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Review

Lipid Replacement Therapy: A natural medicine approach to replacing damaged lipids in cellular membranes and organelles and restoring function☆,☆☆

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ABSTRACT

Lipid Replacement Therapy, the use of functional oral supplements containing cell membrane phospholipids and antioxidants, has been used to replace damaged, usually oxidized, membrane glycerophospholipids that accumulate during aging and in various clinical conditions in order to restore cellular function. This approach differs from other dietary and intravenous phospholipid interventions in the composition of phospholipids and their defense against oxidation during storage, ingestion, digestion and uptake as well as the use of protective molecules that noncovalently complex with phospholipid micelles and prevent their enzymatic and bile disruption. Once the phospholipids have been taken in by transport processes, they are protected by several natural mechanisms involving lipid receptors, transport and carrier molecules and circulating cells and lipoproteins until their delivery to tissues and cells where they can again be transferred to intracellular membranes by specific and nonspecific transport systems. Once delivered to membrane sites, they naturally replace and stimulate removal of damaged membrane lipids. Various chronic clinical conditions are characterized by membrane damage, mainly oxidative but also enzymatic, resulting in loss of cellular function. This is readily apparent in mitochondrial inner membranes where oxidative damage to phospholipids like cardiolipin and other molecules results in loss of transmembrane potential, electron transport function and generation of high-energy molecules. Recent clinical trials have shown the benefits of Lipid Replacement Therapy in restoring mitochondrial function and reducing fatigue in aged subjects and patients with a variety of clinical diagnoses that are characterized by loss of mitochondrial function and include fatigue as a major symptom. This Article is Part of a Special Issue Entitled: Membrane Structure and Function: Relevance in the Cell's Physiology, Pathology and Therapy.

Contents

Abbreviations: ABR, auditory brainstem responses; AD, Alzheimers disease; ADP, adenosinediphosphate; AGEs, advanced glycation end products; ATP, adenosinetriphosphate; CAPD, chronic ambulatory peritoneal dialysis; CDP-DAG, cytidinediphosphate-diacylglycerol; CFS, chronic fatigue syndrome; CL, cardiolipin; CR, caloric restriction; CVD, cardiovascular disease; DAG, diacylglycerol; DAMPs, damage associated molecular patterns; DHA, docosahexaenoic acid; eNOS, endothelial nitric oxide synthase; EPA, eicosapentaenoic acid; EPL, essential phospholipids; ETC, electron transport chain; FA, fatty acid; FDA, US Federal Drug Administration; F-MMM, Fluid—Mosaic Membrane Model; GRAS, generally recognized as safe; HDL, high density lipoproteins; HNE, 4-hydroxynonenal; IL, interleukin; LDL, low density lipoproteins; LRT, lipid replacement therapy; MAM, mitochondria-associated membrane; MAPK, mitogen activated protein kinase; MDA, malondialdehyde; ME, myalgic encephalomyelitis; MetSyn, metabolic syndrome; MIM, mitochondrial inner membrane; MOMP, mitochondrial outer membrane permeabilisation; MPTP, mitochondrial permeability transition pores; mRNA, messenger RNA; mtDNA, mitochondrial DNA; NAFLD, non alchoholic fatty liver disease; NASH, Nonalcoholic Steatohepatitis; NCD, non communicable diseases; NF-κB, nuclear factor kappa B; NLRP3, nucleotide-binding oligomerization domain (NOD)-like receptor protein 3; PAMPs, pathogen-associated molecular patterns; PC, phosphatidylcholine; PE, phosphatidylethanolamine; PG, phosphatidylglycerol; PI, phosphatidylinositol; PS, phosphatidylserine; RC, respiratory chain; RNS, reactive nitrogen species; ROS, reactive oxygen species; TCA, tricarboxcylic cycle; TLR, toll like receptor; TNFα, tumor necrosis factor alpha; tRNA, transfer RNA; UCP, uncoupling protein

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1. General introduction

The use of dietary membrane lipids and oral and intravenous lipid supplements to modify cellular and intracellular membranes in order to improve health or treat specific medical conditions has a rich history [1,2]. Membrane lipids are known to be essential to cellular membrane function and cell viability [3,4], and thus their modification and restoration by exogenous membrane lipids remains a useful approach for maintaining and restoring cellular membrane function [5,6]. Cell membranes control a variety of cellular processes, including whether cells live or die as well as the maintenance of a structural and ionic barriers, intercellular communication networks, transport, secretion, recognition, adhesion and other important cell functions [4,7–9]

Membrane lipids provide at least four major requirements for cellular health [9,10]. They are used as: (*i*) an important energy storage reservoir; (*ii*) the matrix for all cellular membranes, enabling separation of enzymatic and chemical reactions into discrete cellular compartments; (*iii*) bioactive molecules in certain signal transduction and molecular recognition pathways; and (*iv*) important functional molecules that undergo interactions with other cellular constituents, such as proteins and glycoproteins. This latter characteristic is an absolute requirement for the formation, structure and activities of biological membranes [3,4,7–9].

