (transmembrane) proteins may provide a docking site for $FABP_c$ or for enzymes that act on fatty acids (such as acyl-CoA synthetase) (Fig. 2). Thus, these proteins may function to sequester fatty acids in the membrane, and help organize them within specific membrane domains so as to make the fatty acids readily available for subsequent aqueous transport and/or enzymatic conversion.

The membrane-associated (putative) fatty acid transporters CD36, $FABP_{pm}$ and $FATP_s$ (Fig. 2) differ in molecular mass