"Phospholipid, Glycosphingolipid, and Eicosanoid Metabolism"

I. Phospholipid Overview

1. Membrane Lipid Composition

- Membrane lipids are composed of four major types:
    - Phospholipids
    - Sphingolipids
    - Glycolipids
    - Cholesterol

(Only the polar membrane lipids are discussed here)

2. Phospholipid Structure

- Phospholipids are ionic compounds.
- Composed of an alcohol attached by a phosphodiester bond to:
    - Either diacylglycerol (DAG)
    - Or sphingosine

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3. Amphipathic Nature of Phospholipids

- Like fatty acids (FA), phospholipids are amphipathic:
    - Hydrophilic head:
        - Composed of phosphate group plus attached alcohol.
        - Examples of alcohols:
            - Serine
            - Ethanolamine
            - Choline
    - Hydrophobic tail:
        - Composed of fatty acid (FA) or FA-derived hydrocarbons.

4. Role in Cell Membranes

- Phospholipids are the predominant lipids of cell membranes.
- In membranes:
    - The hydrophobic portion of the phospholipid:
        - Associates with nonpolar portions of other membrane constituents:

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        - Glycolipids
        - Proteins
        - Cholesterol

    - The hydrophilic (polar) head:
        - Extends outward
        - Interacts with intracellular or extracellular aqueous environment

5. Functional Roles of Membrane Phospholipids

- Function as a reservoir for intracellular messengers.

- For some proteins, phospholipids serve as anchors to cell membranes.

6. Functions of Nonmembrane Phospholipids

- Serve additional functions in the body:

    - As components of lung surfactant
    - As essential components of bile, where:
        - Their detergent properties aid in cholesterol solubilization

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II. Phospholipid Structure

Two Major Classes of Phospholipids

- Based on backbone structure:

    a. Glycerol-based (from glucose)
    b. Sphingosine-based (from serine and palmitate)

- Both classes:
    - Are structural components of membranes
    - Play a role in the generation of lipid-signaling molecules

A. Glycerophospholipids

Definition and Importance

- Phospholipids that contain glycerol are called:
    - Glycerophospholipids or Phosphoglycerides
- They are:
    - The major class of phospholipids
    - The predominant lipids in membranes

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Phosphatidic Acid (PA) as Core Structure

- All glycerophospholipids contain (or are derivatives of) phosphatidic acid (PA)
- PA structure:
    - Diacylglycerol (DAG) with a phosphate group on carbon 3

Backbone Specificity

- Despite glycerol being a 3-carbon symmetric molecule, in phospholipids:
    - C-1 is not interchangeable with C-3
    - Molecule is directionally dependent

Simplest Form and Precursor

- Phosphatidic acid (PA):
    - Is the simplest phosphoglyceride
    - Serves as the precursor for other members of the group

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1. Formation from Phosphatidic Acid + Alcohol

- PA's phosphate group can be esterified to a compound containing an alcohol group

Examples

Alcohol	Product
Serine + PA	Phosphatidylserine (PS)
Ethanolamine + PA	Phosphatidylethanolamine (PE)
Choline + PA	Phosphatidylcholine (PC) (lecithin)
Inositol + PA	Phosphatidylinositol (PI)
Glycerol + PA	Phosphatidylglycerol (PG)

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2. Cardiolipin

Structure

- Formed by:
    - Two molecules of phosphatidic acid (PA)
    - Esterified through their phosphate groups to an additional molecule of glycerol
- Product: Cardiolipin (also called diphosphatidylglycerol)

Location

- Present in membranes of both:
    - Prokaryotes
    - Eukaryotes
- In eukaryotes:
    - Virtually exclusive to the inner mitochondrial membrane

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Function

- Maintains structure and function of specific respiratory complexes in the electron transport chain

Clinical Note: Antigenicity

- Cardiolipin is antigenic
- In Treponema pallidum (T. pallidum) infection (causative agent of syphilis):
    - Patients develop antibodies (Ab) against cardiolipin
- Wasserman test for syphilis:
    - Detects Ab raised against T. pallidum
    - By exposing patient's serum to cardiolipin as an antigen

Note:

The source of antigenic response to cardiolipin is not well understood — may originate from:

-> Host cardiolipin released due to tissue damage
-> Or from T. pallidum itself

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3. Plasmalogens

Definition

- Ether phosphoglycerides called plasmalogens are formed when:
    - The fatty acid (FA) at carbon 1 of a glycerophospholipid is replaced
    - By an unsaturated alkyl group
    - Attached by an ether linkage (instead of an ester linkage)
    - To the core glycerol molecule

Examples

Tissue	Plasmalogen	Notes
Nerve tissue	Ether analog of Phosphatidylethanolamine	Structure similar to PE
Heart muscle	Ether analog of Phosphatidylcholine	A quantitatively significant ether lipid

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Naming Note

Plasmalogens have "-al" in their names instead of "-yl"

4. Platelet-Activating Factor (PAF)

Structure

- A second example of an ether glycerophospholipid
- Features:
    - Saturated alkyl group in ether linkage to carbon 1 of glycerol
    - Acetyl residue (not a fatty acid) at carbon 2

Synthesis and Action

- Synthesized and released by a variety of cell types
- Binds to surface receptors and triggers:
    - Thrombotic events
    - Acute inflammatory events

