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Investigating the Role of Phospholipids and their Metabolic Pathways: Implications for Health and Approaches to Disease Management

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ABSTRACT

This research examines the vital role of phospholipids in human health and their significance in disease management. Phospholipids, which are fundamental components of cellular membranes, play a key role in various biological functions, including cell signaling and membrane fluidity. The study investigates the structure of phospholipids, emphasizing their amphipathic characteristics and functional diversity. It further explores the pathways of phospholipid metabolism, focusing on the synthesis and degradation processes that maintain cellular homeostasis. Additionally, we analyze disorders associated with dysfunctional phospholipid metabolism, including metabolic syndromes and neurodegenerative diseases, highlighting the need for targeted therapeutic approaches. The study demonstrates the essential role of phospholipid metabolism in preserving cellular integrity and suggests promising directions for future research and clinical applications. By deepening our understanding of Phospholipid metabolism, we aim to identify new avenues for innovative interventions in disease management and enhance health outcomes.

Keywords: Phospholipids; Phosphatidic Acid; Phosphatidylserine; Phosphatidylethanolamine; Phosphatidylcholine; Phosphatidylinositol; Sphingomyelin; Cardiolipin

Abbreviations: PLs: Phospholipids; PA: Phosphatidic Acid; PS: Phosphatidylserine; PE: Phosphatidylethanolamine; PC: Phosphatidylcholine; PI: Phosphatidylinositol; SPLs: Sphingophospholipids; SM: Sphingomyelin; CL: Cardiolipin; LPLATs: Lysophospholipid Ayltransferases; PLAs: Lipid Mediator Production; PAF: Platelet-Activating Factor; E. coli: Escherichia Coli; CMP: Cytidine Monophosphate; FAs: Fatty Acids; PUFAs: Polyunsaturated Fatty Acids; IMM: Inner Mitochondrial Membrane; S1P: Sphingosine-1-Phosphate; CerS: Ceramide Synthase; COA: Coenzyme A; LPC: Lysophosphatidylcholine; RDS: Respiratory Distress Syndrome; HMD: Hyaline Membrane Disease; nRDS: Neonatal Respiratory Distress Syndrome; NPD: Niemann-Pick Disease; NPC: Niemann-Pick Type C Disease; AC: Lysosomal Acid Ceramidase; VSGP: Vertical Supranuclear Gaze Palsy; AC: Lysosomal Acid Ceramidase; BMT: Bone Marrow Transplantation; DPPC: Dipalmitoyl-Phosphatidylcholine; LPC: Lysophosphatidylcholine; NSAIDs: Non-Steroidal Anti-Inflammatory Drugs

Introduction

Cell structure and function rely heavily on membranes, which separate the cell's interior from its environment and define eukaryotic cell compartments, such as the nucleus and organelles [1]. Biological membranes form from lipid properties, typically consisting of phospholipid bilayers with proteins. Membrane proteins are essential for maintaining structure and facilitating material flow, while sugars, attached to lipids and proteins by covalent bonds, are present on only one side of the bilayer. These membrane proteins perform various functions, including acting as receptors for external signals, facilitating the selective transport of molecules, participating in electron transport, and mediating cell interactions in multicellular organisms [1-4]. The bilayer's lipid arrangement is asymmetrical, with higher concentrations of phosphatidylcholine (PC) and sphingomyelin (SM) in the outer leaflet, while the inner leaflet contains more phosphatidylserine (PS) and phosphatidylethanolamine (PE). Phosphatidyli-

nositol (PI), important for signal transmission, is exclusive to the inner leaflet [5]. Phosphatidylserine contributes to membrane potential due to its negative charge, and it is a key acidic phospholipid in the human cerebral cortex, comprising 13–15% of its phospholipids. It is found in the cytoplasmic leaflet of the plasma membrane and is essential for protein docking sites that activate critical signaling pathways, which promote neuronal survival, neurite growth, and synaptogenesis. Modulating phosphatidylserine levels in neuronal membranes significantly affects these signaling processes [6]. Phospholipids are polar and amphipathic, consisting of an alcohol linked to diacylglycerol or sphingosine. They have hydrophilic heads and hydrophobic tails, which are crucial for the cell membrane's structure, serving as reservoirs for intracellular messengers and anchoring proteins. Additionally, they are involved in lung surfactants and bile for cholesterol solubilization (Figure 1A) [3,7]. The human body primarily consists of phospholipids with polyunsaturated fatty acids (PUFAs), particularly in the brain, which may be more vulnerable to ischemia/reperfusion injury. However, brain tissue has higher concentrations of monounsaturated and saturated fatty acids, with PUFAs making up only about 60% of its total phospholipid content, compared to over 90% in the heart and kidney and around 95% in the liver. Additionally, about 65% of brain phosphatidylcholine lacks PUFAs, indicating a lower relative amount of PUFA-containing phospholipids compared to other major organs [8-11]. The brain's phospholipid profile remains stable despite dietary lipids, with lysophosphatidylcholine (LPC) being the only dietary factor that increases brain PUFA content. In neurodegenerative diseases such as Alzheimer's, lower PUFA levels are observed, and although their significance is uncertain, LPC supplementation may increase PUFA levels and help mitigate neurodegeneration [12,13]. Lung surfactants are produced in the endoplasmic reticulum of alveolar type II cells, stored in lamellar bodies, and released via exocytosis in response to signals. Once released, they form a surfactant film on the alveolar surface, which includes multilamellar structures and vesicles. This surfactant plays a crucial role in clearing foreign materials and dead cells from the lungs, significantly contributing to innate immune defense [14-16].

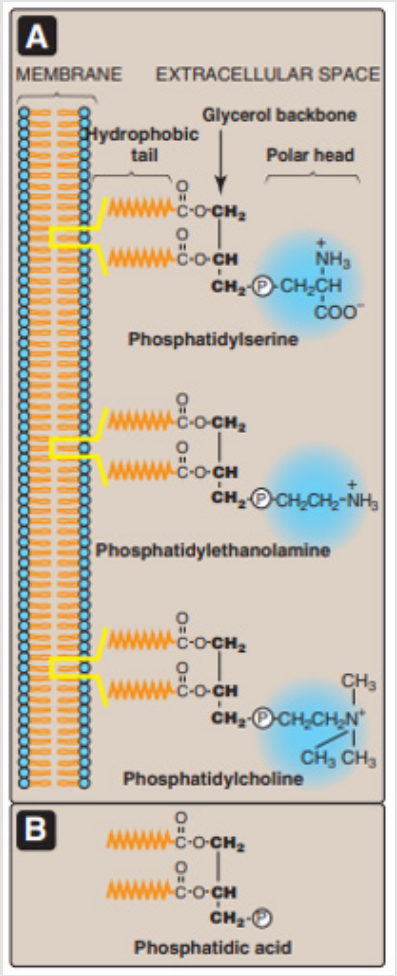

Figure 1:
A. Various Structures of Glycerophospholipids.
B. Phosphatidic Acid. "P = Phosphate group, PO_4^{1-}" [7].

According to [17], research observed that fatty acid levels, composition, and metabolism change in older individuals [18]. These changes are believed to play a significant role in the aging process and may impact overall health and longevity. In older individuals, the balance of omega-3 and omega-6 fatty acids can shift, potentially leading to increased inflammation and susceptibility to age-related diseases. Long-lived model organisms, such as certain worms, flies, and rodent species, often exhibit unique fatty acid profiles that contribute to their extended lifespans. Research using model organisms such as "Caenorhabditis elegans" indicates that specific fatty acids (FAs) can promote lifespan extension when included in the diet. Beneficial fats include monounsaturated oleic acid, palmitoleic acid, cis-vaccenic acid, oleoylethanolamine, and polyunsaturated fats like α-linolenic acid, arachidonic acid, and dihomo-γ-linolenic acid [19-23]. Research indicates that these fats interact with hormonal pathways such as insulin/IGF-1 and mTOR, which are essential for growth and metabolism, potentially maintaining metabolic balance and preventing age-related decline. Studying model organisms, "Caenorhabditis elegans," with their simple genetics and short lifespan, aids in screening dietary compounds for longevity effects. Understanding the beneficial effects of unsaturated fatty acids can reveal insights into aging mechanisms. They may enhance mitochondrial function, reduce oxidative stress, and influence gene expression related to stress and inflammation, promoting cellular health and resilience [24]. Unsaturated FAs primarily operate through classic longevity factors to influence health span and lifespan [25,26]. With age, the phospholipid composition of cell membranes changes, affecting membrane fluidity and cellular communication. Alterations in phosphatidylcholine and sphingolipid levels can disrupt signal transduction and reduce resilience to stressors. Furthermore, lipid raft integrity declines, affecting receptor localization and essential signaling pathways for immune function and metabolic regulation [27].

