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Fatty acids in cell signaling: Historical perspective and future outlook

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A B S T R A C T

Fatty acids are not only important metabolic substrates and building blocks of lipids but are also increasingly being recognized for their modulatory roles in a wide variety of cellular processes including gene expression, together referred to as the 'message-modulator' function of fatty acids. Crucial for this latter role is the bioavailability of fatty acids, which is governed by their interaction with soluble proteins capable of binding fatty acids, i.e., plasma albumin and cytoplasmic fatty acid-binding protein ($FABP_c$), and with both the lipid and protein components of biological membranes, including membrane-associated fatty acid-binding proteins such as the transmembrane protein CD36. Manipulating fatty acid availability holds promise as therapeutic approach for chronic diseases that are characterized by a perturbed fatty acid metabolism.

1. Introduction

The first International Round Table on 'Fatty Acids and Cell Signaling' (FACS) was organized by professor Emmanuel A. Nunez and held near Paris, France, in 1992 [1]. The purpose of that meeting was to discuss the physiological and pathological effects of fatty acids beyond their obvious roles as nutrients and as components of complex lipids. Thus, fatty acids themselves can be seen as blood-borne signals that can act upon cells directly. In addition, fatty acids can become more potent or more specific signals after they have been metabolized, the best known examples of which are the prostaglandins. In general, signaling molecules such as fatty acids and their metabolites can merely accelerate or decelerate chemical reactions or specific processes in cells. With respect to fatty acids, of special importance is their ability to amplify, dampen, or modify signals transmitted by e.g. hormones. This is referred to as the 'message-modulator' function of fatty acids.

Fatty acids and related metabolites are excellently suitable as modulators of homeostatic processes. The brevity and limitation of their presence in time and space in the circulation and in cells allows for a precise regulation of biological processes. Therefore, the (bio) availability of fatty acids is a major determinant of their modulatory function, as will be discussed in more detail below. Manipulation of dietary intake of fatty acids, both the amount and type of fatty acids, also has a major impact on the availability of fatty acids and, therefore, on various biological processes in health and disease.

One of the scientists who early on recognized and subsequently performed pioneering studies on the pivotal role of fatty acids in human physiology is Dr. David F. Horrobin (1939–2003), the founding editor of *Prostaglandins, Leukotrienes and Essential Fatty Acids* [2]. He became interested after learning that the hormone prolactin stimulates the release of essential fatty acids from cells [3]. Horrobin also was inspired by the work of Dr. Hugh M. Sinclair (1910–1990) on essential fatty acids [4] and believed that many diseases involve a lack of fatty acid precursors and might be treated by supplementing with the appropriate fatty acid [5]. Specifically, Horrobin's work focused on evening primrose oil, which contains γ-linolenic acid, an essential n-6 fatty acid that supposedly would alleviate a variety of chronic disease conditions such as breast pain, alcoholism, rheumatoid arthritis, and atopic eczema [6]. He was committed to discovering simple drugs for complex diseases. In addition, he was an advocate of an ambience to express ideas, openly and freely, and for that has helped to create a forum for scientific discussion, amongst others, as founder and editor of scientific journals including *Medical Hypotheses* and *Prostaglandins, Leukotrienes and Essential Fatty Acids*. Taken together, Dr. Horrobin has contributed markedly to our current understanding of the extended role of fatty acids in various aspects of the functioning of the human body.

2. Bioavailability of fatty acids

The hydrophobic nature of (long-chain) fatty acids dictates specific requirements to their presence and transport in aqueous compartments. In blood plasma and the interstitium fatty acids are

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avidly bound by albumin (68 kDa) or are present as fatty ester in lipoproteins. Intracellularly, fatty acids are bound by cytoplasmic fatty acid-binding protein ($FABP_c$; 15 kDa), which acts as the intracellular counterpart of plasma albumin. The FABPs are members of the intracellular lipid-binding protein (iLBP) family and comprise at least nine distinct types each showing a specific tissue distribution pattern [7–9]. Some FABPs not only bind long-chain fatty acids but also selected other lipids such as eicosanoids, bile salts, lyso-phospholipids, and compounds that act as peroxisome proliferators.

Albumin and the FABPs each bind (long-chain) fatty acids with such high affinities that virtually all of the fatty acids present in the aqueous compartment are protein-bound. Thus, in plasma and interstitium the total fatty acid concentration is 100–400 μM while the concentration of non-protein bound fatty acids is several orders of magnitude lower and amounts to only 1–10 nM (Fig. 1) [10,11]. Similarly, for hepatocytes and cardiomyocytes it has been estimated that in the soluble cytoplasm the total fatty acid concentration is up to 50 μM (depending on the metabolic state of the cell) while the non-protein bound fatty acid concentration is only 1–5 nM [12,13]. As a result, albumin and cytoplasmic FABP each provide a buffer for fatty acids, as each fatty acid that is metabolized or undergoes transmembrane transport to another compartment is immediately replenished by the release of another fatty acid from the protein binding site. It should be emphasized that the abundance of albumin in plasma and interstitium (300–600 μM) and that of FABP in the soluble cytoplasm (150–300 μM in hepatocytes and cardiomyocytes) presents with a total buffering capacity that markedly exceeds the total fatty acid concentration in each compartment (Fig. 1). The latter assures that the non-protein bound fatty acid concentration remains low, even under mild pathological conditions (e.g. mild ischemia), so as to keep fatty acids from exerting potential detrimental effects [13].