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Physiological and Immune Effects

- Activates inflammatory cells
- Mediates:
    - Hypersensitivity reactions
    - Acute inflammation
    - Anaphylactic reactions
- Causes:
    - Platelet aggregation and activation
    - Activation of neutrophils and alveolar macrophages to generate:
        - Superoxide radicals (for bacterial killing)
    - Lowering of blood pressure

Note:

- PAF is one of the most potent bioactive molecules known
- Causes effects at concentrations as low as 10^{-11} mol/L

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B. Sphingophospholipids: Sphingomyelin

Structure

- Backbone: Sphingosine (an amino alcohol) — not glycerol
- Structural composition:
    - Long-chain fatty acid (LCFA) attached to the amino group of sphingosine via an amide linkage
        - Forms ceramide
        - Ceramide also serves as precursor of glycolipids
    - Alcohol group at carbon 1 of sphingosine:
        - Esterified to phosphorylcholine
        - Forms sphingomyelin

Significance

- Sphingomyelin is:
    - The only significant sphingophospholipid in humans
    - An important constituent of the myelin sheath of nerve fibers
    - Essential for myelin integrity and function

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Note:

The myelin sheath is a layered, membranous structure that:

- Insulates and protects neuronal axons in the central nervous system (CNS)
- Allows rapid neuronal conduction along axons

III. Phospholipid Synthesis

A. Overview of Glycerophospholipid Synthesis

Mechanisms of Synthesis

- Involves two main pathways:

Pathway	Activated Intermediate	Donor	Acceptor
1. CDP-DAG Pathway	CDP-DAG (cytidinediphosphate-DAG)	PA (from CDP-DAG)	Alcohol
2. CDP-Alcohol Pathway	CDP-alcohol	Phosphomonoester of alcohol (from CDP-alcohol)	DAG (diacylglycerol)

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- In both cases, the CDP-bound structure is an activated intermediate

- CMP (cytidine monophosphate) is released as a side product

Key Concept:

Glycerophospholipid synthesis requires activation:

- Either DAG or the alcohol to be added is activated by linkage with CDP

Note:

This mechanism is analogous to:

- Sugar activation by uridinediphosphate (UDP)

Fatty Acid Composition

- Fatty acids (FA) esterified to glycerol alcohol groups can vary widely:
    - Typically:
        - Saturated FA at carbon 1
        - Unsaturated FA at carbon 2

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- This variation contributes to the heterogeneity of glycerophospholipids

Sites of Synthesis and Transport

- Major site:
    - Smooth endoplasmic reticulum (SER)
- From SER, phospholipids are transported to:
    - Golgi apparatus
    - Organelle membranes
    - Plasma membrane
    - Or are secreted from the cell by exocytosis

Note:

Ether lipid synthesis begins in peroxisomes

- Starting substrate: Dihydroxyacetone phosphate

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B. Phosphatidic Acid (PA)

Central Role

- PA is the precursor of:
    - Other glycerophospholipids
    - Triacylglycerol (TAG)

Synthesis of PA

- Synthesized from:
    - Glycerol 3-phosphate
    - Two fatty acyl-CoA molecules

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Tissue-Specific Synthesis Capacity

Tissue/Cell Type	Can Synthesize Phospholipids?	Can Synthesize TAG?
All cells (except mature RBCs)	Yes	No
Liver, adipose tissue	Yes	Yes
Lactating mammary glands	Yes	Yes
Intestinal mucosal cells	Yes	Yes
Mature erythrocytes	No	No

B. Phosphatidylcholine (PC) and Phosphatidylethanolamine (PE)

General Information

- PC and PE are neutral phospholipids
- They are the most abundant phospholipids in most eukaryotic cells

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- Primary route of synthesis:
    - Uses choline and ethanolamine obtained from:
        - The diet
        - Turnover of body phospholipids

Note:

In the liver, PC can also be synthesized from PS and PE

1. Synthesis from Pre-existing Choline and Ethanolamine Pathway Steps

- Step 1:
    - Choline or ethanolamine is phosphorylated by kinases
- Step 2:
    - Converted to activated form:
        - CDP-choline or CDP-ethanolamine

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- Step 3:
    - Choline phosphate or ethanolamine phosphate is transferred:
        - From the nucleotide
        - To a molecule of DAG (diacylglycerol)
        - CMP is released as a side product

a. Significance of Choline Reutilization

- Although humans can synthesize choline de novo, the amount is:
    - Insufficient for metabolic needs
- Therefore, choline is an essential dietary nutrient

Group	Adequate Intake (AI)
Men	550 mg/day
Women	425 mg/day

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Note:

- Choline is also needed for synthesis of acetylcholine, a neurotransmitter

- Choline deficiency is rare but may lead to:

    - Muscle damage
    - Nonalcoholic fatty liver disease

b. Phosphatidylcholine in Lung Surfactant

DPPC (Dipalmitoylphosphatidylcholine / Dipalmitoyl lecithin)

- Synthesized via the same pathway described above

- In DPPC:

    - Positions 1 and 2 on glycerol are occupied by:
        - Palmitate (a saturated LCFA)

