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Review

The effect of natural and synthetic fatty acids on membrane structure, microdomain organization, cellular functions and human health ☆

Maitane Ibarguren [a,b,*,1], David J. López [a,b,*,1], Pablo V. Escribá [a]

[a] Laboratory of Molecular Cell Biomedicine, University of the Balearic Islands, Palma de Mallorca, Spain
[b] Lipopharma Therapeutics S.L., Palma de Mallorca, Spain

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ABSTRACT

This review deals with the effects of synthetic and natural fatty acids on the biophysical properties of membranes, and on their implication on cell function. Natural fatty acids are constituents of more complex lipids, like triacylglycerides or phospholipids, which are used by cells to store and obtain energy, as well as for structural purposes. Accordingly, natural and synthetic fatty acids may modify the structure of the lipid membrane, altering its microdomain organization and other physical properties, and provoking changes in cell signaling. Therefore, by modulating fatty acids it is possible to regulate the structure of the membrane, influencing the cell processes that are reliant on this structure and potentially reverting pathological cell dysfunctions that may provoke cancer, diabetes, hypertension, Alzheimer's and Parkinson's disease. The so-called Membrane Lipid Therapy offers a strategy to regulate the membrane composition through drug administration, potentially reverting pathological processes by re-adapting cell membrane structure. Certain fatty acids and their synthetic derivatives are described here that may potentially be used in such therapies, where the cell membrane itself can be considered as a target to combat disease. This article is part of a Special Issue entitled: Membrane Structure and Function: Relevance in the Cell's Physiology, Pathology and Therapy.

Contents

1. Introduction

The plasma membrane represents the barrier of life, the structure that separates living cells from their surroundings. For many years, lipids were not considered to be involved in such important events as cell signaling or local hormonal regulation. Indeed, it was many years after linoleic acid (LA) was demonstrated to be an essential dietary constituent that the importance of this finding was recognized by the scientific community [1]. A major milestone was reached in 1979 with the discovery of the first biologically active phospholipid, the platelet-activating factor [2]. Since then, lipids have been found to fulfill some

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* Corresponding authors at: Laboratory of Molecular Cell Biomedicine, Department of Biology, University of the Balearic Islands, Crta. Valldemossa km. 7.5, 07122 Palma, Spain. Tel.: +34 971 17 33 31; fax: +34 971 17 31 84.
E-mail addresses: maitaneibarguren@hotmail.com (M. Ibarguren), davidlopez_95@hotmail.com (D.J. López).

[1] Both authors contributed equally to this work.

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unique biological roles, over and above their function as a source of energy or as simple building blocks of membranes. Indeed, it is now recognized that membrane lipids influence the trafficking of cellular constituents, as well as the activity of membrane proteins and signals.

Cell membranes are composed of thousands of different lipid molecules that interact dynamically to form the transient or stable structures that may be used by many proteins as platforms for their activity, and to enhance their interactions with other proteins. Lipids are a large and diverse group of naturally occurring organic compounds that share common physical properties, such as their solubility in non-polar organic solvents and general insolubility in water. In terms of membrane composition, lipids can be classified into different groups: glycerolipids, sphingolipids and terpene-derived lipids (e.g., sterols). Fatty acids may contribute to complex lipids, although they can be also found as free entities in the membrane. In addition, fatty acids are ubiquitously present in animal fats, vegetable oils or waxes.

Like lipids in general, fatty acids are now no longer considered as a mere energy source but rather, they have generated great interest due to their involvement in human health. In recent years, dietary recommendations have been made to decrease the intake of saturated and trans-fatty acids due to their negative cardiovascular effects, while mono- and polyunsaturated fatty acids are recommended for their cardio-protective benefits [3]. For instance, oleic acid (OA) has been associated with a reduction in blood pressure and a lower incidence of hypertension [4]. Docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) have also been associated with the prevention of cardiovascular diseases and cancer [5], while the omega−6 polyunsaturated fatty acid (PUFA), gamma linolenic acid (γ-LNA), is known to possess anti-inflammatory properties [6]. In addition, altered levels of free fatty acids (FFAs) have been associated with pathological states, as in diseases like obesity, hypertension, diabetes mellitus, coronary heart disease, alcoholism, schizophrenia, Alzheimer's disease (AD), atherosclerosis and cancer [7]. A study carried out on autistic children between 5 and 8 years-of-age showed that they had increased plasma levels of most saturated fatty acids, except for propionic acid, while the concentration of PUFAs was decreased [8]. Other studies showed that both adult and elderly mice reproduced by assisted reproductive technologies, such as in vitro fertilization and intra-cytoplasmic sperm injection, contained lower monounsaturated fatty acid (MUFA) and higher PUFA levels. However, the levels of saturated fatty acids were altered in adult but not in old mice. All these changes might reflect potential effects on the health of animals [9].

In this review, the main effects of natural and synthetic fatty acids as modulators of membrane structure, microdomain organization and cellular signaling are described, focusing on the human health benefits and the new therapeutic approaches that have been developed.

