Repairing the Damaged Plasma Membrane of the Cell and the Membrane-Bound Organelles

Introduction to the Plasma Membrane

The human cell is enveloped in a thin, pliable, elastic structure called the cell membrane or the plasma membrane and is only 7.5 to 10 nanometers thick. It is composed almost entirely of proteins and lipids. There are approximately 5×10^6 lipid molecules in a 1 μm × 1 μm area of lipid bilayer, or about 10^9 lipid molecules in the plasma membrane of a human cell.

The main purpose of the plasma membrane is to separate the inner contents of the cell from its exterior environment, much like the outer layer of the skin separates the body from its environment. In addition to providing a protective barrier around the cell, the plasma membrane regulates which materials pass in and out of the cell.

The plasma membrane envelops the human cell and is also found inside the cell in various intracellular membranes, called organelles. The structure and composition of the plasma membrane are the same for the plasma membrane surrounding the cell as well as for the various intracellular membranes. The only difference among them is the proportions which vary from one type of membrane to the other.

The formation of plasma membranes is based on the structural organization of bilayers of lipids with associated proteins. The lipid content of the plasma membrane ranges from 40 to 80% (of dried weight), which is significant. The two main lipids that predominate quantitatively in the lipid fraction of the plasma membrane are:

- phosphatidylcholine
- phosphatidylethanolamine

The lipid molecules in plasma membranes are amphipathic (or amphiphilic)—that is, they have a hydrophilic ("water-loving") or polar end and a hydrophobic ("water-fearing") or nonpolar end.

Functions of the Plasma Membrane

In addition to the plasma membrane providing a protective barrier around the cell and the intracellular organelles, it has many essential functions:

- **transporting nutrients into the cell**
- **transporting metabolic wastes out of the cell**
- **preventing unwanted materials in the extracellular milieu from entering the cell**
- **preventing loss of needed metabolites**
- **maintaining the proper ionic composition, pH (≈7.2), and osmotic pressure of the cytosol**
- **provides cell to cell communication**
- **provides hormone sensitivity and utilization**
- **support the many enzymatic reactions that occur along their surfaces**

These various functions are carried out by specific transport proteins which restrict the passage of certain small molecules.

The plasma membrane actually has a measurable membrane differential which is the voltage across the plasma membrane. It has been determined that healthy children has a membrane electrical potential up to 90 millivolts, whereas a healthy adult can have up to 70 millivolts. The membrane electrical potential can decline to around 40 millivolts in an individual with a chronic disease and to as low as 15 millivolts in an individual with advanced cancer.

The Lipids Comprising the Plasma Membrane of the Human Cell

The plasma membrane of the human cell and certain intracellular organelles inside the cell are composed of three categories of lipids:

- **Phospholipids (Glycerophospholipids or Phospholycolipids or Phosphoglycerides and Phosphosphingolipids)**
- **Glycolipids**
- **Cholesterol**

Of the three categories of lipids, the most abundant membrane lipids are the phospholipids.

The functions of the plasma membrane determines the lipid compositions of the inner and outer monolayers of the cell plasma membrane. Different mixtures of lipids are found in the membranes of cells of different types. The two sides of the plasma membrane of the human cell reflect this difference:

<u>Outer Layer (the side on the exterior of the cell)</u>

Consists mainly of phosphatidylcholine and sphingomyelin

<u>Inner Layer (the side on the interior of the cell)</u>

Consists mainly of phosphatidylethanolamine and phosphatidylserine and phosphatidylinositol.