Production Site

- Made and secreted by type II pneumocytes

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Function and Location

- Major lipid component of lung surfactant
- Lung surfactant:
    - Is the extracellular fluid layer lining the alveoli
    - Decreases surface tension of this fluid layer
    - Reduces pressure required to reinflate alveoli
    - Prevents alveolar collapse (atelectasis)

Note:

- Surfactant is a complex mixture:
    - 90% lipids
    - 10% proteins
- DPPC is the major component responsible for reducing surface tension

c. Lung Maturity and Clinical Relevance of Surfactant
Fetal Lung Maturity Assessment

- Gauged by: Lecithin/sphingomyelin (L/S) ratio in amniotic fluid

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- Mature lung:
    - L/S ratio $\geqslant 2$
    - Reflects a developmental shift from sphingomyelin to DPPC synthesis
    - Occurs in pneumocytes around 32 weeks' gestation

Respiratory Distress Syndrome (RDS)

Aspect	Details
Condition	Respiratory distress syndrome (RDS) in preterm infants
Cause	Insufficient surfactant production and/or secretion
Impact	Major cause of neonatal deaths in Western countries
Treatment Options	- Glucocorticoids given to mother before delivery to induce gene expression - Postnatal surfactant therapy (natural or synthetic) via intratracheal instillation

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Note:

Acute RDS can also occur in all age groups

- Caused by alveolar damage due to:
    - Infection, injury, or aspiration
- Leads to fluid accumulation in alveoli
- Impairs O_2/CO_2 gas exchange

2. Phosphatidylcholine Synthesis from Phosphatidylserine (Liver-Specific Pathway)

Need for Alternate Pathway

- The liver must produce PC even when free choline is low
- This is essential because the liver:
    - Exports PC in bile
    - PC is a component of plasma lipoproteins

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Stepwise Conversion

Step	Reaction	Enzyme / Donor
1	Phosphatidylserine (PS) → Phosphatidylethanolamine (PE)	PS decarboxylase
2	Phosphatidylethanolamine (PE) → Phosphatidylcholine (PC)	Three methylation steps using S-adenosylmethionine (SAM) as methyl group donor

C. Phosphatidylserine (PS)

Synthesis

- Synthesized in mammalian tissues via the base exchange reaction
    - In this reaction:
        - Ethanolamine group of phosphatidylethanolamine (PE) is exchanged for free serine

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Function and Properties

- Reaction is reversible, but primarily used for PS production for membrane synthesis
- Carries a net negative charge

Note:

PS has a role in blood clotting

D. Phosphatidylinositol (PI)

Synthesis

- Synthesized from:
    - Free inositol
    - CDP-DAG

Fatty Acid Composition

- PI is an unusual phospholipid because:
    - Most frequently contains:
        - Stearic acid at carbon 1
        - Arachidonic acid at carbon 2

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- Serves as a reservoir of arachidonic acid in membranes
    - Provides substrate for prostaglandin (PG) synthesis when needed

Charge

- Like PS, PI has a net negative charge

Membrane Asymmetry and Transport

Phospholipids	Localization in Membrane
PS and PI	Primarily on the inner leaflet of the plasma membrane

- Membrane asymmetry is maintained by:
    - ATP-dependent enzymes:
        - Flippases
        - Floppases

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1. Role in Signal Transduction Across Membranes

Formation of Second Messengers

- Phosphorylation of membrane-bound PI forms polyphosphoinositides such as:
    - Phosphatidylinositol 4,5-bisphosphate (PIP_2)

Cleavage of PIP_2

- Triggered by:
    - Binding of neurotransmitters, hormones, and growth factors to:
        - G protein-coupled receptors (GPCRs) like the α_1-adrenergic receptor
    - Activates Gq α-subunit

Products and Actions

Product	Function
Inositol 1,4,5-trisphosphate (IP_3)	Mobilizes intracellular Ca^{2+}
Diacylglycerol (DAG)	Activates protein kinase C (PKC)

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- IP_3 and DAG work synergistically to trigger specific cellular responses

Conclusion

- Signal transduction across the membrane is successfully accomplished

2. Role of Phosphatidylinositol (PI) in Membrane Protein Anchoring

GPI Anchor Mechanism

- Specific proteins can be covalently attached to membrane-bound PI via a carbohydrate bridge

Example: Lipoprotein Lipase

- Function: Degrades triacylglycerol (TAG) in lipoprotein particles
- Location: Attached to capillary endothelial cells
- Anchor Type: Glycosyl phosphatidylinositol (GPI) anchor

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- Additional Notes

- GPI-linked proteins are also found in:

    - Parasitic protozoans, such as:
        - Trypanosomes
        - Leishmania

- GPI anchoring allows:

    - Increased lateral mobility of the protein on the extracellular plasma membrane surface

- Cleavage mechanism:

    - Protein can be cleaved from anchor by phospholipase C

Clinical Note: GPI Deficiency

- Disease:

    - Paroxysmal nocturnal hemoglobinuria (PNH)

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- Mechanism:

Deficiency in the GPI synthesis in hematopoietic cells -> Blood cells lack GPI-anchored protective proteins -> Some GPI-anchored proteins protect blood cells from immune attack -> Cells not recognized as "self" -> Complement-mediated lysis of RBCs -> Hemolysis (destruction of red blood cells)

E. Phosphatidylglycerol and Cardiolipin

Phosphatidylglycerol (PG)