Phospholipid in the Brain and Gut

According to [28], the brain and nervous system are particularly abundant in phospholipids, exhibiting a more varied lipid composition than other tissues in the body [29,30] and have long been thought to play a role in brain maturation and functionality [31]. This provides part of the rationale for utilizing phospholipids to enhance or preserve brain health and cognitive processes. Research has shown that dietary phospholipids confer numerous health benefits, particularly by enhancing cognitive function throughout the lifespan [32,33]. It's important to note that in humans, cognition includes all biological processes related to attention, learning, memory, reasoning, judgment, decision-making, problem-solving, and understanding, ultimately contributing to knowledge creation and application. In rodents, cognitive assessment primarily focuses on evaluating learning, memory, and attention [34]. According to [35], phospholipids constitute over 60% of the total membrane lipids found in neurons [36,37]. They share a similar structure, featuring two fatty acids linked to the sn-1 and sn-2 positions (sn- refer to specific carbon locations on the glycerol backbone of glycerol-based lipids like phospholipids and triglycerides) along with a diverse phosphate headgroup attached at the sn-3 position of the glycerol backbone (Figure 2). Depending on the headgroup at the sn-3 position, phospholipids can be categorized into several types: phosphatidylcholine (PC), phosphatidylserine (PS), phosphatidylethanolamine (PE), phosphatidylinositol (PI), phosphatidic acid (PA), and cardiolipin [38]. Among these, PE is the most prevalent phospholipid in the mammalian brain [39]. Additionally, synaptic microdomains display distinct phospholipid compositions: PS is predominantly found in vesicle membranes, while PE and PC are more concentrated in postsynaptic peri-synaptic densities and lipid rafts, respectively [40,41]. The dynamic remodeling of phospholipids facilitates the rapid alterations in membrane morphology necessary for synaptic transmission, highlighting the importance of maintaining a critical phospholipid composition for the integrity of synaptic structures [40,42].

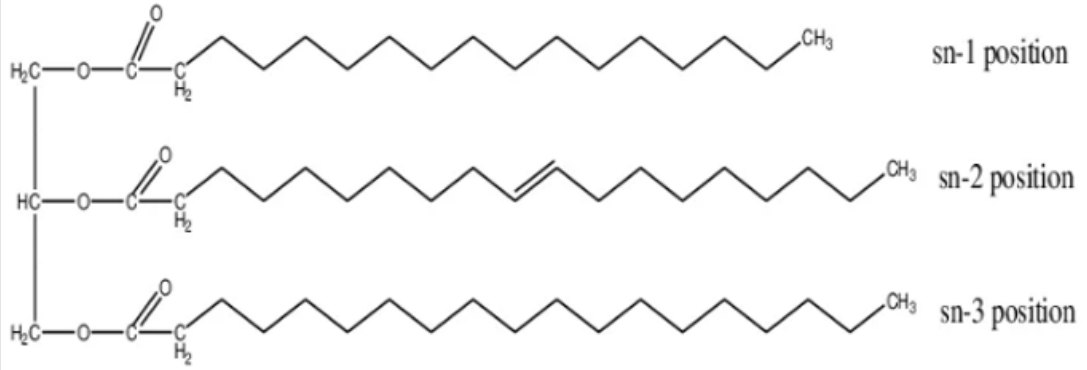

Figure 2: The relative positions of the fatty acids in the sn-1, sn-2, and sn-3 positions in a triglyceride structure.

In Alzheimer's disease (AD) patients, lower levels of unsaturated phosphatidylcholines in plasma correlate with hippocampal atrophy. Higher levels of certain unsaturated PCs are associated with slower cognitive decline. Conversely, the accumulation of PC-O is linked to worsening tau pathology, increased vesicular release, and neuronal loss. Thus, specific unsaturated PCs appear crucial for maintaining neuronal function [43-45]. Certain gut bacteria, particularly those in the Bacteroidetes phylum, produce phospholipids, such as sphingolipids, that are essential for gut health. A deficiency in these metabolites is linked to increased intestinal inflammation. Additionally, the microbiota-gut-brain axis suggests a connection between gut bacteria and brain health, highlighting the need for further research on the implications of bacteria-derived phospholipids [46-49]. The brain and gut communicate through the microbiota-gut-brain axis, with gut microbiota crucial for brain development. This microbiota begins at birth and evolves, initially dominated by aerobic bacteria before anaerobic bacteria take over. Research shows a link between gut microbiota and cognitive function, as seen in studies with germ-free or antibiotic-treated animals that showed impaired memory, which improved with specific probiotics. Additionally, combinations of dairy lipids and probiotics support the maturation of the gut microbiota. Phospholipids may enhance cognition by modulating the gut microbiota, as diets enriched with phospholipids altered gut composition in piglets. However, the relationship between phospholipids and the microbiota-gut-brain axis remains poorly understood, necessitating further research into how dietary phospholipids affect brain function and related systems, such as neurotransmission and the HPA axis [47-65].

Phospholipids: Biological and Chemical Structure

There are two phospholipid categories: glycerol-based and sphingosine-based. Both are essential for cell membrane structure and in producing lipid-signaling molecules. Glycerol-based phospholipids, such as phosphatidylcholine and phosphatidylethanolamine, are characterized by a glycerol backbone attached to two fatty acid chains and a phosphate group. These lipids play a crucial role in maintaining the fluidity and integrity of cell membranes, allowing for proper cellular function and communication. Sphingosine-based phospholipids, on the other hand, include sphingomyelin, which is a key component of the myelin sheath that insulates nerve fibers. This category of phospholipids is derived from sphingosine, an amino alcohol, and is involved in signal transduction and cell recognition processes. Both types of phospholipids are not only structural elements but also participate actively in cellular signaling pathways. They are involved in various physiological processes, including apoptosis, cell growth, and immune responses, underscoring their versatility and importance in biological systems [66].

Glycerophospholipids

Glycerophospholipids, also known as phosphoglycerides, are a type of phospholipid that includes glycerol. They represent the primary class of phospholipids. Glycerophospholipids are derived from phosphatidic acids, which are formed when a glycerol molecule has two of its hydroxyl groups (OH) esterified by fatty acids (FAs), with the third hydroxyl group esterified by phosphoric acid. The second carbon (C2) of the glycerol moiety is asymmetric, leading to the formation of stereoisomers. In nature, glycerophospholipids typically exhibit L configuration. The carbon atoms are numbered according to the rules of stereospecific numbering (sn), with the carbon bearing the hydroxyl group esterified with phosphate designated as C3 (Figure 1B). Phosphatidic acid is the most basic phosphoglyceride and serves as the precursor for the other members of this category [67]. The de novo pathway generates various glycerophospholipids with different polar heads, including phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylserine (PS), phosphatidylinositol (PI), phosphatidylglycerol (PG), and Cardiolipin (CL) [68].

- Choline + PA → phosphatidylcholine (lecithin) (PC).
- Ethanolamine + PA → phosphatidylethanolamine (cephalin) (PE).
- Serine + PA → phosphatidylserine (PS).
- Inositol + PA → phosphatidylinositol (PI).
- Glycerol + PA → phosphatidylglycerol (PG).

Glycerophospholipid acyl chains are remodeled through reactions involving "phospholipase As, acyl-CoA synthases, transacylases, and lysophospholipid acyltransferases (LPLATs)". This remodeling, known as the Lands' cycle, creates diverse cellular glycerophospholipids. While research has focused on lipid mediator production (PLAs), recent studies identified various LPLATs from AGPAT and MBOAT families. Isolated LPLATs exhibit promiscuous substrate specificities, suggesting that understanding these enzymes is crucial for appreciating membrane glycerophospholipid diversity and its impact on lipid mediators and membrane properties [69].

Cardiolipin

Cardiolipin (CL) is formed when two molecules of PA are esterified through their phosphate groups to a single glycerol molecule, resulting in diphosphatidylglycerol (Figure 3). This compound is present in both bacteria and eukaryotes. In eukaryotic cells, cardiolipin is predominantly located in the inner mitochondrial membrane, where it plays a crucial role in maintaining the function of specific respiratory complexes of the electron transport chain. Cardiolipin is an antigen recognized by antibodies against "Treponema pallidum", the bacterium responsible for syphilis [70].

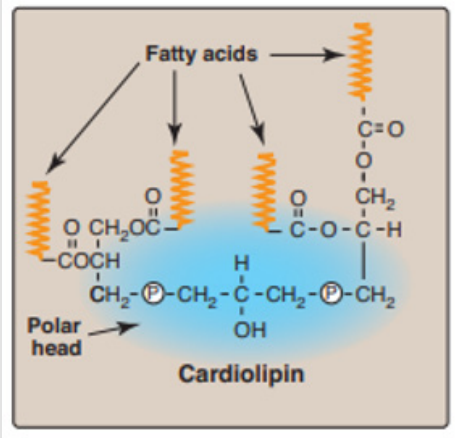

Figure 3: Structure of Cardiolipin [7].

Plasmalogens

Plasmalogens are formed when the fatty acid at carbon 1 of a glycerophospholipid is substituted with an unsaturated alkyl group, linked by an ether connection rather than an ester to the core glycerol molecule. For instance, phosphatidylethanolamine (found abundantly in nerve tissue, (Figure 4A)) is a plasmalogen structurally akin to phosphatidylethanolamine. Additionally, phosphatidylcholine (which is abundant in heart muscle) represents another significant ether lipid found in mammals [7].