With respect to the cellular uptake of fatty acids, albumin acts merely as a large-capacity buffer for non-protein bound fatty acids while cytoplasmic FABP functions as a sink for incoming fatty acids. Studies with genetically manipulated mouse models have shown that cytoplasmic FABP displays a permissive action (rather than a regulatory role) in cellular fatty acid uptake. Thus, in skeletal muscle of mice with an homozygous deletion of heart-type FABP, the fatty acid uptake rate was reduced by 42–45% while in skeletal muscle from heterozygous mice, in which the FABP protein expression was 34% of that of wild-type mice, fatty acid uptake was not altered compared to that in wild-type animals [14]. As a result, cytoplasmic FABP plays an important, yet permissive, role in fatty acid uptake into muscle.

3. Control of cellular fatty acid uptake at the plasma membrane

In the past there has been considerable debate on the mechanism by which fatty acids traverse the plasma membrane to enter the soluble cytoplasm [15]. The dispute centered around the rate-limiting kinetic step in this process and whether one or more membrane proteins could facilitate and/or regulate the overall uptake process. When considering the cellular uptake of fatty acids, the physical transport can be regarded to comprise (i) entry of the fatty acid into the outer leaflet of the lipid bilayer, whereby the hydrocarbon chain intercalates between the chains of the phospholipid and the carboxyl group localizes at the aqueous interface (adsorption), (ii) translocation of the fatty acid to the inner leaflet, whereby the polar carboxyl group moves through the bilayer interior and re-positions at the opposite interface ('flip-flop'), and (iii) movement of the fatty acid into the intracellular aqueous phase and its hydration (desorption). Detailed biophysical studies have disclosed that the fatty acid adsorption step and the subsequent flip-flop of fatty acids in a phospholipid bilayer are very fast for virtually all fatty acid types, but that desorption from the membrane will be the rate-limiting step of transmembrane transport [16]. Fatty acid desorption also is strongly dependent on chain length and degree of unsaturation of the fatty acid [17]. For dietary fatty acids measured values of desorption kinetics have revealed half-life times in the ms to s range, which would be fast enough to support intracellular metabolism [17]. Based on these findings it was concluded that the lipid bilayer of the plasma membrane does not represent a barrier for fatty acids and that, therefore, cellular fatty acid uptake can occur by (passive) diffusion without the need for membrane proteins to facilitate the process [16].

From a theoretical perspective it would be undesirable to have fatty acids pass biological membranes without control. Indeed, several membrane-associated fatty acid-binding proteins have been identified and shown to be involved in the fatty acid uptake process. Interestingly, these membrane proteins, often referred to as 'fatty acid transporters', function not only in facilitating but also in regulating fatty acid entry into the cell. This is currently viewed to occur by adsorbing fatty acids from the extracellular media, modulating their transport into and across the membrane, and segregating or organizing fatty acids for subsequent intracellular transport and metabolism [18]. Furthermore, one of these fatty acid transporters, i.e., CD36, was found to regulate fatty acid uptake in muscle by a mechanism that resembles that of GLUT4-mediated cellular glucose uptake. Thus, following an acute stimulus

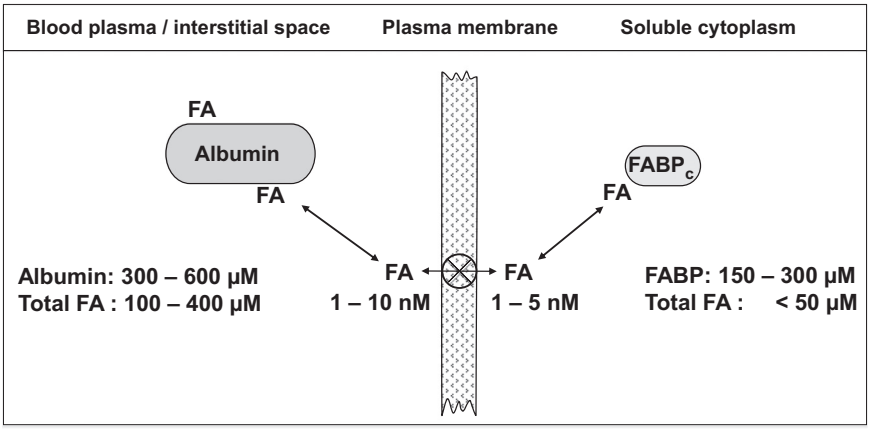

Fig. 1. Fatty acid transport across the plasma membrane. Comparison of concentrations of soluble binding proteins, i.e., albumin (68 kD) in plasma or interstitial space and cytoplasmic FABP (15 kD) in the cellular cytoplasm, and (non-protein bound) fatty acids on both sides of the plasma membrane of hepatocytes or cardiac myocytes. FA, long-chain fatty acid; FABP, fatty acid-binding protein.

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