- Found in large concentrations in mitochondrial membranes

- Precursor of cardiolipin (diphosphatidylglycerol)

Synthesis of Phosphatidylglycerol

- Synthesized from:

    - CDP-DAG
    - Glycerol 3-phosphate

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Synthesis of Cardiolipin

- Formed by:
    - Transfer of DAG 3-phosphate from CDP-DAG
    - To a preexisting molecule of phosphatidylglycerol

F. Sphingomyelin

General Information

- Sphingomyelin is a sphingosine-based phospholipid

- Found in:
    - Cell membranes
    - Myelin sheath

Synthesis of Sphingomyelin

Stepwise Pathway

1. Condensation Reaction:
    - Reactants:
        - Palmitoyl-CoA
        - Serine

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- Products Lost:
  - CoA
  - Carboxyl group of serine as CO_2

- Cofactor Required:
  - Pyridoxal phosphate (Vitamin B_6 derivative)

Note:

Pyridoxal phosphate is also required in other decarboxylation reactions, e.g.,

- PE from PS

- Catecholamines from tyrosine

2. Reduction Step:

- Product is reduced to sphinganine (dihydrosphingosine)
- Requires NADPH

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3. Acylation Step:

- Sphinganine is acylated at the amino group
- FA used: one of various long-chain fatty acids (LCFA)

4. Desaturation:

- Forms ceramide
- Ceramide is the immediate precursor of:
  - Sphingomyelin
  - Other sphingolipids

5. Transfer of Phosphorylcholine:

- Donor: Phosphatidylcholine (PC)
- Phosphorylcholine is transferred to ceramide
- Products:
  - Sphingomyelin
  - Diacylglycerol (DAG)

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Biological Importance

Ceramides

- Function:
  - Maintain the skin's water-permeability barrier
- Clinical Note:
  - Decreased ceramide levels are linked to several skin diseases

Sphingomyelin Composition

Tissue/Structure	Predominant Fatty Acids in Sphingomyelin
Myelin sheath	Lignoceric acid, Nervonic acid (longer-chain FAs)
Gray matter of the brain	Stearic acid

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IV. Phospholipid Degradation

General Overview

- Degradation of phosphoglycerides is performed by phospholipases.
- These enzymes are found in:
    - All tissues
    - Pancreatic juice
- Toxins and venoms often have phospholipase activity.
- Several pathogenic bacteria produce phospholipases that:
    - Dissolve cell membranes
    - Allow the spread of infection

Sphingomyelin Degradation

- Sphingomyelin is degraded by the lysosomal phospholipase sphingomyelinase.

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A. Phosphoglycerides

Enzyme Action

- Phospholipases hydrolyze the phosphodiester bonds of phosphoglycerides.
- Each phospholipase cleaves the phospholipid at a specific site.

Formation of Lysophosphoglycerides

- Removal of the FA from carbon 1 or 2 of a phosphoglyceride:
    - Produces a lysophosphoglyceride
    - This is the substrate for lysophospholipases

Role in Cell Signaling

- Phospholipases release molecules that can serve as:
    - Second messengers:
        - DAG (Diacylglycerol)
        - IP_3 (Inositol 1,4,5-triphosphate)

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    - Substrates for the synthesis of messengers:
        - Example: Arachidonic acid

Functions Beyond Degradation

- Phospholipases are responsible not only for degrading phospholipids but also for remodeling them.

Remodeling Example

- Phospholipases A_1 and A_2 remove specific FA from membrane-bound phospholipids.
- These removed FAs can be replaced with different FAs using:
    - Fatty acyl CoA transferase

Functional Applications

- This mechanism is used to:
    - Create the unique lung surfactant DPCC

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    - Ensure that carbon 2 of:
        - Phosphatidylinositol (PI)
        - Sometimes Phosphatidylcholine (PC)
        - Is bound to arachidonic acid

Clinical Note: Barth Syndrome

- Barth syndrome is a rare X-linked disorder.
- Characterized by:
    - Cardiomyopathy
    - Muscle weakness
    - Neutropenia
- Caused by defects in cardiolipin remodeling

B. Sphingomyelin Degradation

Stepwise Degradation

1. Sphingomyelin → Ceramide

    - Enzyme: Sphingomyelinase
    - Type: Lysosomal enzyme, a phospholipase C
    - Action: Removes phosphorylcholine from sphingomyelin

2. Ceramide → Sphingosine + Free Fatty Acid (FA)

    - Enzyme: Ceramidase

Biological Role of Degradation Products

- Ceramide and sphingosine:

    - Regulate signal transduction pathways
    - Influence protein kinase C activity
        - Affects phosphorylation of protein substrates
    - Promote apoptosis

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Clinical Condition: Niemann-Pick Disease (Types A and B)
Cause

- Autosomal recessive disorder
- Due to deficiency of sphingomyelinase
- Leads to inability to degrade sphingomyelin

Type A Niemann-Pick Disease (Infantile Form)

Feature	Details
Enzymatic activity	<1% of normal sphingomyelinase activity
Lipid accumulation	Mainly sphingomyelin
Primary sites of accumulation	Liver and spleen
Organ effect	Hepatosplenomegaly
Histology	Macrophages engorged with sphingomyelin → foamy appearance
CNS involvement	Yes → rapid and progressive neurodegeneration
Ocular sign	Cherry-red spot in the macula due to lipid accumulation and edema
Prognosis	Death in early childhood
Prevalence	More common in Ashkenazi Jewish population

