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Review

Multiple bonds for the lipid interest ☆

Lars Kuerschner *, Christoph Thiele *

Life & Medical Sciences Institute (LIMES), University of Bonn, Carl-Troll-Str. 31, D-53115 Bonn, Germany

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ABSTRACT

Polyene lipids and alkyne lipids allow study of lipid organization, dynamics and metabolism. Both types of lipids contain multiple bonds as the essential functional group, leading to minimal disturbance of the hydrophobic properties on which the characteristic behavior of lipids is based. Polyene lipids can directly be traced due to their intrinsic fluorescence, while alkyne lipids need the copper-catalyzed click reaction to an azido-reporter for detection. This review describes recent developments in synthesis and application of both types of lipid analogs with emphasis on metabolic tracing and microscopy imaging. This article is part of a Special Issue entitled Tools to study lipid functions.

1. Introduction

Cells contain a complex lipid network [1] with a vast number of lipid species generated by cellular enzymes. The majority of lipids possess pronounced hydrophobic properties favoring an embedding in cellular membranes, and cells establish an intriguing spatio-temporal pattern of the various lipids at the different membrane loci [2]. Cell biological studies on lipid metabolism, localization, trafficking, and regulation as well as on lipid–lipid and lipid–protein interactions critically depend on suitable research tools. For decades scientists have been using lipid analogs, radio- or spin-labeled and fluorescent, in combination with various analysis and detection methods. The isotope-labeled lipids represent structurally optimal analogs allowing for very sensitive detection and have proven invaluable for studies on lipid metabolism e.g. of cholesterol [3]. However, their use in combination with modern analysis techniques, like mass spectrometry or microscopy is impracticable or inconvenient. Fluorescent lipid analogs featuring NBD- [4], Bodipy- [5], anthracene- [6], pyrene- [7], and diphenylhexatriene-groups [8] have substituted here and numerous excellent reviews on their applications have been written [9–14]. Non-fluorescent spin-labeled analogs have been especially useful for the study of lipid–protein interactions [15], lipid dynamics [16] and asymmetry [17] and are reviewed separately (see: Freed, J. et al., this issue).

Employing any analog in an experimental study one has to be aware of the probes limitations. Regarding fluorescent analogs it has to be noted that most fluorescent labels are rigid structures of considerable size and bulkiness but lipids are relatively small molecules often with complex physicochemical and biological properties. Attached to lipids these tags tend to negatively influence the lipid properties resulting in altered lipid metabolism, localization, or trafficking. Hence, one should consider the application of methods that do not rely on probes e.g. CARS (see: Wang, M.C. et al., this issue), or the use of traceable analogs with minimal impact on important lipid properties. Such probes include polyene lipids and alkyne lipids that have conjugated double bonds and a single triple bond, respectively, embedded in their hydrocarbon structures. This text aims to review recent studies employing polyene or alkyne lipids, highlighting their advantages, considering limitations, and summarizing their use in investigations on lipid metabolism, localization and trafficking.

2. Polyene lipids

Polyene lipids (Fig. 1) are lipid analogs containing a conjugated double bond system in the hydrocarbon portion. Conjugation shortens the participating bonds concomitant to kinking and rotationally arresting the involved hydrocarbon segment. However, the polyene lipids are uniquely similar to natural lipids with respect to important biological and biophysical properties [18]. Polyene lipids are intrinsically fluorescent and the number of conjugated bonds determines their spectral properties. A naturally occurring polyene-fatty acid with four such bonds, parinaric acid [19], possesses short-wavelength UV excitation and emission limiting its suitability for fluorescence microscopy [20].