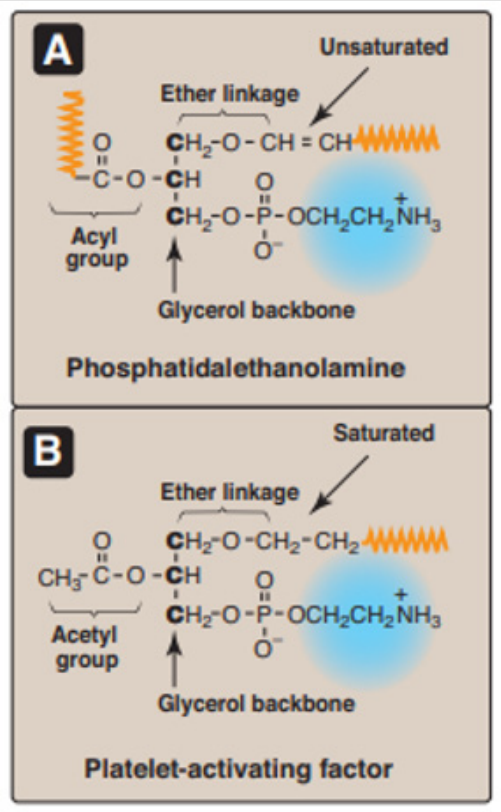

Figure 4:
A. Plasmalogen phosphatidylethanolamine.
B. Platelet-activating factor [7].

Platelet-Activating Factor (PAF)

Platelet-activating factor (PAF) is a unique ether glycerophospholipid characterized by a saturated alkyl group linked to carbon 1 via an ether bond, and an acetyl residue—rather than a fatty acid—attached to carbon 2 of the glycerol backbone (Figure 4B). PAF is produced and released by various cell types. It interacts with surface receptors, initiating powerful thrombotic and acute inflammatory responses. Notably, PAF:

- Activates inflammatory cells
- Mediates hypersensitivity and acute inflammatory reactions, including anaphylactic responses
- Induces platelet aggregation and degranulation
- Stimulates neutrophils and alveolar macrophages to produce superoxide radicals
- PAF is recognized as one of the most potent bioactive molecules, exerting effects at concentrations as low as 1012 mol/L [7,71,72].

Sphingophospholipids (SPLs)

Sphingolipids are distinct from traditional lipids due to their structure, where glycerol is replaced by sphingosine (Figure 5), which is amide-linked to a fatty acid and phosphate group. A notable example is sphingomyelin (SM), composed of sphingosine and choline. These lipids are amphipathic, essential for maintaining cell membrane structure and fluidity, and are abundant in the myelin sheath of nerve cells, aiding in insulation and signal transmission. Sphingolipids play roles in cell signaling, affecting growth, differentiation, and apoptosis. Their importance in normal cellular function and disease pathology has prompted ongoing research into targeting sphingolipid metabolism for therapeutic strategies in conditions such as neurodegenerative diseases and cancer [73].

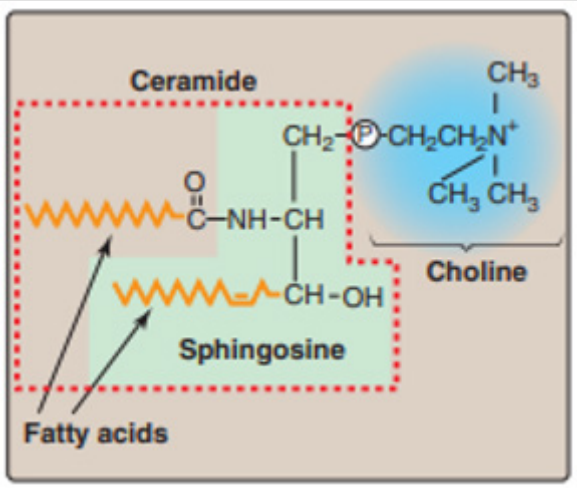

Figure 5: The structure of sphingomyelin, highlighting the sphingosine (within the green box) and ceramide components (enclosed in the dashed box) [7].

Phospholipid Metabolism

Lipid metabolism is vital for cellular homeostasis, and its disruption is linked to various health issues. Recent studies show that lipids are key regulators of immune cell functions, influencing immune responses, cell types, metabolic pathways, and cytokine levels in both healthy and diseased states [74]. Fatty acids (FAs) form the primary structural elements of membrane lipids, including glycerophospholipids and sphingolipids, and function as a significant energy source through mitochondrial β-oxidation and the catabolism of the tricarboxylic acid cycle (citric acid cycle) [75]. Excessive amounts of circulating lipids have been associated with metabolic diseases [76,77] and cancer [78]. The predominant phospholipid found in mammalian cells is phosphatidylcholine (PC). Several other phospholipids, such as phosphatidylethanolamine (PE), phosphatidylserine (PS), sphingomyelin (SM), cardiolipin (CL), and phosphatidylinositol (PI), as well as their phosphorylated derivatives, play vital roles as membrane constituents (Table 1). Additionally, mammalian cell membranes contain other lipids, such as cholesterol and glycosphingolipids [79]. In mammalian cells, where PC is the major phospholipid, Escherichia coli (E. coli) lacks PC, SM, PI, and cholesterol, with PE as the most abundant phospholipid. Furthermore, the outer membrane of this Gram-negative bacterium is primarily composed of lipopolysaccharides rather than phospholipids and contains the unique, complex lipid. Despite significant differences in lipid composition between *E. coli* membranes and those of mammalian cells, prokaryotic cells like *E. coli* can still perform many of the fundamental functions carried out in mammalian cells [80]. The functionality of proteins embedded in the

membranes of eukaryotic cells is heavily influenced by the composition of membrane phospholipids [81]. Different types of mammalian cells and tissues possess specific phospholipid profiles, and significant alterations in these phospholipid contents are generally poorly tolerated. Furthermore, various organelles within mammalian cells exhibit distinct phospholipid compositions; however, these variations are typically quantitative rather than qualitative [79-82].

Table 1: Lipid Composition of a Typical Nucleated Mammalian Cell [7].

	Percentage of total lipids[a]
Phosphatidulcholine	45-55
Phosphatidylethanolamine	15-25
Phosphatidynositol	10-15
phosphatidylserine	05-10
Phosphatic acid	1-2
Sphingomyelin	05-10
Cardiolipin	02-05
Phosphatidylgycerol	<
Glycosphingolipids	02-05
Cholestrol	10-20

Phospholipid Metabolism in Mitochondria

Phospholipid metabolism in mitochondria is crucial for health, and cardiolipin (CL) is vital for the stability and function of the inner mitochondrial membrane. Proper CL synthesis from phosphatidylglycerol (PG) is essential, as disruptions can lead to conditions such as cardiomyopathy or Barth syndrome [83]. Although cardiolipin (CL) is a small part of the inner mitochondrial membrane (IMM), phosphatidylcholine (PC) (40%) and phosphatidylethanolamine (PE) (30%) dominate both inner and outer mitochondrial membranes. Phosphatidylinositol (PI) (10–15%) and phosphatidylserine (PS) (5%) are present in smaller amounts, with brain mitochondria containing higher PS levels than other tissues. [84,85]. Mitochondria also contain substantial amounts of PG, which constitutes the majority of the total tissue PG stores. It is theorized that, since PG is a precursor to CL, maintaining high levels is vital for optimal mitochondrial health [86]. Phospholipid synthesis in mitochondria typically occurs via one of two pathways. Phospholipids such as PE and PG can either be imported or synthesized directly within the mitochondria. In contrast, PC and PS must first be synthesized in the endoplasmic reticulum before being transported into the mitochondria [87]. Similar to PE and PG, CL is synthesized directly in the mitochondria but undergoes a unique remodeling step that can vary slightly across tissue types (Figure 6) [88].

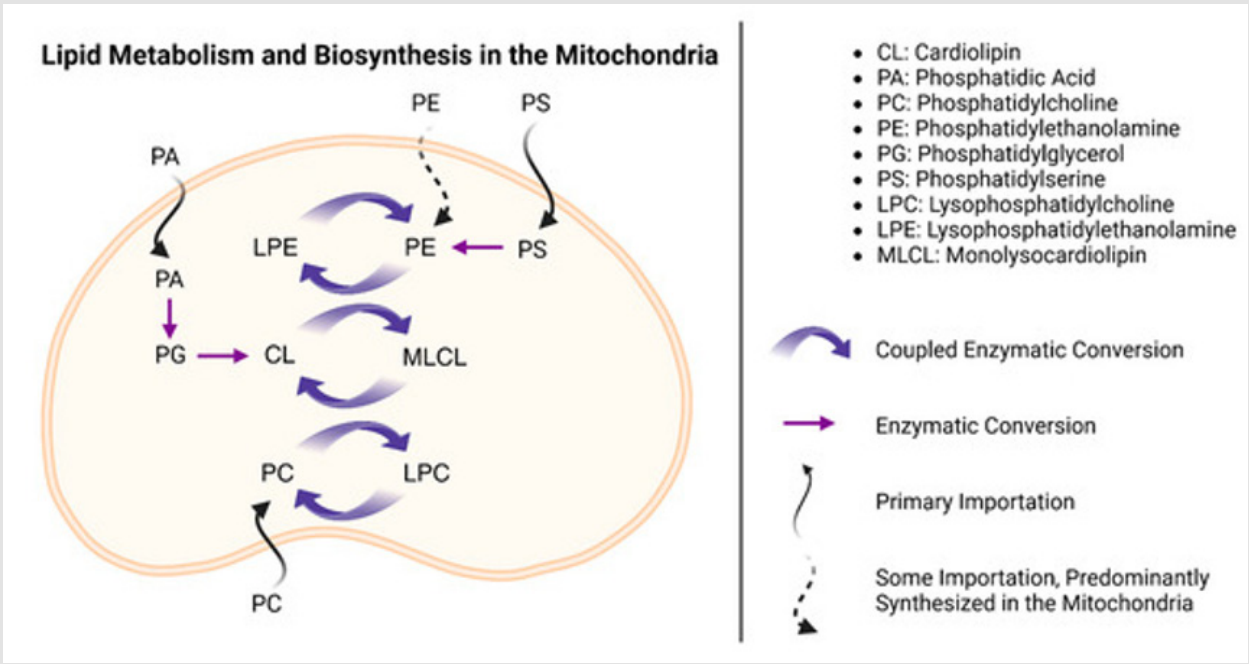

Figure 6: illustrates phospholipid biosynthesis in mitochondria, detailing the import patterns of precursor phospholipids, the biosynthetic pathways that convert them, and cardiolipin's role in phospholipid remodeling [49].