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Type B Niemann-Pick Disease (Chronic Form)

Feature	Details
Enzymatic activity	Up to 10% of normal sphingomyelinase activity
CNS involvement	Minimal or none
Affected organs	Lungs, spleen, liver, bone marrow
Age of onset	Later onset
Survival	Longer survival time
Clinical course	Chronic form of the disease

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Niemann-Pick Disease Type C (NPC)

Cause ->	Mutation in NPC1 or NPC2 genes
Function of affected genes ->	Involved in processing endocytosed cholesterol
Accumulated substances ->	Both cholesterol and sphingomyelin

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V. Glycolipid Overview

Definition

- Glycolipids are molecules that contain both:
    - A carbohydrate component
    - A lipid component

Chemical Structure

- Glycolipids are derivatives of ceramides
- Like sphingomyelin, they are built on:
    - A long-chain fatty acid (LCFA) attached to:
    - The amino alcohol sphingosine
- Therefore, they are more accurately termed:
    - Glycosphingolipids

Note:

Ceramides are the precursors of both:

- Phosphorylated sphingolipids (e.g., sphingomyelin)

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- Glycosylated sphingolipids (i.e., glycolipids)

Membrane Role

- Glycosphingolipids are:
    - Essential membrane components throughout the body
    - Found in greatest abundance in nerve tissue
- Location in membrane:
    - Outer leaflet of the plasma membrane
    - Site of interaction with extracellular environment

Functions

- Involved in:
    - Cellular interaction regulation (e.g., adhesion, recognition)
    - Growth
    - Development

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Lipid Rafts

- Membrane glycosphingolipids, along with:
    - Cholesterol
    - GPI-anchored proteins
- Together form:
    - Lipid rafts—laterally mobile microdomains in the plasma membrane
- Functions of lipid rafts:
    - Organize and regulate:
        - Membrane signaling
        - Trafficking functions

Antigenic Properties

- Glycosphingolipids are antigenic
- They serve as the basis for:
    - ABO blood group antigens

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    - Embryonic antigens (specific to fetal developmental stages)
    - Tumor antigens

Note:

- The carbohydrate portion is the antigenic determinant
- The lipid portion serves as the membrane anchor

Clinical Significance

- Cell surface receptors:
    - Glycosphingolipids act as receptors for:
        - Cholera toxin
        - Tetanus toxin
        - Certain viruses and microbes
- Lysosomal storage disorders:
    - Caused by:
        - Inability to degrade glycosphingolipids properly

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    - Result:
        - Lysosomal accumulation of glycosphingolipids

- Transformed cells:

    - Changes in the carbohydrate portion of glycosphingolipids (and glycoproteins) are:
        - Characteristic of transformed cells
        - Associated with dysregulated growth

VI. Glycosphingolipid Structure

Key Structural Differences from Sphingomyelin

- Glycosphingolipids do not contain phosphate

- Their polar head group is:

    - A monosaccharide or oligosaccharide
    - Attached directly to ceramide via an O-glycosidic bond

- The number and type of carbohydrate moieties determine the type of glycosphingolipid

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A. Neutral Glycosphingolipids

1. Cerebrosides (Ceramide Monosaccharides)

Sugar Attached	Glycosphingolipid Formed	Notes
Galactose	Ceramide–galactose (Galactocerebroside)	Most common cerebroside in myelin
Glucose	Ceramide–glucose (Glucocerebroside)	Intermediate in synthesis and degradation of more complex glycosphingolipids

Note:

Members of galacto- or glucocerebrosides may differ by the type of FA attached to the sphingosine.

- Distribution:
    - Found predominantly in the brain and peripheral nerves
    - Highly concentrated in the myelin sheath

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2. Ceramide Oligosaccharides (Globosides)

- Formed by attaching additional monosaccharides to a glucocerebroside
    - Example: Ceramide–glucose–galactose (also known as lactosylceramide)
- Additional sugars may include:
    - Substituted monosaccharides, such as N-acetylgalactosamine

B. Acidic Glycosphingolipids

Definition

- Negatively charged at physiologic pH
- Source of negative charge:
    - N-acetylneuraminic acid (NANA) – in gangliosides
    - Sulfate groups – in sulfatides

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1. Gangliosides

Structure and Composition

- Most complex glycosphingolipids
- Found primarily in:
    - Ganglion cells of the CNS
    - Especially at nerve endings
- Derived from:
    - Ceramide oligosaccharides
- Contain:
    - One or more molecules of NANA (derived from CMP-NANA)
- Example: GM2

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Notation

Prefix	Indicates
G	Ganglioside
M, D, T, Q	Number of NANA units: Mono, Di, Tri, Quatro
Additional subscript	Monomeric sequence of carbohydrate attached to ceramide

Clinical Significance

- Gangliosides are involved in lipid storage disorders
- These disorders result in accumulation of NANA-containing glycosphingolipids

2. Sulfatides

Structure

- Sulfoglycosphingolipids
- Chemically: Sulfated galactocerebrosides

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- Possess negative charge at physiologic pH