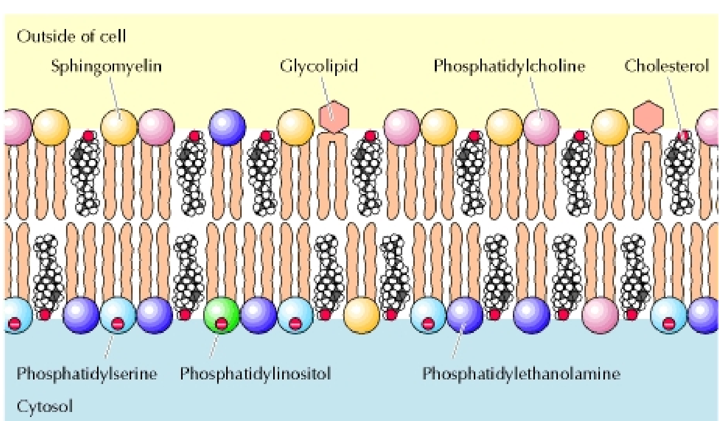

Figure 1. Lipid components of the plasma membrane

The outer leaflet consists predominantly of phosphatidylcholine, sphingomyelin, and glycolipids, whereas the inner leaflet contains phosphatidylethanolamine, phosphatidylserine, and phosphatidylinositol. Cholesterol is distributed in both leaflets. The net negative charge of the head groups of phosphatidylserine and phosphatidylinositol is indicated. (Source: The Cell: A Molecular Approach. 2nd edition., The Molecular Composition of Cells)

The mitochondria, an intracellular organelle, contains two membranes and consists primarily of phosphatidylcholine, phosphatidylethanolamine, phosphatidylinositol, phosphatidylserine, and phosphatidic acid. These phospholipids are asymmetrically distributed between the two halves of the membrane bilayer of the mitochondria. The inner mitochondrial membrane contains a specific phospholipid called phosphatidylglycerol and is the precursor for cardiolipin. Cardiolipin is predominantly found in the inner mitochondrial membrane.

Lipids constitute approximately 50% of the mass of most cell membranes, although this proportion varies depending on the type of membrane. Plasma membranes, for example, are approximately 50% lipid and 50% protein.

The lipid composition of different cell membranes also varies:

	Plasma membrane			
Lipid	**E. coli**	**Erythrocyte**	**Rough endoplasmic reticulum**	**Outer mitochondrial membranes**
Phosphatidylcholine	0	17	55	50
Phosphatidylserine	0	6	3	2
Phosphatidylethanolamine	80	16	16	23
Sphingomyelin	0	17	3	5
Glycolipids	0	2	0	0
Cholesterol	0	45	6	<5

Source: Data from P. L. Yeagle, 1993. The Membranes of Cells, 2nd ed. San Diego, CA: Academic Press.

Membrane compositions are indicated as the mole percentages of major lipid constituents.

Another source lists the lipid compositions of different cell membranes:

	PERCENTAGE OF TOTAL LIPID BY WEIGHT					
LIPID	**LIVER CELL PLASMA MEMBRANE**	**RED BLOOD CELL PLASMA MEMBRANE**	**MYELIN**	**MITOCHONDRION (INNER AND OUTER MEMBRANES)**	**ENDOPLASMIC RETICULUM**	***E. COLI*BACTERIU**
Cholesterol	17	23	22	3	6	0
Phosphatidylethanolamine	7	18	15	25	17	70
Phosphatidylserine	4	7	9	2	5	trace
Phosphatidylcholine	24	17	10	39	40	0
Sphingomyelin	19	18	8	0	5	0
Glycolipids	7	3	28	trace	trace	0
Others	22	13	8	21	27	30

(Source: Molecular Biology of the Cell. 4th edition., The Lipid Bilayer; Alberts B, Johnson A, Lewis J, et al. New York: Garland Science; 2002.)

Phospholipids that Compose the Plasma Membrane

Plasma membranes contain 4 major and 1 minor phospholipids:

- **Major phospholipids**
  - phosphatidylcholine
  - phosphatidylethanolamine
  - phosphatidylserine
  - sphingomyelin
- **Minor phospholipids**
  - phosphatidylinositol

These major phospholipids together account for more than 50% of the lipid in most membranes. Phosphotidylinositol is present in smaller quantities in the plasma membrane but provide important functions like cell signaling.