2. Effects of natural and synthetic fatty acids on membrane structure

Fatty acids may exert structural effects on membranes, either as free entities (i.e. FFA) or as part of other molecules such as phospholipids and triacylglycerides. The interaction of FFA with membranes and their incorporation in more complex molecules occurs within minutes. Thus, it is observed that externally added OA in phosphatidylcholine (PC) giant unilamellar vesicle solutions induces vesicle swelling after 3 min [10], indicating that the insertion of the FFA within the membrane structure takes place within that period of time. Another study also described a destabilization of giant unilamellar vesicles composed of palmitoyl-oleoyl-phosphatidylcholine:phosphatidylethanolamine:sphingomyelin:cholesterol (POPC:PE:SM:Cho; 1:1:1:1; mol ratio) after 3-min incubation with OA, arachidonic acid (ARA) and DHA [11]. Interestingly, the same effect was observed when using their 2-hydroxylated, synthetic analogs 2-hydroxyoleic (2OHOA), 2-hydroxyarachidonic (2OHARA) and 2-hydroxydocosahexaenoic (2OHDHA) acid [11]. Concerning the esterification of natural FFA, it is known that the omega−3 eicosapentanoic acid may be detected as part of phospholipids and triacylglycerols in rat liver, brain and heart within 5 min after intravenous infusion [12]. Moreover, the synthetic FFA, 2OHOA, has also been detected in PC, PE, phosphatidylinositol and phosphatidylserine from U118 human, glioma cells, 2–24 h after incubation with this lipid [13]. All in all, the rapid insertion of FFA into membranes and their incorporation in more complex molecules enable these acyl chains to induce changes in the structure of lipid bilayers.

Since the seventies, the effects of fatty acids on model membrane structure have been studied using a variety of techniques, including differential scanning calorimetry (DSC) [14–17], fluorescence spectroscopy [18–20], electron spin resonance [21,22], light scattering [23], electrophoresis [24], nuclear magnetic resonance [25], scanning densitometry [26] and differential thermal analysis [17]. Together, these studies have shown that long-chain saturated fatty acids increase the gel-to-fluid phase (L_{β}-to-L_{α}) transition temperature (also known as melting temperature, Tm) of phospholipid bilayers, whereas short-chain or *cis*-unsaturated fatty acids decrease the Tm. Thus, the length and degree of unsaturation of natural FFAs affect their impact on membrane lipid structure [27]. The perturbations induced by these fatty acids on membrane lipid structure involve changes in membrane fluidity, phase behavior, permeability, membrane fusion, lateral pressure and flip-flop dynamics. For instance, it has been proposed that FFAs perturb the lipid bilayer, and that they disturb the protein–lipid interactions in human erythrocyte membranes [28].

The addition of unsaturated FFAs to liposomes formed by DPPC has also been studied; DHA and EPA particularly producing a broadening and a shift of the Tm values of DPPC to lower temperatures (Table 1). The phase transition temperature and 1,6-diphenyl-1,3,5-hexatriene (DPH) fluorescence anisotropy values at 37 °C decrease progressively with increasing amounts of unsaturated fatty acids, while Triton X-100 solubilization is facilitated by the presence of unsaturated fatty acids. These data suggest that the tightly packed DPPC bilayer becomes more disordered and fluid when it contains DHA and EPA [29].

Membrane fluidity plays an important role in cellular functions since the activity of membrane proteins is modulated by the surrounding lipid environment. In this case, lipids may influence the optimal conformation for the catalytic activity of proteins by changing the membrane's biophysical properties [30]. For instance, it was proposed that FFAs affect non-specific interactions with the lipid bilayer,

Table 1
Changes in the phase transition temperature of phospholipids upon incubation with different hydroxylated and non-hydroxylated fatty acids.

Lipid under study	Fatty acid	Effect	Technique	Reference
DPPC	30 mol% SA	41.3 °C	[a]DSC, FL	[29]
L_{β}-to-L_{α} 40.8 °C	30 mol% OA	37.5 °C		
	30 mol% EPA	36.3 °C		
	30 mol% DHA	36.2 °C		
DEPE	5 mol% SA	66 °C	XRD	[34]
L_{α}-to-H_{II} 65.5 °C	5 mol% OA	53 °C	XRD, ^{31}P NMR	[34,35]
	5 mol% EA	59 °C	XRD	[34,36]
	5 mol% 2OHOA	55 °C	DSC, XRD	
POPE	2.5 mol% OA	51 °C	XRD	[34]
L_{α}-to-H_{II} 70 °C				
DMPC	5 mol% SA	24.3 °C	DSC	[38]
L_{β}-to-L_{α} 23.4 °C	5 mol% OA	22.6 °C		
	5 mol% (+)-Ricinoleic acid	22.0 °C		
	5 mol% R/S-2-OH octadecanoic acid	24.3 °C		
	5 mol% R/S-2-OH hexadecanoic acid	24.5 °C		
	5 mol% R/S-3-OH hexadecanoic acid	24.3 °C		

[a] DSC, differential scanning calorimetry; FL, fluorescence spectroscopy; XRD, X-ray diffraction; and NMR, nuclear magnetic resonance.