Location

- Found predominantly in:
    - Brain
    - Kidneys

VII. Glycosphingolipid Synthesis and Degradation

Site of Synthesis

- Occurs primarily in the Golgi apparatus
- Involves sequential addition of glycosyl monomers
- Donor molecules: UDP-sugar donors
- Acceptor molecule: A growing glycosphingolipid

Mechanism:

Similar to glycoprotein synthesis

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A. Enzymes Involved in Synthesis

- Enzymes: Glycosyltransferases
- Specific for:
    - The type of glycosidic bond
    - The location of glycosidic bond formation
- Substrate recognition:
    - Can act on both glycosphingolipids and glycoproteins

Note:

Enzyme specificity ensures correct carbohydrate structure and orientation

B. Sulfate Group Addition

Sulfation Mechanism

- Sulfate donor: 3′-phosphoadenosine-5′-phosphosulfate (PAPS)

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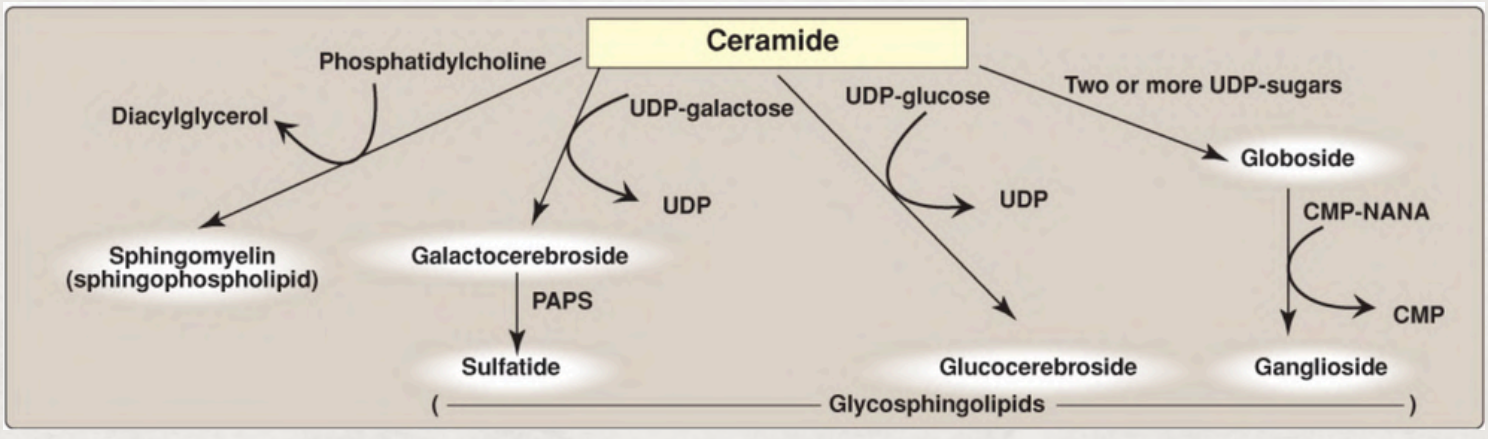
- Catalyzing enzyme: Sulfotransferase
- Reaction site:
    - Adds sulfate to the 3′-hydroxyl group of galactose in galactocerebroside
- Product:
    - Sulfatide–galactocerebroside 3-sulfate

Note:

PAPS is also the sulfur donor in:

- Glycosaminoglycan synthesis
- Steroid hormone catabolism

Overview of sphingolipid synthesis.



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C. Glycosphingolipid Degradation

Mechanism of Degradation

- Glycosphingolipids are internalized by phagocytosis

Role of Lysosomes

- Lysosomes contain all enzymes required for glycosphingolipid degradation
- Fusion of lysosomes with phagosomes occurs

Enzymatic Process

- Lysosomal enzymes cleave specific bonds
- Reaction type: Hydrolytic and irreversible

Degradation Rule:

"Last on, first off"

→ The last group added during synthesis is the first removed during degradation

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Clinical Insight

- Defects in degradation of polysaccharide chains in:
    - Glycosphingolipids
    - Glycosaminoglycans
    - Glycoproteins
- Result in lysosomal storage diseases

D. Sphingolipidoses

Normal Physiology

- In healthy individuals:
    - Synthesis = Degradation of glycosphingolipids
    - Result: Stable membrane levels

Pathology

- If a specific lysosomal acid hydrolase is:
    - Partially or totally missing
    - A sphingolipid accumulates

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Disease Category

- Lysosomal lipid storage diseases due to such deficiencies are called:
    - Sphingolipidoses

Clinical Manifestations

- Particularly affect nerve tissue
- Consequences:
    - Neurologic deterioration
    - Can lead to early death

Note

- Some sphingolipidoses also result from defects in lysosomal activator proteins
- e.g., Saposins (facilitate access of hydrolases to short carbohydrate chains during degradation)

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1. Common Properties of Sphingolipidoses

Enzyme Deficiency

- In each classic form:
    - A specific lysosomal hydrolytic enzyme is deficient
    - Result: Single sphingolipid accumulates (the substrate for the deficient enzyme)
- Note:
    - The rate of biosynthesis of the accumulating lipid is normal

Disease Progression

- Disorders are progressive
- Many are fatal in childhood
- However, extensive phenotypic variability is seen
    - Example: Types A and B in Niemann-Pick disease

