New Bioactive Lipids in Pathophysiology and Membrane Lipid Therapy

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Abstract

Membranes are primarily made up of a lipid bilayer and proteins, and they serve as a checkpoint for signals and other chemicals entering and exiting the body. Diet, pathophysiological processes, and nutritional/pharmaceutical therapies can all influence their composition. Lipids play essential structural and functional roles in addition to serving as an energy source. For example, fatty acyl moieties in phospholipids have different effects on human health depending on their saturation, carbon length, and isometry. These and other membrane lipids have very precise impacts on the lipid bilayer structure, which controls how signalling proteins interact with one other. Normalization of these modifications or regulatory actions that control membrane lipid composition have therapeutic potential because lipid changes have been linked to major illnesses. Membrane lipid treatment, also known as membrane lipid replacement, has emerged as a cutting-edge technology platform for nutraceutical interventions and drug development. This technology has been verified by several clinical trials and medicinal treatments based on a better understanding of membrane structure and function. The molecular underpinning of this novel method is examined in this review, which describes how membrane lipid composition and structure affect protein-lipid interactions, cell signalling, disease, and therapy (e.g., fatigue and cardiovascular, neurodegenerative, tumor, infectious diseases).

Keywords: Melitherapy • Lipid replacement • Lipid switches • Pathophysiology

Introduction

The human body is made up of trillions of cells that work together to keep everything running smoothly. In this setting, health problems are caused by cellular changes that impact physiological processes [1], and these changes might result in macromolecule malfunctions and/or aberrant levels of metabolites, hormones, and other substances. Despite the fact that membrane lipid changes play a role in many diseases [2,3], most pathophysiological research have focused on protein function or gene expression. As a result, the majority of disease-fighting medicines have focused on proteins and nucleic acids, according to our understanding of their structure and function. New ways to controlling membrane shape and lipid composition have recently emerged. A number of different therapeutic strategies fall under the umbrella of lipid replacement (LRT) [4] or membrane lipid therapy (MLT or melitherapy), all of which share the common feature of regulating cell physiology by inducing relevant changes to the plasma membrane (PM) or the lipids in organelles. The importance of lipids in biological membranes, their participation in pathophysiological processes, and the development of therapeutics focusing on membrane lipid control and/or replacement are all discussed in this article. Despite the fact that cell signalling has primarily been studied from the perspective of proteins that drive and transmit signals, as well as the resulting regulation of gene expression, lipids play an important role in message transmission. Membrane lipids have a number of functions, one of which is to co-localize signalling partners in order to amplify incoming signals via productive protein-protein interactions in specific membrane microdomains. As a result, alterations in membrane lipids have an impact on critical cellular processes as proliferation [5,6], cell migration [7], cytokinesis [8], programmed cell death [9], and so on. Protein-lipid interactions, particularly those involved in the translocation of proteins to or from the membrane to form the signals at this cell barrier, can be drastically altered by changes in membrane lipid composition or structure. These changes can be quite small for some reactions, involving only a few number of membrane lipids and proteins, such as phosphatidylinositol 3,4,5-triphosphate (PI3K) interactions [10]. Regulating the lipid composition of the cell membrane and the translocation of signalling membrane proteins, on the other hand, constitute crucial membrane lipid switches that trigger events critical to physiological processes for activities that cause considerable changes in cells. The presence of lipid structures in cellular membranes, especially organelle membranes, is determined by the lipid content of those membranes. Membrane lipids can take on a variety of supramolecular shapes because they are polymorphic. The most prevalent arrangement of lipids in cells is the lamellar phase (lipid bilayer), particularly the L fluid lamellar phase (or liquid crystalline or liquid disordered -Ld), which is linked with substantial lipid and protein mobility. Lipids form various more tightly packed lamellar structures under different conditions, such as the gel phase (L), pseudo-crystalline phase (Lc), torn membranes (P), and ordered solid or liquid phases (So or Lo). Temperature, lipid composition, water content, lateral pressure, pH, and ionic strength are all factors that influence the varied circumstances and lipid membrane phases. Phospholipids with a cylindric shape, such as phosphatidylcholine (PC) and sphingomyelin, create a lamellar phase and can pack tightly (SM). Nonlamellar phases are formed when lipids with an inverted cone structure (e.g., lysophospholipids) or a truncated cone with a short polar head (e.g., phosphatidylethanolamine (PE) or diacylglycerol (DAG) induce curvature in the membrane. These phases, which can be structured into hexagonal (HI or HII) or cubic phases, are uncommon in healthy cells and provide favourable sites for the localization of certain signalling proteins involved in biological processes including budding and fusion/fission. Lipids keep the structure and composition of the cell's numerous organelles in check, and they're structured into fine-tuned lipid phases that help them do their jobs. PC and PE, glycerophospholipids, are key components of the endoplasmic reticulum (ER), Golgi, and mitochondria, whereas cholesterol (Cho), PC, and SM, as well as endosomes and lysosomes, are major components of the PM. Cardiolipin, for example, is a unique lipid found in mitochondriA. Different lipids can be generated in specific organelles and transported to their final destination to serve as a barrier, scaffold (for integral and peripheral membrane proteins, for example), and/or active lipids. Furthermore, the remaining lipid species, such as the frequency of sphingolipids in the renal cortex, acylcarnitines in skeletal muscle, and ubiquinone in cardiac tissue, fluctuate more quantitatively than qualitatively. In mice models, SM is mostly found in the brain and kidney, whereas PE is mostly found in the spleen. Furthermore, the lipidome often corresponds with the expression of genes involved in lipid metabolism, implying that lipidomics could be used to identify metabolic diseases and link them to specific enzymatic activity abnormalities. Specific lipid species can be packed and structured in small domains that influence diverse cell processes while generating lipidic structures in membranes. Lipid rafts, caveolae, and clathrin-coated pits are examples of these domains that can be found in the PM and various organelles. Lipid rafts are membrane microdomains rich in sphingolipids and Cho, which provide favourable conditions for particular proteins' activity. Some protein receptors important for homeostasis and lipid metabolism regulation, such as the TNFR1 (tumour necrosis factor receptor 1) or the insulin receptor, are found in lipid rafts or Cho-enriched microdomains (IR). Furthermore, one of the primary trans fatty acids, elaidic acid, causes inflammation by interacting with lipid rafts and their toll-like receptors (TLRs). In contrast, lipid rafts have been suggested to sequester epidermal growth factor receptors (EGFRs), preventing their activation, despite the fact that lipid rafts can also activate these receptors. These structures can be observed in the interior membranes of cells that regulate many cell processes, such as raft-like microdomains in mitochondria following Chol and disialoganglioside GD3 buildup in response to apoptotic signalling in neurodegenerative diseases.