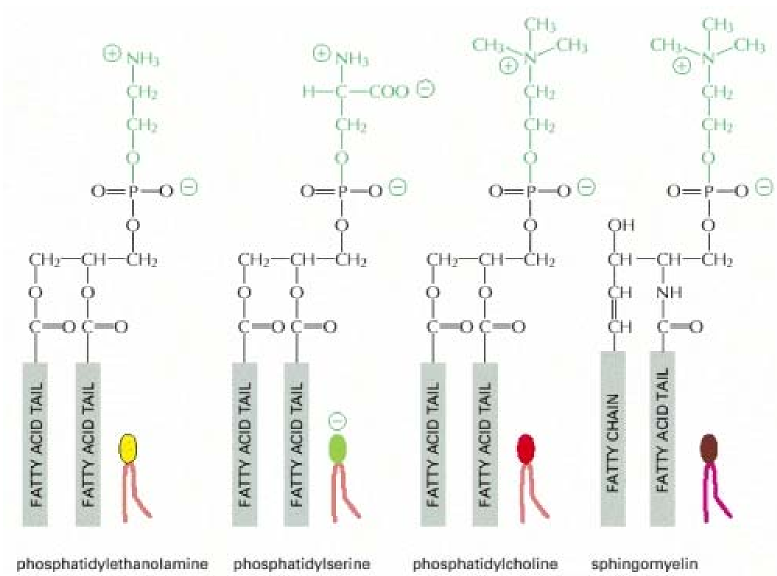

Figure 2. Four major phospholipids in mammalian plasma membranes

Note that different head groups are represented by different colors. All the lipid molecules shown are derived from glycerol except for sphingomyelin, which is derived from serine. (Source: Molecular Biology of the Cell. 4th edition., The Lipid Bilayer; Alberts B, Johnson A, Lewis J, et al. New York: Garland Science; 2002.)

Phosphatidylcholine

Phosphatidylcholine is a vital substance found in every cell of the human body.

Phosphatidylethanolamine

Phosphatidylethanolamines are found in all living cells, composing 25% of all phospholipids. In humans, they are found particularly in nervous tissue such as the white matter of brain, nerves, neural tissue, and in spinal cord, where they make up 45% of all phospholipids. 1

Phosphatidylserine

Phosphatidylserine is a component of the cell membrane. It plays a key role in cell cycle signaling, specifically in relationship to apoptosis.

Sphingomyelin

Sphingomyelin is a type of sphingolipid found in animal cell membranes, especially in the membranous myelin sheath that surrounds nerve cell axons. It usually consists of phosphocholine and ceramide, or a phosphoethanolamine head group; therefore, sphingomyelins can also be classified as sphingophospholipids.

Phosphatidylinositol (minor phospholipid)

Phosphatidylinositol forms a minor component on the cytosolic side of eukaryotic cell membranes.

Phosphorylated forms of phosphatidylinositol are called phosphoinositides and play important roles in lipid signaling, cell signaling and membrane trafficking.

Phosphatidylglycerols (Cardiolipin)

Phosphatidic acid reacts with CTP, producing CDP-diacylglycerol, with loss of pyrophosphate. Glycerol-3-phosphate reacts with CDP-diacylglycerol to form phosphatidylglycerol phosphate, while CMP is released. The phosphate group is hydrolysed forming phosphatidylglycerol.

Two phosphatidylglycerols form cardiolipin, the constituent molecule of the mitochondrial inner membrane. 2

Phosphatidic acid

Phosphatidic acids are the acid forms of phosphatidates, a part of common phospholipids, major constituents of cell membranes. phosphatidic acids are the simplest diacyl-glycerophospholipids.

The role of phosphatidic acid in the cell can be divided into three categories:

- Phosphatidic acid is the precursor for the biosynthesis of many other lipids
- The physical properties of phosphatidic acid influence membrane curvature
- Phosphatidic acid acts as a signaling lipid, recruiting cytosolic proteins to appropriate membranes

The conversion of phosphatidic acid into diacylglycerol (DAG) by LPPs is the commitment step for the production of phosphatidylcholine, phosphatidylethanolamine and phosphatidylserine. In addition, DAG is also converted into CDP-DAG, which is a precursor for phosphatidylglycerol, phosphatidylinositol and phosphoinositides.

Phosphatidic acid is essential for lipid synthesis and cell survival, yet, under normal conditions, is maintained at very low levels in the cell.

Glycolipids

The role of glycolipids is to maintain stability of the membrane and to facilitate cellular recognition. 3

Carbohydrates are found on the outer surface of all eukaryotic cell membranes. They extend from the phospholipid bilayer into the aqueous environment outside the cell where it acts as a recognition site for specific chemicals as well as helping to maintain the stability of the membrane and attaching cells to one another to form tissues.