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Genetic Variability

- A single disorder can be caused by multiple mutations in one gene

Mode of Inheritance

Disease	Inheritance Pattern
Most sphingolipidoses	Autosomal recessive
Fabry disease	X-linked

Epidemiology

- Incidence is low in most populations
- Higher frequency in Ashkenazi Jewish population:
    - Gaucher disease
    - Tay-Sachs disease
    - Niemann-Pick disease

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- Tay-Sachs disease also has high frequency in:
    - Irish Americans
    - French Canadians
    - Louisiana Cajuns

2. Diagnosis and Treatment

Diagnostic Approaches

- Enzyme activity measurement in:
    - Cultured fibroblasts
    - Peripheral leukocytes
- DNA analysis
- Histologic examination of affected tissue:
    - Tay-Sachs: Shell-like inclusion bodies
    - Gaucher disease: Crumpled tissue paper appearance of the cytosol
- Prenatal diagnosis:
    - Using cultured amniocytes or chorionic villi

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Treatment Options

Gaucher Disease

- Macrophages engorged with glucocerebroside
- Treated by:
    - Recombinant human enzyme replacement therapy
        - Note: Extremely high cost
    - Bone marrow transplantation
        - Rationale: Macrophages are derived from hematopoietic stem cells
    - Substrate reduction therapy:
        - Drug: Miglustat
        - Action: Reduces glucosylceramide, the substrate of the deficient enzyme

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Fabry Disease

- Globosides accumulate in vascular endothelial lysosomes of:
    - Brain
    - Heart
    - Kidneys
    - Skin
- Treated by:
    - Recombinant human enzyme replacement therapy
        - Note: Extremely high cost

VIII. Eicosanoids: Prostaglandins, Thromboxanes, and Leukotrienes

Definition and Origin

- Eicosanoids = Prostaglandins (PGs), Thromboxanes (TXs), and Leukotrienes (LTs)

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Definition and Origin

- Eicosanoids = Prostaglandins (PGs), Thromboxanes (TXs), and Leukotrienes (LTs)

- Name derived from:

    - Their origin from ω-3 and ω-6 polyunsaturated fatty acids
    - Fatty acids contain 20 carbons
    - ("Eicosa" = 20)

Potency and Range of Effects

- Extremely potent compounds

- Elicit wide range of effects:

    - Physiologic (e.g., inflammatory response)
    - Pathologic (e.g., hypersensitivity)

Functions

- Ensure:

    - Gastric integrity
    - Renal function

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- Regulate:
    - Smooth muscle contraction (notably in:
        - Intestine
        - Uterus)
    - Blood vessel diameter
- Maintain:
    - Platelet homeostasis

Comparison to Hormones

- Similar to hormones in effect
- Differences from endocrine hormones:
    - Produced in very small amounts
    - Synthesized in almost all tissues
    - Not made in specialized glands
    - Act locally, not transported via blood to distant sites

Storage and Metabolism

- Not stored

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- Have extremely short half-life
- Rapidly metabolized into inactive products

Mechanism of Action

- Biological actions mediated by:
    - Plasma membrane G protein-coupled receptors (GPCRs)
- Receptors are:
    - Different in different organ systems
    - Typically influence cyclic adenosine monophosphate (cAMP) production

A. Prostaglandin and Thromboxane Synthesis

1. Arachidonic Acid as Precursor

- Arachidonic acid:
    - An ω-6 fatty acid
    - Contains 20 carbons and four double bonds
    - Classified as an eicosatetraenoic fatty acid

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- Immediate precursor of predominant human prostaglandins (PGs)
    - Specifically, series 2 PGs (those with two double bonds)

2. Source of Arachidonic Acid

- Derived from:
    - Elongation and desaturation of linoleic acid
        - Linoleic acid is an essential ω-6 fatty acid
- Incorporation:
    - Arachidonic acid is incorporated into membrane phospholipids
    - (typically phosphatidylinositol [PI])
    - Attached at carbon 2 of the glycerol backbone

3. Release Mechanism

- Released from PI by phospholipase A_2
- Triggered in response to various signals
    - Example: Rise in intracellular calcium levels

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4. Other PG Series

- Series 1 PGs:
    - Contain one double bond
    - Derived from ω-6 eicosatrienoic fatty acid (dihomo-γ-linolenic acid)
- Series 3 PGs:
    - Contain three double bonds
    - Derived from eicosapentaenoic acid (EPA), an ω-3 fatty acid

5. Prostaglandin H_2 Synthase (PGH_2 Synthase)

- First step in PG and TX synthesis:
    - Oxidative cyclization of free arachidonic acid → PGH_2
- Catalyzed by PGH_2 synthase (a.k.a. prostaglandin endoperoxide synthase)

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a. Location and Catalytic Activities

- Endoplasmic reticulum membrane-bound enzyme
- Contains two catalytic activities:
    - Fatty acid cyclooxygenase (COX):
        - Requires two molecules of O_2
    - Peroxidase:
        - Requires reduced glutathione

b. Products

- PGH_2 is converted into:
    - A variety of prostaglandins (PGs)
    - Thromboxanes (TXs)
- Conversion is carried out by cell-specific synthases