Glycerophospholipid Synthesis Pathways

Glycerophospholipid synthesis involves two main pathways:

- Donation of Phosphatidic Acid: This pathway occurs when phosphatidic acid is transferred from CDP-diacylglycerol to an alcohol.
- Donation of Phosphomonoester: In this alternative pathway, the phosphomonoester of the alcohol is donated from CDP-alcohol to 1,2-diacylglycerol [7,89,90] (Figure 7).

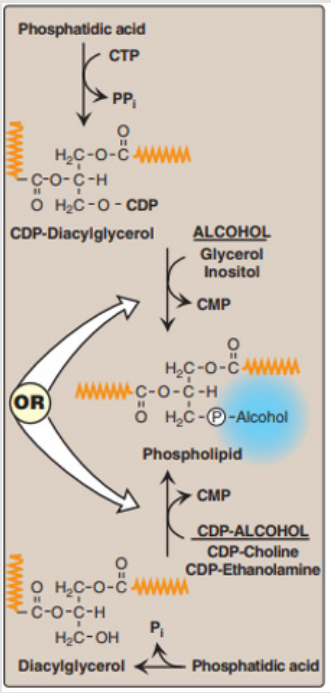

Figure 7: Illustrates how the activation of either diacylglycerol or alcohol through linkage to a nucleoside diphosphate (CDP) enhances the synthesis of phospholipids [7].

In both pathways:

- CDP-bound structures act as "activated intermediates" in glycerophospholipid synthesis, releasing cytidine monophosphate (CMP) as a byproduct.
- Activation is essential, akin to sugar activation via uridine diphosphate (UDP).
- Fatty acids esterified to glycerol alcohol groups vary, increasing compound diversity.
- Most phospholipids are synthesized in the smooth endoplasmic reticulum, then transported to the Golgi apparatus for distribution to organelle membranes, the plasma membrane, or secretion via exocytosis.
- Lipid synthesis may also occur in peroxisomes [7,91].

Synthesis of Phosphatidic Acid (PA)

Phosphatidic acid (PA) acts as a vital precursor for a range of phosphoglycerides. The synthesis involves glycerol phosphate combined with two fatty acyl coenzyme A (CoA) molecules, with PA serving as a precursor to triacylglycerol. Notably, nearly all cells, except for mature erythrocytes, possess the ability to synthesize phospholipids. The capability is critical for maintaining cellular membrane integrity and facilitating membrane-related functions. Phosphatidic acid not only contributes to lipid biosynthesis but also plays a role in cell signaling pathways, where it acts as a lipid messenger. The unique structure of PA allows it to interact with various proteins, influencing processes such as cell growth, survival, and differentiation. Understanding the dynamics of PA and its derivatives is thus essential for comprehending broader metabolic and physiological processes within the cell [92].

Synthesis of Phosphatidylcholine (PC) and Phosphatidylethanolamine (PE)

According to [93], phosphatidylcholine (PC) and phosphatidylethanolamine (PE) are key glycerophospholipids in eukaryotic cells, crucial for cellular membranes and various functions. PC is essential for the production of second messengers and lipid mediators, and its

disruption affects cell growth and membrane dynamics. PE is important for autophagy, cell division, and protein folding, and serves as a precursor for protein modifications [94-101]. Both phosphatidylcholine (PC) and phosphatidylethanolamine (PE) are intermediates in synthesizing glycerophospholipids. In eukaryotes, PE is formed via the CDP-ethanolamine branch of the Kennedy pathway, decarboxylation of phosphatidylserine (PS), or base exchange with PS. PC is synthesized through the CDP-choline branch of the Kennedy pathway or by methylating PE. In addition to de novo synthesis, both PE and PC can be generated by the acylation of lysophospholipids that cells uptake from their surroundings [98,102-106]. PC and PE are key phospholipids in eukaryotic cells. They are primarily synthesized from dietary choline and ethanolamine or from the turnover of body phospholipids. In the liver, PC can also be produced from PS and PE [107]. The synthesis of PC and PE involves their phosphorylation by kinases, forming activated compounds CDP-choline or CDP-ethanolamine. Choline phosphate or ethanolamine phosphate is then transferred to diacylglycerol, releasing CMP. Since humans cannot produce sufficient choline, it is an essential dietary nutrient and is crucial for synthesizing the neurotransmitter acetylcholine [108] (Figure 7).

Phosphatidylserine (PS)

Phosphatidylserine (PS) is a key component of cell membranes, constituting 5–10% of total cell lipids. As an anionic phospholipid, it binds to proteins and participates in various biological processes, including enzyme activation and neurotransmission. Dysregulation of PS metabolism is linked to CNS diseases such as Alzheimer's, Parkinson's, major depressive disorder, stroke, and autism. PS supplementation has shown benefits for patients with these conditions and can inhibit neuroinflammation, offer neuroprotection, and enhance cognitive function. The main pathway for PS synthesis in mammalian tissues is facilitated by a base-exchange reaction, in which ethanolamine from PE is exchanged for free serine (Figure 8). Although this reaction is reversible, it is primarily utilized to generate the PS necessary for membrane synthesis. [109].

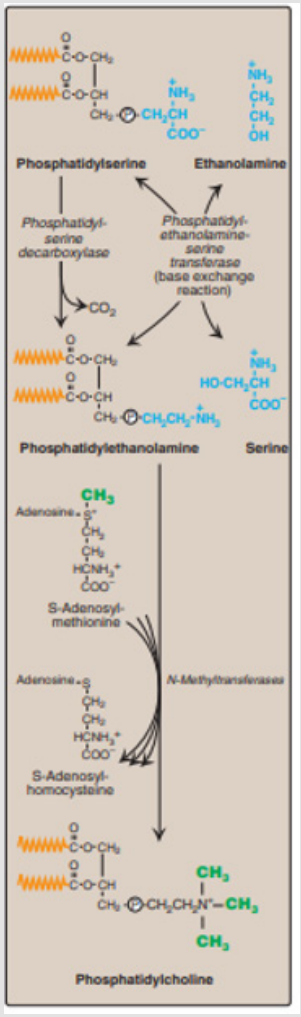

Figure 8: The conversion of phosphatidylserine into phosphatidylcholine within the liver [7].

Phosphatidylinositol (PI)

Phosphatidylinositol (PI) is synthesized from free inositol and CDP-diacylglycerol. This phospholipid is unique because it often contains stearic acid at carbon 1 and arachidonic acid at carbon 2 of the glycerol backbone. Consequently, PI acts as a reservoir for arachidonic acid within membranes and provides a substrate for prostaglandin synthesis when needed [110]. The phosphorylation of membrane-bound phosphatidylinositol results in the formation of polyphosphoinositides, such as phosphatidylinositol 4,5-bisphosphate (PIP2) (Figure 9) [111]. The degradation of PIP2 by phospholipase C occurs when various neurotransmitters, hormones, and growth factors bind to cell membrane receptors (Figure 10). The degradation products, inositol 1,4,5-trisphosphate (IP3) and diacylglycerol (DAG), facilitate the mobilization of intracellular calcium and the activation of protein kinase C, which work together to trigger specific cellular responses. Thus, signal transmission across the membrane is achieved [112]. Specific proteins can be covalently linked to membrane-bound phosphatidylinositol (PI) via carbohydrate bridges (Figure 11), such as alkaline phosphatase and acetylcholinesterase. GPI-anchored proteins, found in various parasitic protozoans, have greater mobility on the plasma membrane due to being anchored to lipids rather than integrated into the membrane. These proteins can be cleaved by phospholipase C, releasing diacylglycerol. A deficiency in GPI synthesis in hematopoietic cells may cause paroxysmal nocturnal hemoglobinuria, a hemolytic condition [7].