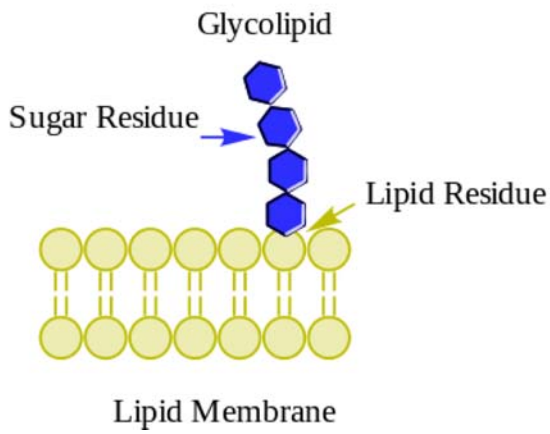

Figure 3. Glycolipid attached to lipid residue

The lipid complex is most often composed of either a glycerol or sphingosine backbone, which gives rise to the two main categories of glycolipids:

- glyceroglycolipids
- sphingolipids

The heads of glycolipids contain a sphingosine with one or several sugar units attached to it. The hydrophobic chains belong either to:

- **two fatty acids – in the case of the phosphoglycerides, or**
- **one fatty acid and the hydrocarbon tail of sphingosine – in the case of sphingomyelin and the glycolipids**

Glycolipids occur in all animal cell plasma membranes, where they generally constitute about 5% of the lipid molecules in the outer monolayer. They are also found in some intracellular membranes.

The most complex of the glycolipids, the gangliosides, contain oligosaccharides with one or more sialic acid residues, which give gangliosides a net negative charge. More than 40 different gangliosides have been identified. They are most abundant in the plasma membrane of nerve cells, where gangliosides constitute 5–10% of the total lipid mass; they are also found in much smaller quantities in other cell types.

Cholesterol

Cholesterol is a sterol, and is biosynthesized by all animal cells, and is an essential structural component of all animal cell membranes; essential to maintain both membrane structural integrity and fluidity. Cholesterol enables animal cells to dispense with a cell wall (to protect membrane integrity and cell viability), thereby allowing animal cells to change shape and animals to move (unlike bacteria and plant cells, which are restricted by their cell walls).

Cell membranes require high levels of cholesterol – typically an average of 20% cholesterol in the whole membrane, increasing locally in raft areas up to 50% cholesterol. 4

Within the cell membrane, cholesterol also functions in intracellular transport, cell signaling and nerve conduction. Recent studies show that cholesterol is also implicated in cell signaling processes, assisting in the formation of lipid rafts in the plasma membrane, which brings receptor proteins in close proximity with high concentrations of second messenger molecules. 5

In multiple layers, cholesterol and phospholipids, both electrical insulators, can facilitate speed of transmission of electrical impulses along nerve tissue. For many neuron fibers, a myelin sheath, rich in cholesterol since it is derived from compacted layers of Schwann cell membrane, provides insulation for more efficient conduction of impulses. 6

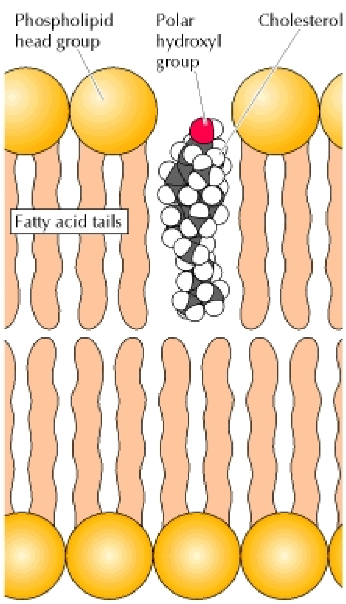

Figure 4. Insertion of cholesterol in a membrane

Cholesterol inserts into the membrane with its polar hydroxyl group close to the polar head groups of the phospholipids.

Organelles of the Human Cell

An organelle is a specialized sub-unit within a cell that serves a specific function. Most organelles of the cell are covered by membranes composed primarily of lipids and proteins.