2. Introduction to membrane lipids

The most common membrane lipids are the glycerophospholipids [9,10]. These are essential for membrane structure and are found in the membranes of all lower and higher living species, but other phospholipid forms, such as the substitution of sphingosin for glycerol (sphingomyelins or ceramide-1-phosphorylcholines), are also commonly found in cell membranes, mainly on their exterior surfaces [9,10]. Another common membrane constituent is cholesterol, the only sterol found in abundance in membranes [4,6,9,10]. In addition, there are also acylglyerols, fatty acids (FAs) and many other minor lipid constituents of cellular membranes of largely unknown function [9,10].

The membrane glycerophospholipids have attached FA chains that are ester-linked to the glycerol group. The nature and saturation of the attached FA chains of the phospholipids generate dramatic effects on membrane packing and fluidity [10–12]. Unsaturated FAs, such as oleic acid and linoleic acid, confer a high degree of conformational flexibility of the unsaturated hydrocarbon chains within membranes due to their occupying a slightly wedge-shaped space. This generally results in looser packing and a more fluid membrane [3,11,13]. In contrast, saturated FA, such as stearic acid and palmitic acid, confer rigidity that results in a less fluid or more organized membrane [12].

There are lipid compositional differences between different membranes of the cell [9,10,12,14]. The concentrations of sterols (cholesterol and cholesterol esters) and sphingolipids (sphingomyelin, ceramide and gangliosides) increase from the endoplasmic reticulum to the cell surface [9,10,14]. For example, cholesterol/phospholipid ratios increase from 0.1 in the endoplasmic reticulum membranes to 1.0 in the plasma membrane [9]. In addition, sphingolipids such as gangliosides are quite asymmetrically distributed on the outer surface leaflets of cell membranes [15]. Similarly, other neutral lipids, such as phosphatidylcholine (PC), reside preferentially on the outer leaflet or surface of the cell membrane, whereas anionic phospholipids, such as phosphatidylserine (PS) and phosphatidylinositol (PI) tend to reside on the inner leaflet of the cell membrane. The asymmetric distributions of lipids between inner and outer membrane leaflets as well as in the plane of the membrane are important in determining key membrane physical properties (deformation, curvature, compression, expansion) and functional interactions within membranes [11,15–17,20–22].

There are also important differences in the lateral organization of lipids in membranes [18,20,21]. Lipid cooperative behavior ensures that lipids organize laterally in the plane of the membrane in a non-random, non-uniform fashion [18,20,21].

The matrix of cellular membranes is largely formed by glycerophospholipids, especially PC and phosphatidylethanolamine (PE), the most abundant phospholipids along with sphingomyelins in cell membranes [10,12,14,16,17]. Under physiological conditions membrane phospholipids are present in various fluid, semi-solid and solid phases that are organized into domains characterized by different lipid spatial arrangements and rates of rotational and lateral movements [9,10,18,20,21]. The different lipid phases (domains) in membranes have profound consequences for membrane properties, organization and activities [14–22].

3. Cell membrane structure and membrane models

The most important observation on membranes over the last 100 years was that of Gorter and Grendel, who proposed that membrane lipids must be present in a bilayer configuration [23]. Indeed, an asymmetric lipid bilayer forms the matrix of all biological membranes [4,9,11,15–17,19–24]. This hypothesis was used by Danielli and Davson [25] and later by Robertson [26,27] as the basis for tri-layer models of membrane structure. The tri-layer models, such as the Unit Membrane Model [28], possessed unfolded membrane proteins bound to the head groups of phospholipids on each side of the lipid bilayer by electrostatic and other forces [26,27].

The current accepted model for cellular membranes, at least at the sub-micrometer scale, is the Fluid-Mosaic Membrane Model (F-MMM) [29]. At the time the F-MMM was introduced, the accepted model for cellular membrane structure was still the tri-layer membrane model