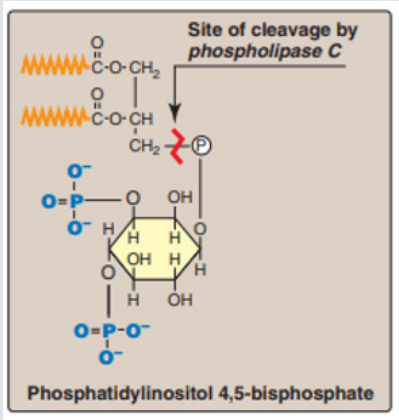

Figure 9: Structure of phosphatidylinositol 4,5-bisphosphate (PIP2). Cleavage by phospholipase C produces IP3 and DAG [7].

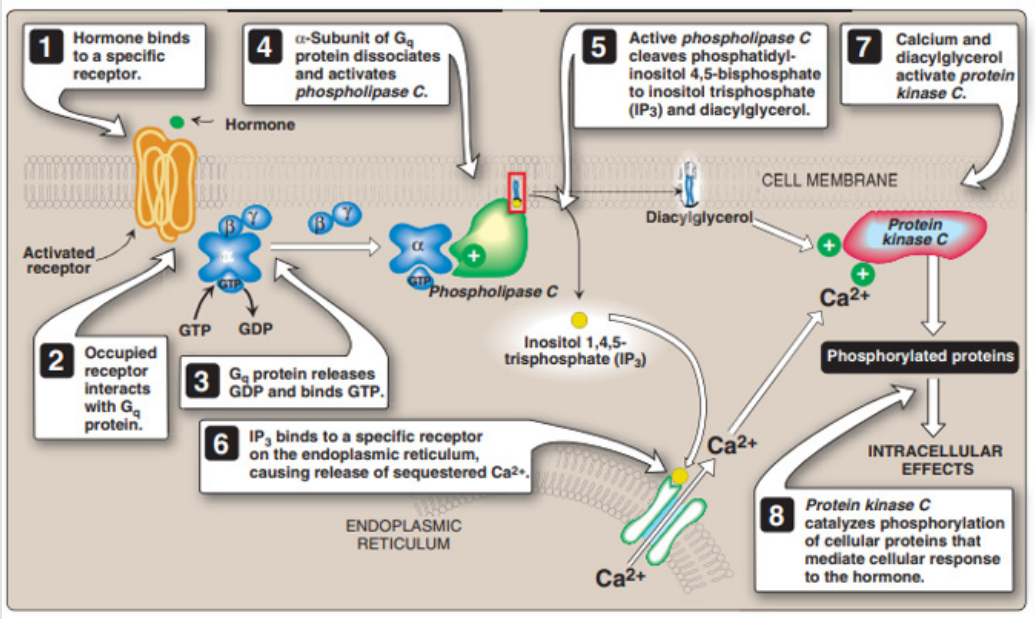

Figure 10: Role of inositol trisphosphate and diacylglycerol in intracellular signaling [7].

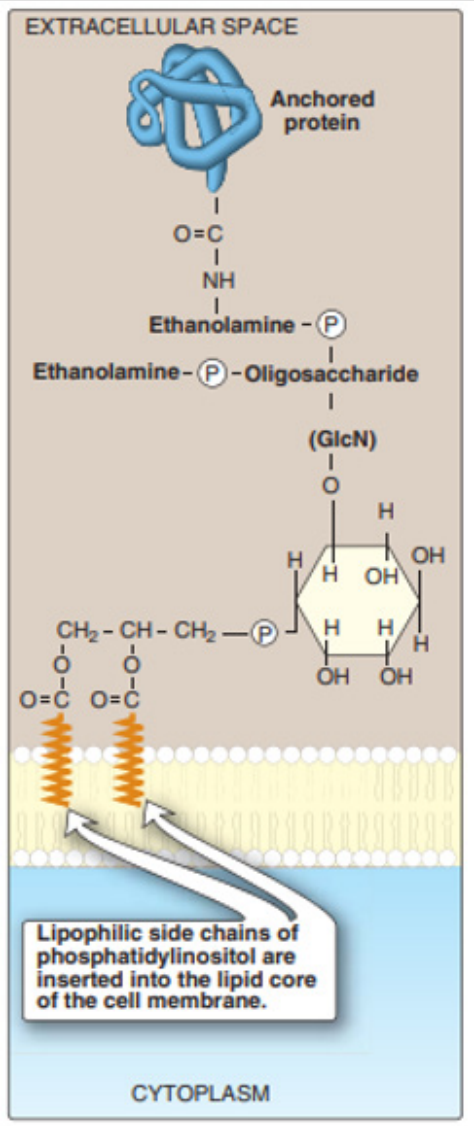

Figure 11: Example of a glycosyl phosphatidylinositol (GPI) membrane protein anchor. GlcN = glucosamine [7].

Phosphatidylglycerol (PG) and Cardiolipin (CL)

Phosphatidylglycerol is present in substantial amounts within mitochondrial membranes and serves as a precursor to cardiolipin. It is synthesized through a two-step reaction involving CDP-diacylglycerol and glycerol 3-phosphate [113]. Cardiolipin (diphosphatidylglycerol) consists of two molecules of phosphatidic acid linked by a single glycerol molecule. Its synthesis occurs via the transfer of diacylglycerol phosphate from CDP-diacylglycerol to an existing molecule of phosphatidylglycerol [79].

Sphingomyelin (SM)

Sphingomyelin (SM), a sphingosine-based phospholipid, forms a major structural component of nerve tissue membranes. Palmitoyl-CoA condenses with serine, releasing CoA and the carboxyl group (as CO_2). This reaction is similar to the decarboxylation reactions involved in PE synthesis from PS and the production of regulators from amino acids. This reaction, akin to decarboxylation in PE synthesis and the creation of regulators from amino acids, requires pyridoxal phosphate (vitamin B6) as a coenzyme. The resulting product is reduced with NADPH to form sphinganine, which is acylated with a long-chain fatty acid and desaturated to form ceramide, a precursor to sphingomyelin. A ceramide with a 30-carbon fatty acid aids skin structure and water permeability. Phosphorylcholine from phosphatidylcholine transfers to ceramide to yield sphingomyelin and diacylglycerol. Sphingomyelin in the myelin sheath mainly consists of longer-chain fatty acids, while gray matter sphingomyelin primarily contains stearic acid [114].

Degradation of Phospholipids

Phosphoglycerides are degraded by phospholipases present in all tissues and pancreatic juice. Certain toxins and venoms exhibit phospholipase activity, while various pathogenic bacteria produce phospholipases that disrupt cell membranes, facilitating the spread of infection. Sphingomyelin is specifically degraded by the lysosomal phospholipase known as sphingomyelinase [114].

Degradation of Phosphoglycerides

Phospholipases play a crucial role in hydrolyzing the phosphodiester bonds of phosphoglycerides, with each enzyme targeting a specific site on the phospholipid [115,116]. The primary enzymes involved in this degradation process are illustrated in (Figure 12). The removal of a fatty acid from carbon 1 or 2 of a phosphoglyceride results in the formation of a lysophosphoglyceride, which serves as the substrate for lysophospholipases. Phospholipases also release molecules that can act as messengers (such as DAG and IP3) or serve as substrates for the synthesis of messengers (such as arachidonic acid). In addition to degrading phospholipids, phospholipases also "remodel" them. For instance, phospholipases A1 and A2 can remove specific fatty acids from membrane-bound phospholipids, which can then be substituted with alternative fatty acids via fatty acyl-CoA transferase. This process is essential for creating the unique lung surfactant, DPCC, and ensuring that carbon 2 of PI (and occasionally of PC) is linked to arachidonic acid [7].

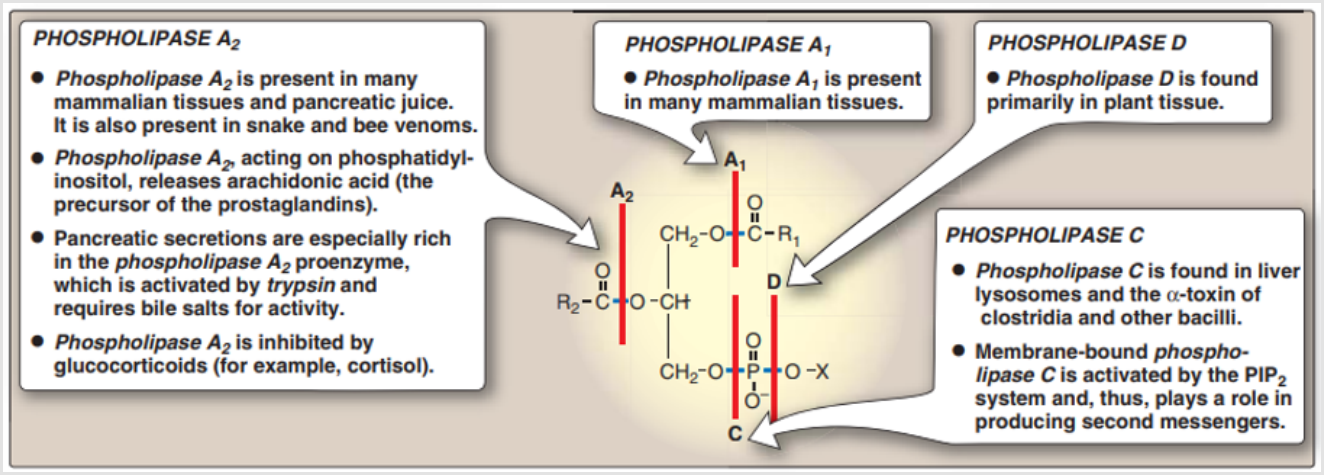

Figure 12: The Breakdown of Glycerophospholipids by Phospholipases [7].