Organelles either have a single-membrane compartment or a double-membrane compartment.

There are 10 organelles in the human cell that have either a single or double membrane. There are 3 organelles with double membranes and 7 organelles with single membranes. The organelles of the cell with membranes are as follows:

Organelle	Function	Membrane Structure
Autophagosome	vesicle that sequesters cytoplasmic material and organelles for degradation	Double membrane
Endoplasmic reticulum	translation and folding of new proteins (rough endoplasmic	Single membrane

	reticulum), expression of lipids (smooth endoplasmic reticulum)	
Golgi apparatus	sorting, packaging, processing and modification of proteins	Single membrane
Lysosomes	breakdown of large molecules (e.g., proteins + polysaccharides)	Single membrane
Melanosome	pigment storage	Single membrane
Mitochondria	energy production from the oxidation of glucose substances and the release of adenosine triphosphate	Double membrane
Nucleus	DNA maintenance, controls all activities of the cell, RNA transcription	Double membrane
Peroxisome	breakdown of metabolic hydrogen peroxide	Single membrane
Vacoule	storage, transportation, helps maintain homeostasis	Single membrane
Vesicle	material transport	Single membrane

Organelles with double membranes are often critical to the function of the cell, each serveing a different purpose. There are 3 organelles that have double membranes:

- **Mitochondria**
- **Nucleus**
- **Autophagosome**

Mitochondria

A mitochondrion (singular for mitochondria) contains outer and inner membranes composed of phospholipid bilayers and proteins. Due to the double membrane structure of the mitochondrion, there are five distinct parts to a mitochondrion. They are:

- **the outer mitochondrial membrane**
- **the intermembrane space (the space between the outer and inner membranes)**
- **the inner mitochondrial membrane**
- **the cristae space (formed by infoldings of the inner membrane)**
- **the matrix (space within the inner membrane)**

The mitochondrial membrane contains the major classes of phospholipids found in all cell membranes, including phosphatidylcholine, phosphatidylethanolamine, phosphatidylinositol, phosphatidylserine, and phosphatidic acid, as well as phosphatidylglycerol, the precursor for cardiolipin; which is predominantly located in the mitochondria.

The outer mitochondrial membrane, which encloses the entire organelle, has a protein-to-phospholipid ratio similar to that of the human plasma membrane (about 1:1 by weight). It contains large numbers of integral membrane proteins called porins.

In the inner mitochondrial membrane, the protein-to-lipid ratio is 80:20, in contrast to the outer membrane, which is 50:50. 7

The inner membrane is rich in cardiolipin. Cardiolipin contains four fatty acids rather than two, and may help to make the inner membrane impermeable. Unlike the outer membrane, the inner membrane doesn't contain porins, and is highly impermeable to all molecules.

Nuclear Membrane

The nuclear envelope, otherwise known as nuclear membrane, consists of two cellular membranes, an inner and an outer membrane, arranged parallel to one another and separated by 10 to 50 nanometres (nm). The nuclear envelope completely encloses the nucleus and separates the cell's genetic material from the surrounding cytoplasm, serving as a barrier to prevent macromolecules from diffusing freely between the nucleoplasm and the cytoplasm. 8 The outer nuclear membrane is continuous with the membrane of the rough endoplasmic reticulum.

Autophagosome

An autophagosome is a spherical structure with double layer membranes. It is the key structure in macro autophagy, the intracellular degradation system for cytoplasmic contents (e.g., abnormal intracellular proteins, excess or damaged organelles) and also for invading microorganisms.

After formation, autophagosomes deliver cytoplasmic components to the lysosomes. The outer membrane of an autophagosome fuses with a lysosome to form an autolysosome. The lysosome's hydrolases degrade the autophagosome-delivered contents and its inner membrane. 9

Damage and Degradation to the Cell Membrane

When cell membranes are intact their receptor surface is able to perform all necessary functions. Communication between cells, and even within the cell components, flows easily. Once the membrane is damaged this communication is disrupted, and the cell cannot function properly, due to the failure of cellular signaling.