Membrane Lipid Therapy in Historical Perspective

The recognition of the role of lipids and lipid structures in molecular and cellular events; (2) the identification of membrane lipid composition and structural alterations in human diseases; (3) a description of the molecular, cellular, physiological, and pharmacological actions of lipids and their analogues to combat pathological processes; and finally, (4) the integration of this knowledge into the rational use of lipids and their analogues to combat pathological processesEarly discoveries revealed the importance of lipid membranes in pathophysiological processes from a historical perspective. In platelet membranes from patients with haematological diseases, significant lipid changes were discovered in 1939. Similarly, the beneficial and harmful effects of certain lipids in cardiovascular disease have long been recognised. Furthermore, a link between inflammation and lipids in both blood (plasma) and cell membranes has long been established. Numerous studies support the role of lipids in cardiovascular disease and related metabolic syndrome-related illnesses such diabetes and obesity. The abundance of literature linking lipid changes to human diseases motivated researchers to dig deeper into the involvement of lipids and lipid structures in these pathological occurrences. Following the description of the fluid mosaic model of the structure of cell membranes, a fundamental aspect relevant to the development of melitherapy, the involvement of lipids and lipid structures in molecular and cellular events, was first addressed.

Arthropod-Borne Pathogens

Viruses, on the other hand, aren't the only pathogens that utilise the host cell's lipids to infect it and may be vulnerable to LRT. For arthropod-borne pathogens, for example, lipid control is critical regardless of whether they are viruses, bacteria, or protozoa, or whether they operate extracellularly or intracellularly. Bacteria from the genera Anaplasma, Ehrlichia, and Borrelia have been found to utilise host cell Cho and various fatty acids to proliferate. The usage of host phospholipids is also required for Anaplasma and Ehrlichia to survive. Plasmidium, Leishmania, and Trypanosoma are among the arthropod-borne protists that require at least one of the lipid groups indicated above for survival and growth. Cho, fatty acids, phospholipids, and sphingolipids from the host cell are required for flavivirus replication when transmitted by arthropods. These findings have inspired the development of innovative vector-borne illness medicines that rely on lipid composition manipulation, and LRT falls into this category. In fact, medications that target lipid metabolism have been proven in mouse models to reduce arboviral and parasite infection. Free Cho; fatty acid production; LDs; particular lipids in the membrane; membrane fluidity; the distribution of receptors and co-receptors; lipid rafts; lipid-based defence systems in human hosts are all targets and chances for treating or preventing pathogen infections. Controlling inflammatory processes is utilised as a symptomatic treatment in addition to fighting the pathogen. Overall, chemicals implicated in LRT or that change the nature of the membrane, weakening pathogen infection, are currently available. Crosstalk between lipid metabolism and inflammatory signalling pathways presents promising therapeutic prospects when contemplating lipid-based defence methods in human hosts. Cho production is inhibited when type I interferon (IFN) signalling is activated, and vice versa. As a result, inhibiting Cho biosynthesis in vitro appears to protect against MHV-68 and HIV-1. Reduced lipid production also reduces lipid raft stability, and Miglustat-Zavesca (a drug now used to treat hereditary illnesses affecting fat metabolism) has shown promise in inhibiting harmful pro-inflammatory activity in vitro. In conclusion, LRT and other techniques focused at targeting lipids on the infectious agent or the host present a promising landscape, especially since many of them are currently on the market for other purposes.

Conclusion

The composition of lipids is critical for cellular homeostasis. Lipid abnormalities are linked to a variety of disorders, and lowering their levels offers therapeutic promise. Membrane lipid treatment, also known as membrane lipid replacement, is currently being used in medication development and nutraceutical therapies. This technology, which is founded on an understanding of cell membrane composition, structure, and functions, has been verified by several clinical trials and medicinal products. The molecular and cellular basis of this therapeutic approach is described in this review, which explains how membrane lipid composition and structure affect protein-lipid interactions, cell signalling, cell physiology, pathophysiology, and therapy, with a focus on oncology, neurodegeneration, and infectious diseases.

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