Degradation of Sphingomyelin

Sphingomyelin is broken down by sphingomyelinase, a lysosomal enzyme that hydrolytically cleaves phosphorylcholine, resulting in the formation of ceramide. This ceramide is subsequently processed by ceramidase, yielding sphingosine and a free fatty acid (Figure 13) [117]. The released ceramide and sphingosine play crucial roles in regulating signal transduction pathways, partly by affecting the activity of protein kinase C, which in turn influences the phosphorylation of its protein substrates. Additionally, they promote apoptosis [118].

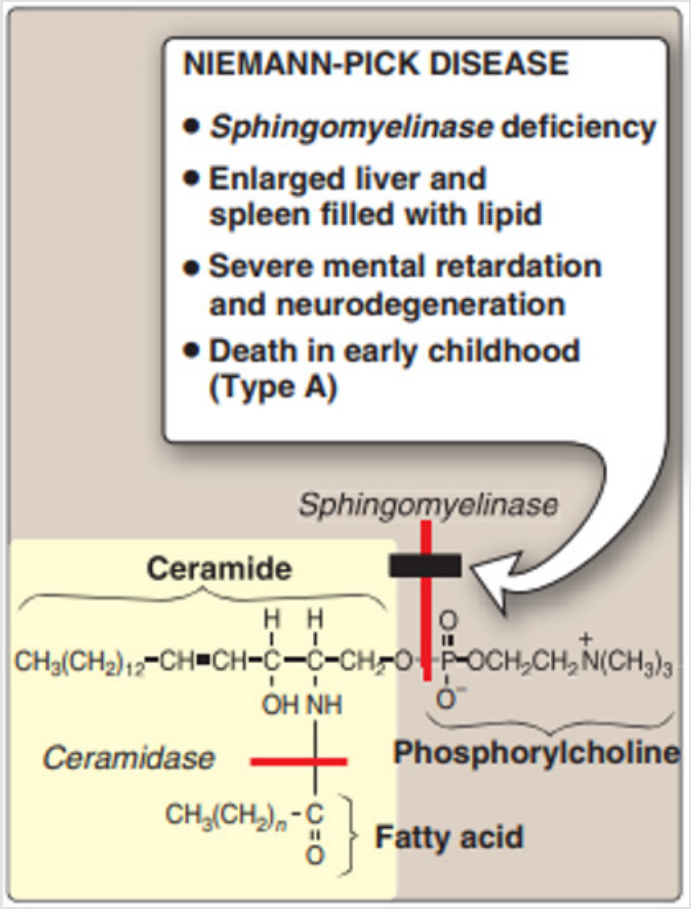

Figure 13: Breakdown of sphingomyelin [7].

Phospholipid Metabolism Disorders

Among the phospholipids predominantly found in the plasma membrane of mammalian cells are PC, PS, PE, PI, and SM [46,119]. The composition of these phospholipids (PC, PS, PE, SM, and PI) can be influenced by specific diseases and their progression. Recent metabolomics research indicates that phospholipids and their metabolites hold promise as diagnostic biomarkers for human diseases. Lysosomal lipid storage diseases are a group of inherited metabolic disorders characterized by the accumulation of complex lipids in cells and tissues. Normally, macromolecules such as complex lipids and oligosaccharides are continuously broken down in the acidic environments of endosomes and lysosomes into their basic building blocks. These resultant catabolites are then transported to the cytosol for reuse in cellular metabolism. However, when lysosomal function is compromised due to a defect in a specific catabolic process, this degradation does not occur properly, leading to the build-up of undegraded compounds [120]. Lysosomal lipid storage diseases include sphingolipidoses, Niemann-Pick type C disease (NPC), Wolman disease, and a milder variant, cholesteryl ester storage disease [121]. Sphingolipidoses are inherited lipid storage disorders caused by genetic defects in proteins involved in lysosomal catabolism. All sphingolipidoses are inherited in an autosomal recessive manner, except for Fabry disease, which follows an X-linked recessive pattern of inheritance [122]. Glycosphingolipids are broken down through a strictly sequential pathway in humans. For nearly every step in the degradation process, there is a corresponding disease associated with a defective enzyme or an activator protein. Lactosylceramide can be degraded by two distinct enzyme/activator systems [123]. Consequently, no known single enzyme defect leads to isolated lactosylceramide accumulation. However, lactosylceramide may accumulate alongside other sphingolipids when multiple cofactors are absent, as seen in cases of prosaposin deficiency [124].

Niemann-Pick Disease (NPD) (Types A and B)

Niemann-Pick disease (Types A and B) is an autosomal recessive disorder caused by the inability to degrade sphingomyelin. The enzyme that is deficient in this condition is sphingomyelinase, a type of phospholipase C [125].

- In the severe infantile form (Type A, characterized by less than 1% normal activity), the liver and spleen become the primary sites for lipid accumulation, leading to significant enlargement of these organs.
- The accumulated lipid mainly consists of sphingomyelin, which cannot be degraded (Figure 14).

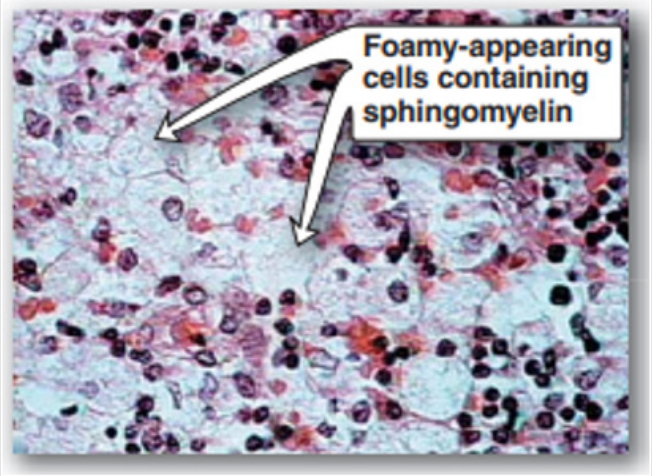

Figure 14: Accumulation of lipids in spleen cells from a patient diagnosed with Niemann-Pick disease [7].

Infants affected by this lysosomal storage disorder experience rapid and progressive neurodegeneration due to sphingomyelin deposits in the central nervous system, resulting in early childhood mortality. In contrast, a milder variant (Type B, with 5% or more enzyme activity) causes minimal to no damage to neural tissue, but affects the lungs, spleen, liver, and bone marrow. This leads to a chronic form of the disease with a life expectancy extending into adulthood. While Niemann-Pick disease occurs across all ethnic groups, Type A is more prevalent in the Ashkenazi Jewish population compared to the general population [7]. Type A NPD patients typically present with hepatosplenomegaly and failure to thrive within their first year. Approximately 50% of these infants exhibit a cherry-red spot in the macula. The disease progresses rapidly, leading to severe neurodegeneration characterized by profound hypotonia and an inability to reach developmental milestones. Sadly, most infants with type A NPD do not survive past their third year of life [126,127]. In type A NPD patients, the brain is typically atrophic, with swollen ganglion cells with pale, vacuolated cytoplasm. These cells contain membrane-bound inclusions. There is a noticeable loss of cells in the cerebral and cerebellar cortices of infants with type A, accompanied by gliosis in both gray and white matter. Some regions of the white matter exhibit demyelination. Foam cells can also be found in the leptomeninges, the Tela choroidea, the endothelium, and the perivascular spaces of cerebral blood vessels [128]. Additionally, lipid-laden macrophages and neutrophils are present in the airways of patients with types A and B NPD. Studies involving ASMKO mice have shown that these airway macrophages are functionally impaired [110].

In contrast, Type B NPD patients show no clear signs of central nervous system (CNS) involvement; however, they may experience significant hepatosplenomegaly, often accompanied by signs of liver failure [129-131]. These patients commonly have elevated serum triglycerides and LDL cholesterol, while HDL cholesterol tends to be low. Additionally, pulmonary function is frequently compromised due to lung involvement. Some may present with a reddish-brown halo around the macula, and in some cases, a distinct cherry-red spot can be observed. There are also reports of patients exhibiting characteristics that fall between types A and B NPD [132]. Additionally, morphologic alterations may be observed in the basal ganglia, brainstem, spinal cord, and autonomic ganglia. However, little is known about the structural changes occurring in the brains of type B NPD patients. Foam cells are similarly present in Hepatocytes, Kupffer cells, and Bile duct epithelium in the livers of types A and B patients. Liver biopsies from a group of 17 adults with type B NPD indicated that most specimens showed varying degrees of fibrosis, ranging from minimal to significant cirrhosis [36]. Research using the mouse model of NPD (ASM-KO mice) suggests that ASM deficiency leads to the overexpression of cathepsin B, which promotes liver fibrosis, aligning with these clinical observations [133]. Sphingomyelin storage has also been identified in several other cell types, including dermal fibroblasts, Macrophages, vascular endothelial cells, vascular smooth muscle cells, Perineurium, and Schwann cells [134].