There are a number ways in which cell membranes can be damaged, which eventually leads to pathology and illness. This is true of both the cell and its outer membrane barrier or cell membrane, and the membrane structures inside the cell. Various factors can contribute to damage to the cell membrane, such as:

- **Acetaldehyde**
- **Aging**
- **Alcohol**
- **Excessive Saturated Fatty Acids**
- **Lipid peroxidation**
- **Oxidization of cell membrane**
- **Recreational Drugs**
- **Smoking**
- **Toxin exposure (toxins stored in the lipid environment)**
- **Trans-fatty acids 10 11**

Aging causes detrimental changes in membrane phospholipid composition. Phosphatidylcholine is one of the main types of phospholipids in the cell membrane, and its concentration within the cell membrane decreases with age, whereas sphingomyelin and cholesterol both increase with age.

The changes in the relative amounts of phosphatidylcholine and sphingomyelin are especially great in tissues. Plasma membranes associated with the aorta and arterial wall show a 6-fold decrease in phosphatidylcholine and sphingomyelin ratio with aging. Sphingomyelin also increases in several diseases, including atherosclerosis. The sphingomyelin content can be as high as 70-80% of the total phospholipids in advanced aortic lesion. 12

Decreased cell membrane fluidity and decomposition of cell membrane integrity, as well as break down of cell membrane repair mechanisms, are associated with various disorders, including liver disease, atherosclerosis, several cancers and ultimately cell death.

Fatty acids within the cell membrane degrade when dietary fats are either oxidized (lipid peroxides can form within the body as well) or contain trans fatty acids.

Plasma membranes are one of the preferential targets of reactive oxygen species which cause lipid peroxidation. This process modifies membrane properties such as fluidity, a very important physical feature known to modulate membrane protein localization and function. 13

Numerous reports have established that lipid peroxidation contributes to cell injury by altering the basic physical properties and structural organization of membrane components. Oxidative modification of polyunsaturated phospholipids has been shown, in particular, to alter the intermolecular packing, thermodynamic, and phase parameters of the membrane bilayer. 14 15

Damage to the Double Membrane Structure of the Mitochondria

Damage to mitochondrial components, especially the delicate inner mitochondrial membrane, leads to the release of toxic proteins, including caspases and other enzymes. These proteins are normally confined in the mitochondria, but once released these proteins go through several steps that trigger the formation of a potent inflammatory molecular complex called an inflammasome.

New evidence has placed inflammasomes at the center stage of complex diseases like metabolic syndrome and cancer, as well as the regulation of the microbial ecology in the intestine and the production of ATP. 16

Once the inner membrane of the mitochondria is damaged, its core ability to produce energy in the form of ATP and to maintain optimal mitochondrial nutrient uptake and utilization necessary for ATP production are impaired.

The inner mitochondrial membrane is also one of the most sensitive membranes of the cell to oxidative damage. This is because of its unique membrane structure and the presence of a very oxidation-sensitive phospholipid, cardiolipin. Cardiolipin is functionally required for the electron transport system.

When mitochondrial cardiolipin and to a lesser degree other phosphatidyl phospholipids are damaged by oxidation, the chemical/electrical potential across the inner mitochondrial membrane is altered due to an increasingly “leaky” membrane that allows protons and ions to move across the membrane. This occurs because the oxidized membrane phospholipids no longer form a tight ionic/electrical “seal” or barrier.

Significant oxidative damage to mitochondrial membranes represents the point-of-no-return of programmed cell death pathways that culminate in apoptosis or regulated cell death leading to necrosis. 17

Repairing the Damaged Cell Membrane with Lipid Replacement Therapy®

The good news is that damaged lipids can be replaced. In fact, a young healthy cell usually replaces damaged lipids in its membranes. However, due to aging, eating a poor diet, exposure to environmental toxins, getting infections and certain illnesses, it becomes necessary to proactively replace the damaged lipids with new lipids.

This can be done using Lipid Replacement Therapy (LRT®), which provides for the consumption of lipids that are the same as found in the cell membrane and organelle membranes.

A product developed and manufactured by Nutritional Therapeutics Inc., called NTFactor®, is intended to reverse the damage done to our cells and mitochondria by oxidative stress through the process of Lipid Replacement Therapy®.

The NTFactor® formula is a unique combination that allows the healthy phospholipids to stay intact during transport through the body.