Abbreviations: NBD, N-(7-nitrobenz-2-oxa-1,3-diazol-4-ol); Bodipy, borondifluorodipyrromethene; CARS, coherent anti-Stokes Raman spectroscopy; DAG, diacylglycerol; DAPI, 4′,6-diamidino-2-phenylindole; DGAT2, diacylglycerol-acyl-transferase 2; ER, endoplasmic reticulum; FRET, Förster resonance energy transfer; PA, phosphatidic acid; PC, phosphatidylcholine; PE, phosphatidylethanolamine; SM, sphingomyelin

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* Corresponding authors. Tel.: +49 228 7362816; fax: +49 228 7362650.
E-mail addresses: lars.kuerschner@uni-bonn.de (L. Kuerschner), cthiele@uni-bonn.de (C. Thiele).

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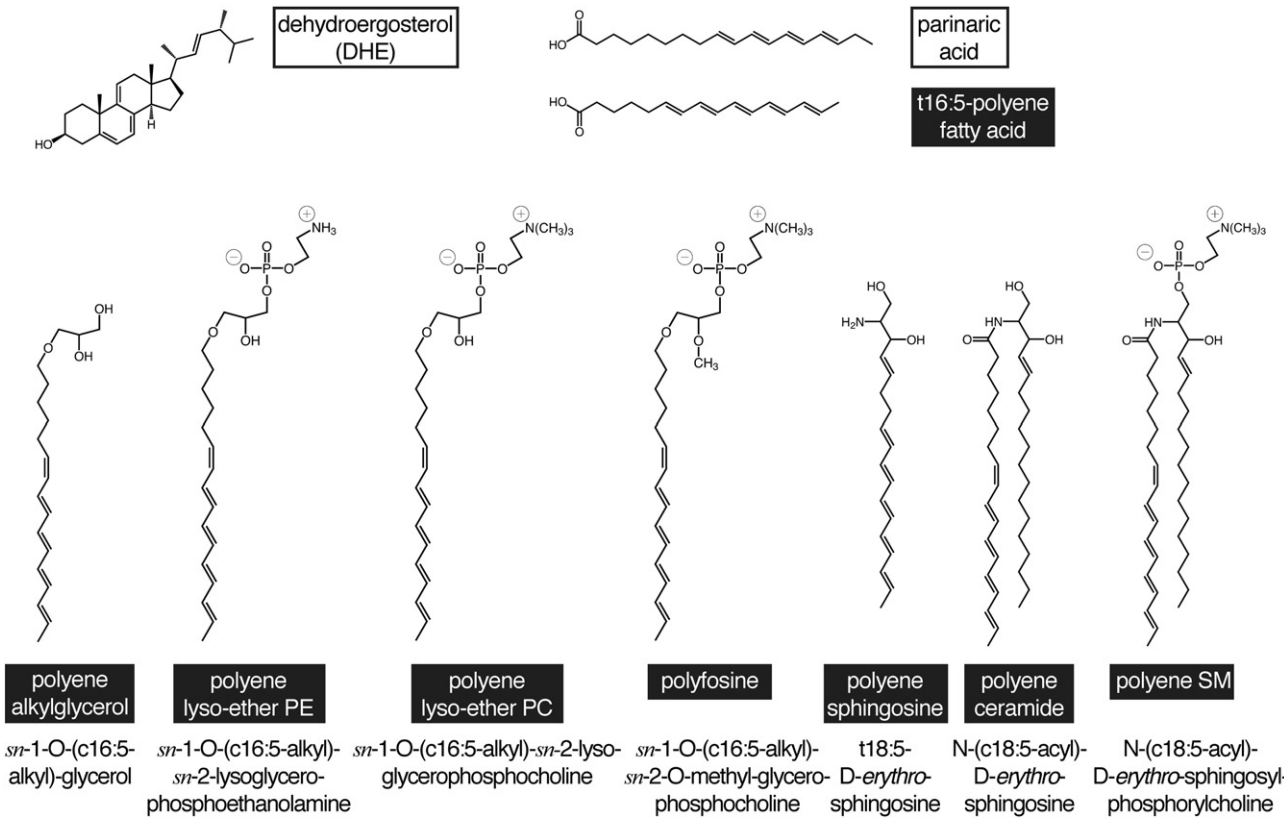

Fig. 1. Chemical structures of selected polyene lipids. Natural (white boxed) polyene lipids include dehydroergosterol and parinaric acid containing 3 and 4 conjugated double bonds, respectively. Synthetic polyene lipids with 5 conjugated double bonds, pentaenes, are shown with simplified (black boxed) and systematic names following the established nomenclature in ref [18]. Pentaene acyl or alkyl chains are denoted as follows: *cis/trans* configuration of the ω-10 double bond, followed by the number of carbon atoms and the number of double bonds, separated by a colon. The double bonds at ω-8, ω-6, ω-4, and ω-2 positions are in *trans* configuration.