Large, lipid-rich foam cells are found in various organs, including the liver, spleen, lymph nodes, adrenal cortex, lung airways, and bone marrow, in patients with types A and B Niemann-Pick Disease

(NPD) [134]. These cells exhibit a mulberry-like appearance due to the accumulation of lipid droplets that stain for phospholipids. Some of these cells are pigmented due to the presence of ceroids. Microscopic observations (electron microscopy) often reveal concentrically lamellated, myelin-like structures.

Niemann-Pick Disease Types A and B Diagnostic Procedures: The hallmark of both types A and B NPD is insufficient ASM (Acid Sphingomyelinase) activity. Therefore, measuring this enzyme activity in accessible cells, such as circulating leukocytes or cultured skin fibroblasts, is the standard confirmatory diagnostic method [135,136]. The presence of vacuolated cells in peripheral blood smears or bone marrow may indicate the disease, but this is not conclusive without enzymatic and/or genetic verification. Recently, dried blood spot enzymatic assays have also been developed to identify patients with types A and B NPD [137]. When considering the differential diagnosis for types A and B NPD, it's essential to include Gaucher disease and type C NPD. Reliable biochemical and/or genetic testing can easily differentiate these conditions in a reputable laboratory [138].

Niemann-Pick Disease Type C

Niemann-Pick C disease refers to disorders marked by distinctive abnormalities in the intracellular transport of endocytosed cholesterol, leading to the accumulation of unesterified cholesterol in lysosomes and late endosomes [139-146]. Significant progress has been made in identifying two genetic complementation groups [147,148] and in subsequently discovering the two associated genes [149,150]. NPC1 is implicated in 95% of families [148], including those with type D [151]. NPC2 is linked to rare families, with about 30 documented cases to date. While the exact functions of the NPC1 and NPC2 proteins remain unclear, current understanding suggests they operate in a coordinated manner and play a role in the postlysosomal/late endosomal transport of cholesterol and other substances [152-154]. Thus, Niemann-Pick diseases can be classified into two distinct groups: acid sphingomyelinase deficiencies (caused by SMPD1 mutations, which include types A, B, and intermediate forms) and Niemann-Pick type C, which involves disruptions in the trafficking of endocytosed cholesterol (due to NPC1 or NPC2 mutations). The classification of type D as a separate entity is no longer warranted. No patient should be categorized as having "Niemann-Pick disease" without specifying the subgroup—either acid sphingomyelinase deficiency or type C [155]. The clinical manifestations of Niemann-Pick C disease (NPC) are highly variable, with age of onset spanning from the perinatal period to well into adulthood, even into the seventh decade of life. Likewise, patient lifespans can vary significantly, from just a few days to over 60 years. However, most cases tend to result in death between the ages of 10 and 25 [155,156-159].

The clinical spectrum outlined below has been derived from multiple extensive surveys [157-164]. NPC is traditionally recognized as a neurovisceral disorder. Notably, visceral involvement (affecting the liver, spleen, and occasionally the lungs) and neurological or psychiatric symptoms occur at different stages and follow entirely independent trajectories. Except for a small group of patients who may die at birth or within the first six months due to hepatic or respiratory failure, and rare adult cases, all individuals will eventually experience a progressive and fatal neurological condition. When systemic disease is present, it always precedes the onset of neurological symptoms; however, approximately 15% of all patients, and nearly half of those with adult-onset, may have minimal or even absent systemic involvement at the time of diagnosis. In typical cases, the neurological disorder primarily manifests as cerebellar ataxia, dysarthria, dysphagia, and progressive dementia, with many patients exhibiting characteristic vertical supranuclear gaze palsy (VSGP) [165]. Additional common features include cataplexy, seizures, and dystonia, while psychiatric disturbances are prevalent among late-onset patients. Recognizing VSGP is crucial, yet this sign is frequently overlooked early on, as slow pursuit may persist despite impaired saccade velocity. Cataplexy, particularly when triggered by laughter, is another specific symptom [166,167]. Outside the perinatal period, systemic disease is generally mild and well-tolerated. It has been noted that splenomegaly can fluctuate and may diminish over time. Severe lung involvement has been documented in a few patients, but it is not common.

Recent reviews have categorized various clinical forms by age group [152,157], and this summary will follow suit. For each age category, except perinatal cases, it is important to differentiate patients who present with systemic involvement [162] from those who begin their neurological disease (even if they had earlier visceral symptoms). It is essential to recognize that the age of onset for systemic symptoms does not correlate with the onset of neurological disease (the latter can emerge years or even decades later). However, a connection exists between the age at which neurological symptoms begin and the overall progression of the disease as well as lifespan. Classifying patients by the age at onset of neurological symptoms [156,161,168], regardless of when the first symptom appeared, is highly beneficial for genetic counseling, natural history studies, and clinical practice. Except for the notably distinct severe early infantile neurological form, recent large-scale studies have shown an overlap between neurological forms, indicating a continuum [156].

Farber Disease

Sphingolipidoses represent a subgroup of lysosomal storage disorders marked by the abnormal accumulation of various phospholipids containing a sphingosine group. The clinical manifestations are varied, affecting neurovisceral, visceral, or purely neurological systems [169]. Farber disease is a rare condition characterized as a ceramide storage disease characterized by an inherited deficiency of lysosomal acid ceramidase (AC). This enzyme is a heterodimer composed of two subunits [170] derived from a common precursor processed in late endosomes and lysosomes [171,172]. AC plays a crucial role in catalyzing the breakdown of ceramide into sphingosine and a fatty acid within lysosomes, a process that requires Sap-D [173]. In-

terestingly, the enzyme can also catalyze the reverse reaction [174]. The most notable clinical symptoms include painful and progressive joint deformities, subcutaneous nodules known as lipogranulomas, and gradually worsening hoarseness. AC is vital for embryonic survival; studies with AC knockout mice indicate that they do not survive past the 2-cell stage and experience apoptotic death [175]. Recent research indicates that AC improves oocyte and embryo quality, thereby positively influencing outcomes of in vitro fertilization [176].

Farber disease is a rare, recessive lipid-metabolism disorder characterized by a deficiency of lysosomal acid ceramidase, leading to ceramide accumulation. This abnormal storage occurs within the lysosomes of various organs and tissues, leading to the progressive development of subcutaneous nodules (lipogranulomata) and granulomatous infiltrations in the joints, larynx, liver, spleen, lungs, heart, and central nervous system. Approximately 50% of documented cases of classic Farber disease manifest during early infancy, presenting a distinctive triad of symptoms: painful joint swelling, subcutaneous nodules (lipogranulomata), progressive hoarseness, difficulties with feeding and breathing, poor weight gain, and intermittent fever. Neurological symptoms are common among most patients; however, assessing neurological function can be challenging due to joint pain. Diagnosis is often suggested by the noticeable appearance of cachexia, flexion contractures, periarticular swelling, and subcutaneous nodules. Confirmation of the diagnosis can be achieved through [169]:

- Demonstrating reduced or absent acid ceramidase levels in leukocytes or cultured fibroblast samples
- Identifying two mutations in the ASAH gene
- The presence of perivascular aggregates of foamy histiocytes
- • Detection of "Farber bodies" (crescent-shaped structures within Schwann cells) via electron microscopy in biopsy samples
- Elevated ceramide levels in cultured cells and urine

Currently, the treatment for Farber disease is primarily palliative. Bone marrow transplantation (BMT) in two classic Farber patients showed improvements in somatic symptoms, though it did not significantly affect CNS involvement. BMT may be considered for patients with mild or absent neurological symptoms [169].

Respiratory Distress Syndrome (RDS)

The synthesis pathway for phosphatidylcholine (PC) and phosphatidylethanolamine (PE) produces dipalmitoyl-phosphatidylcholine (DPPC), essential for lung surfactant secreted by Type II pneumocytes. DPPC forms a fluid layer in the alveoli, reducing surface tension and preventing collapse. Surfactant is crucial for preventing respiratory distress syndrome (RDS) in preterm infants, linked to neonatal mortality. The L/S ratio in amniotic fluid assesses fetal lung maturity; a ratio of 2 or higher indicates readiness around 32 weeks. Glucocorticoids are given to mothers to accelerate lung maturation, and surfactants may be administered to treat RDS in infants and adults [177,178]. According to [179], lung surfactant consists of a blend of phospholipids (PLs) and surfactant-associated proteins [180,181]. Pulmonary surfactant is a sophisticated blend of phospholipids (80%), proteins (10%), and neutral lipids (10%). It is produced, secreted, and recycled by alveolar type II epithelial cells (AT-II), primarily functioning to lower alveolar surface tension at the air–liquid interface, thereby ensuring mechanical stability for gas exchange [182]. The components of surfactant also play a role in innate immunity and are crucial for the host's defense mechanisms against infections [182,183]. Phospholipids make up the majority of the surfactant composition, with phosphatidylcholine (PC) and phosphatidylglycerol (PG) being the most prevalent. Other minor phospholipids, such as phosphatidylinositol (PI), phosphatidylethanolamine (PE), phosphatidylserine (PS), sphingomyelin (SM), and lysophosphatidylcholine (LPC), account for the remaining phospholipid distribution [184]. The key surface-active molecule is disaturated dipalmitoyl-PC (DPPC), which constitutes about 50% of PC [185]. Maintaining low surface tension at the alveolar surface is critical to prevent pressure gradients across the alveolar lining and thus avoid premature airway collapse. Under dynamic compression, DPPC can decrease surface tension to nearly zero values in vitro [186].