NT Factor Lipids® is based on U.S. Patent No. 8,877,239. The lipid blend of NTFactor® includes:

- **Phosphatidic acid (PA)**
- **Phosphatidyl-choline (PC)**
- **Phosphatidyl-ethanolamine (PE)**
- **Phosphatidyl-glycerol(PG) – (precursor for cardiolipin (CL))**
- **Phosphatidyl-inositol (PI)**
- **Phosphatidyl-serine (PS)**
- **Digalactosyldiacylglyceride (DGDG)**
- **Monoglactosyldiacylglyceride (MGDG)**

NTFactor® uses a form of a stable oral supplement that emulates the amount and composition of the mitochondrial lipids assures that inappropriate oxidative membrane damage is prevented, damaged membrane phospholipids are replaced and mitochondrial membrane permeability is maintained in the optimal range.

Obtaining Phospholycolipids through Diet

Phospholycolipids can be obtained generally in the diet from meat, egg yolks, fish, turkey, chicken and beef. Organ meats and egg yolks are among the best food sources of phosphoglycolipids, however, one would have to consume large portions of these foods at every meal to obtain the benefit of lipid replacement, which is unlikely and unhealthy.

The various lipids can be found in the following foods:

Phosphatidylcholine

Phosphatidylcholine can be obtained from egg yolk or soybeans. Phosphatidylcholine is a major component of egg, soy and sunflower lecithin.

Lecithin's are mostly phospholipids, composed of phosphoric acid with choline, glycerol or other fatty acids usually glycolipids or triglyceride. Glycerophospholipids in lecithin include phosphatidylcholine, phosphatidylethanolamine, phosphatidylinositol, phosphatidylserine, and phosphatidic acid.

Phosphatidylethanolamine

Phosphatidylethanolamine is primarily found in lecithin.

Phosphatidylinositol

Phosphatidylinositol can be found in lecithin.

Phosphatidylserine

Phosphatidylserine can be found in meat and fish. Only small amounts of phosphatidylserine can be found in dairy products or in vegetables, with the exception of white beans and soy lecithin.

Phosphatidylserine (PS) content in different foods

Food	PS Content in mg/100 g
Bovine brain	713
Atlantic mackerel	480
Chicken heart	414
Atlantic herring	360
Eel	335
Offal (average value)	305
Pig‵s spleen	239
Pig's kidney	218
Tuna	194
Chicken leg, with skin, without bone	134
Chicken liver	123
White beans	107

Soft-shell clam	87
Chicken breast, with skin	85
Mullet	76
Veal	72
Beef	69
Pork	57
Pig’s liver	50
Turkey leg, without skin or bone	50
Turkey breast without skin	45
Crayfish	40
Cuttlefish	31
Atlantic cod	28
Anchovy	25
Whole grain barley	20
European hake	17
European pilchard (sardine)	16
Trout	14
Rice (unpolished)	3
Carrot	2
Ewe‘s Milk	2
Cow‘s Milk (whole, 3.5%	1

fat)	
Potato	1

(Source: Souci SW, Fachmann E, Kraut H (2008). Food Composition and Nutrition Tables. Medpharm Scientific Publishers Stuttgart)

Sphingomyelin

Sphingomyelin can be obtained from eggs or bovine brain.

Cholesterol

All animal-based foods contain cholesterol in varying amounts. Cholesterol can be obtained from cheese, egg yolks, beef, pork, poultry, fish, and shrimp. Cholesterol is not found in plant-based foods.

Resources:

Healthy Aging with NT Factor®

Nutricology – NTFACTOR® ADVANCED PHYSICIANS FORMULA

Nutricology – NTFACTOR® ENERGYLIPIDS CHEWABLES

Nutricology – NTFACTOR® COQ10 CHOCOLATE CHEWABLES

Nutricology – NTFACTOR® ENERGYLIPIDS POWDER

Nutricology – NTFACTOR® HEALTHY AGING

Nutrasal – PhosChol®

Life Extension – HepatoPro (Polyunsaturated Phosphatidylcholine)

Bronson – Lecithin Granules

Swanson Health Products – Egg Yolk Lecithin

Premier Research Labs – Premier Lecithin Granules

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