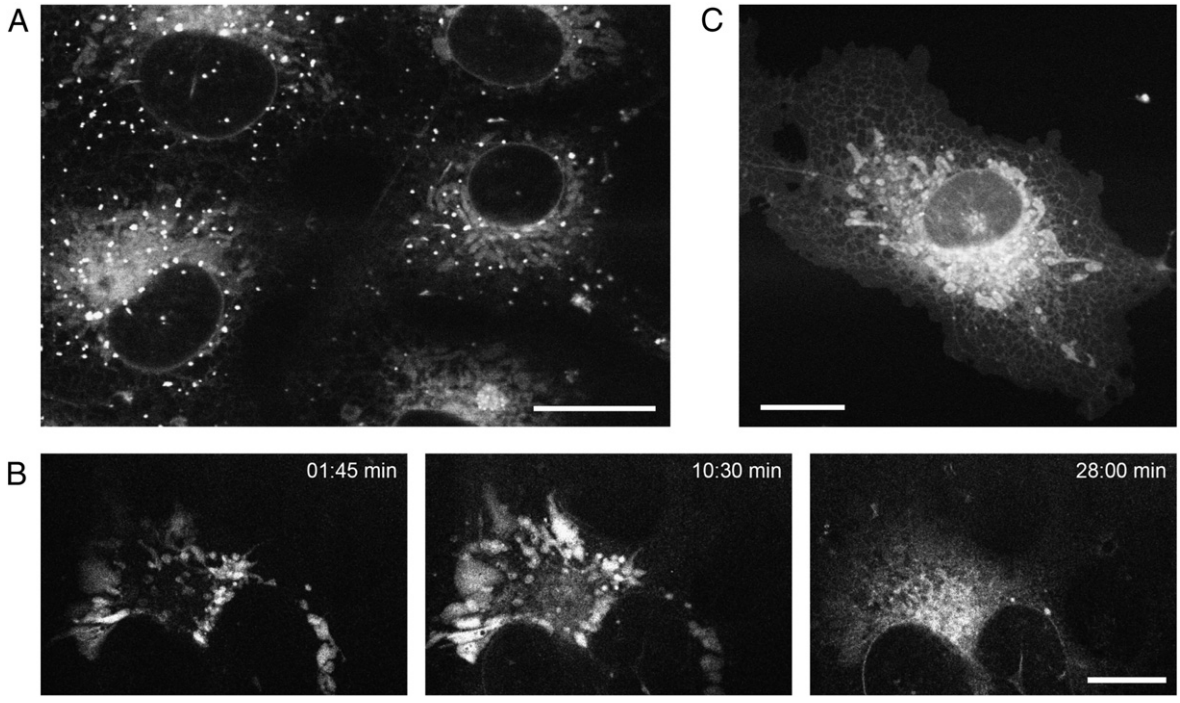

Fig. 2. Fluorescent micrographs of COS7 kidney epithelial cells showing the localization of (A&C) cellular polyene lipids derived from a polyene fatty acid, and (B) Nile Red-positive membranes in cells not incubated with polyene lipid. Employing two-photon-excitation lipid localization was imaged in living cells after incubation with 50 μM t16:5-polyene fatty acid for (A) 1 h, or (C) the indicated times by video microscopy. Panel C shows still images from the Supplemental Movie 1, after image processing using a de-noising filter. Experimental details have been described in ref [33]. Bars, 20 μm.