There are four surfactant proteins: SP-A, SP-B, SP-C, and SP-D. SP-B and SP-C are hydrophobic proteins that assist in the adsorption of the surfactant film, while SP-A and SP-D are hydrophilic and contribute to innate immunity. A hereditary deficiency in SP-B can result in severe respiratory failure, whereas a deficiency in SP-C can lead to acute and chronic lung diseases [187,188]. Animal studies of SP-A deficiency have shown increased vulnerability to respiratory tract infections, whereas SP-D knockout mice exhibit heightened alveolar macrophage infiltration, AT-II cell hyperplasia, and excessive phospholipid production, which can result in emphysema [189]. Primary surfactant deficiency, often due to lung immaturity, is a hallmark of neonatal respiratory distress syndrome (nRDS), and exogenous surfactant replacement is associated with improved clinical outcomes [190]. Comprehensive reviews provide detailed insights into surfactant composition, metabolism, and function [184-189,191]. Respiratory distress syndrome (RDS) [192], also referred to as hyaline membrane disease (HMD), is a primary cause of neonatal respiratory distress, particularly in preterm infants [193]. While RDS predominantly affects infants born before 35 weeks of gestational age, older infants with delayed lung maturation from various causes may also be impacted [194]. In recent years, the prognosis for RDS has improved significantly thanks to the increased administration of antenatal steroids to enhance pulmonary maturity, early postnatal surfactant therapy to address surfactant deficiency, and advanced ventilation techniques to reduce lung damage in premature infants [195]. Infants with RDS typically exhibit symptoms such as tachypnea, cyanosis, grunting, subcostal and intercostal retractions, and nasal flaring.

They may also experience oliguria accompanied by mild generalized edema. The demand for oxygen can escalate quickly, often exceeding the levels seen in infants with transient tachypnea of the newborn (TTN) [196].

The severity of respiratory distress is evaluated using the Silverman-Anderson Score and Downes' Score. The Silverman-Anderson Retraction Score is particularly suited for preterm infants with HMD, whereas the Downes' Score offers a more comprehensive assessment applicable across different gestational ages and conditions. Scoring should be conducted at half-hour intervals, and a chart should be maintained to track progress. An increasing requirement for FiO2 to maintain oxygen saturation levels of 90-92% in preterm infants and 94-96% in term infants is a sensitive indicator of the severity and progression of distress [197-199]. Respiratory distress syndrome (RDS) in premature infants continues to be the primary life-threatening neonatal condition, affecting 1 to 2% of newborns, despite advancements in antenatal steroid and surfactant therapies. RDS is mainly linked to a developmental deficiency in the synthesis, intracellular processing, and secretion of pulmonary surfactant, which is essential for lowering surface tension at the air–liquid interface of the distal conducting airways and alveoli [200,201].

Cancer and its Relation to Phospholipids

According to [55], Numerous studies show that phospholipids (PLs) can inhibit tumors and metastasis. Cancer cell membranes differ from those of normal progenitor cells, losing adhesive qualities that allow them to detach and migrate, leading to metastasis. In breast and prostate cancers, higher concentrations of lipid rafts rich in cholesterol make these cells more sensitive to apoptosis. Thus, altering lipid raft composition and density could affect cancer cell viability and metastasis [202,203]. Several studies have examined phospholipids (PLs) for their potential to inhibit cancer growth. An in vitro study showed that phosphatidylcholine (PC) from soy and egg yolk restricted hepatic cancer cell growth in a dose-dependent manner. Rat studies demonstrated that PC and menaquinone-4 (vitamin K2) supplementation reduced nodule formation and liver lesions compared to controls. While the combined effects of PC and menaquinone-4 were stronger, PC alone also significantly reduced cancer cell numbers by promoting apoptosis via death ligands [204,205]. Co-administering non-steroidal anti-inflammatory drugs (NSAIDs) with phospholipids (PLs) not only reduces gastrointestinal side effects and enhances pain relief but also inhibits cancer cell growth. Cancer patients often experience GI issues from NSAIDs, so PL-bound formulations could help minimize these risks while providing anticancer benefits. For instance, research found that combining soybean-derived phosphatidylcholine with NSAIDs, especially Ibuprofen-PC, was more effective at inhibiting DNA synthesis in colon cancer cells (SW-480) than NSAIDs alone. This effect is independent of COX-2 inhibition and is mediated by the suppression of phosphoinositol-specific phospholipase C, leading to reduced cancer cell growth [206].

Marine phospholipids from squid and starfish, rich in n-3 fatty acids, have been shown to inhibit the growth of chemically induced colon cancer cells in vitro. Rats fed phosphatidylcholine (PC) from these sources exhibited higher apoptosis rates, due to increased lipid peroxidation that affected cellular membranes. Combining DHA or EPA (EPA is best for reducing inflammation and protecting heart health, while DHA is essential for brain function, memory, and eye health) with sodium butyrate (NaBt) enhanced these effects. Additionally, the combination of PC with starfish phosphatidylserine (PS) inhibited tumor growth and promoted cell differentiation in vivo, especially when NaBt was included. While the exact mechanism by which n-3 fatty acids inhibit tumor growth is not fully understood, phospholipids appear to enhance their effects, suggesting their potential as chemotherapy agents for colon cancer [207-209]. A mouse model showed that dietary sphingomyelin significantly reduces the incidence of colon cancer. Sphingolipid metabolites, such as sphingosine, sphingosine-1-phosphate, and ceramide, may induce apoptosis in human adenoma cells, thereby contributing to this protective effect [210,211]. Recent studies showed that empty liposomes made of hydrogenated PC and cholesterol have a strong antimetastatic effect in pancreatic tumor models, without affecting primary tumor growth. The action appears linked to hydrogenated lysoPC, a degradation product of PC generated by phospholipase A2 in aggressive cancer cells. This compound is absorbed by tumor cells, increasing the levels of hydrogenated fatty acids in membranes and reducing adhesion to endothelial cells and platelets, both of which are crucial for metastasis. In a model with B16.F10 mouse melanoma cells, hydrogenated lysoPC pretreatment cut metastatic lesions by over 50% [212-216].

Summary

This study summary delves into the intricate world of phospholipid metabolism, highlighting its critical roles in health and disease management. Phospholipids, including glycerophospholipids, cardiolipin, plasmalogens, the platelet-activating factor, and sphingophospholipids like sphingomyelin, form the structural basis of cellular membranes and participate in various biological processes. The study explores the synthesis and degradation pathways of these compounds, emphasizing the importance of phospholipid metabolism in mitochondria and the brain. Key metabolic processes include the synthesis of phosphatidic acid (PA), phosphatidylethanolamine (PE), phosphatidylcholine (PC), phosphatidylserine (PS), phosphatidylinositol (PI), and cardiolipin (CL), as well as the breakdown of phosphoglycerides and sphingomyelin. Disruptions in phospholipid metabolism can lead to serious disorders, such as Niemann-Pick disease (Types A, B, and C), characterized by abnormal lipid storage and associated with neurological and systemic symptoms. Diagnostic procedures for these conditions are crucial for early detection and management. Other related disorders include Farber disease and Respiratory Distress Syndrome (RDS), underscoring the diverse impact of phospholipid metabolism on human health. Overall, this research underscores the importance of understanding phospholipid metabo-

lism not only for its fundamental biological significance but also for its potential to develop therapeutic strategies for related disorders. Moreover, the research emphasizes the role of diet and lifestyle in modulating phospholipid metabolism. Nutritional interventions, such as omega-3 fatty acid supplementation, have shown potential in enhancing membrane fluidity and function, thereby supporting overall cellular health. These findings suggest that personalized dietary recommendations could become an integral part of managing conditions associated with phospholipid dysregulation.

Conclusion

In conclusion, this comprehensive exploration of phospholipid metabolism not only provides valuable insights into its complex biological roles but also opens the door to innovative treatments. Continued research in this field is essential to fully unravel the intricacies of phospholipid functions and to translate these findings into effective clinical applications. Future studies should focus on identifying the specific mechanisms by which phospholipids influence cellular processes and contribute to various diseases. By employing cutting-edge technologies such as CRISPR gene editing, high-resolution imaging, and advanced computational models, scientists can gain a deeper understanding of these molecules. Moreover, interdisciplinary collaborations between biochemists, pharmacologists, and clinicians will be crucial in bridging the gap between laboratory discoveries and patient care. As we advance in our knowledge, the potential for developing targeted therapies that manipulate phospholipid pathways becomes increasingly promising, offering hope for treating a range of conditions from inflammatory diseases to neurological disorders.

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