6. Structural Differences

- Prostaglandins (PGs):
    - Contain a five-carbon ring

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- Thromboxanes (TXs):
    - Contain a six-membered heterocyclic oxane ring

7. Isozymes of PGH_2 Synthase

- Two isozymes:
    - COX-1:
        - Constitutively expressed in most tissues
        - Required for:
            - Healthy gastric tissue maintenance
            - Renal homeostasis
            - Platelet aggregation
    - COX-2:
        - Inducible in select tissues
        - Induced by:
            - Products of activated immune and inflammatory cells
        - Increased PG synthesis due to COX-2:
            - Mediates:
                - Pain
                - Heat
                - Redness
                - Swelling (inflammation)
                - Fever of infection

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2. Synthesis Inhibition of Prostaglandins (PG) and Thromboxanes (TX)

A. General Inhibition Mechanisms

- PG and TX synthesis can be inhibited by unrelated compounds.

B. Inhibition by Cortisol

- Cortisol is a steroidal anti-inflammatory agent.
- Mechanism:
    - Inhibits phospholipase A_2 activity.
    - Prevents the release of arachidonic acid from membrane phospholipids.
    - Since arachidonic acid is the precursor of PG and TX, this halts their synthesis.

C. Inhibition by NSAIDs

- Examples: Aspirin, indomethacin, phenylbutazone
- Class: Nonsteroidal anti-inflammatory drugs (NSAIDs)

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- Mechanism:
    - Inhibit both COX-1 and COX-2
    - Prevent synthesis of PGH_2 (the parent compound of PG and TX)

1. Side Effects of COX-1 Inhibition

- Systemic COX-1 inhibition → side effects:
    - Stomach damage
    - Kidney impairment
    - Impaired blood clotting

- Basis of aspirin's toxicity

2. Unique Effect of Aspirin

- Unlike other NSAIDs, aspirin also induces:
    - Lipoxins (anti-inflammatory mediators from arachidonic acid)
    - Resolvins and protectins (inflammation-resolving mediators from EPA)

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D. COX-2 Specific Inhibitors (Coxibs)

- Designed to:
    - Inhibit COX-2 (inflammatory mediator)
    - Preserve COX-1 physiologic functions
- Example: Celecoxib
    - Only FDA-approved coxib currently

B. Thromboxanes and Prostaglandins in Platelet Homeostasis

1. Thromboxane A_2 (TXA_2)

- Produced by COX-1 in activated platelets
- Functions:
    - Promotes platelet adhesion and aggregation
    - Contracts vascular smooth muscle
    - Enhances blood clot formation (thrombogenesis)

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2. Prostacyclin (PGI_2)

- Produced by COX-2 in vascular endothelial cells
- Functions:
    - Inhibits platelet aggregation
    - Stimulates vasodilation
    - Impairs thrombogenesis

3. Balance Between TXA_2 and PGI_2

- Opposing effects of TXA_2 and PGI_2:
    - Restrict thrombus formation to sites of vascular injury
    - Maintain vascular homeostasis

4. Aspirin's Antithrombogenic Effect

- Irreversibly acetylates both COX-1 (in platelets) and COX-2 (in endothelium)
- TXA_2 synthesis in platelets:
    - Permanently inhibited (platelets lack a nucleus, cannot resynthesize COX-1)

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- PGI_2 synthesis in endothelial cells:
    - Can recover (endothelial cells have a nucleus, can resynthesize COX-2)

a. Clinical Application: Low-Dose Aspirin Therapy

- Prevents stroke and heart attacks
- Mechanism:
    - Reduces TXA_2-mediated thrombus formation
    - PGI_2 production recovers, maintaining anti-thrombogenic effect

C. Leukotriene (LT) Synthesis

1. Pathway Overview

- Substrate: Arachidonic acid
- Enzyme family: Lipoxygenases (LOXs)

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- Mechanism:
    - Arachidonic acid is converted into linear hydroperoxy (-OOH) acids
    - Pathway is distinct from the cyclooxygenase (COX) pathway used in PG and TX synthesis

2. Example Reaction: 5-LOX Pathway

- Enzyme: 5-lipoxygenase (5-LOX)
- Product:
    - Converts arachidonic acid into 5-hydroperoxy-6,8,11,14-eicosatetraenoic acid (5-HPETE)
    - 5-HPETE is a key intermediate
- Further conversion:
    - 5-HPETE is converted into various leukotrienes (LTs) containing four double bonds
    - Final leukotriene products vary depending on the tissue type

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3. Biological Role of Leukotrienes

- Key functions:
    - Mediate allergic responses
    - Promote inflammation

4. Clinical Significance

- Pharmacologic intervention:
    - 5-LOX inhibitors and leukotriene receptor antagonists are used for:
        - Asthma management
        - Allergic inflammation

- Important Note:
    - LT synthesis is inhibited by cortisol
    - LT synthesis is not inhibited by NSAIDs

5. Aspirin-Exacerbated Respiratory Disease (AERD)

- Also known as: NSAID-exacerbated respiratory disease

- Occurs in: ~10% of individuals with asthma

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- Cause:
    - Use of NSAIDs → inhibition of COX pathway
    - Leads to shunting of arachidonic acid metabolism toward excess LT production
- Result:
    - Worsening of respiratory symptoms

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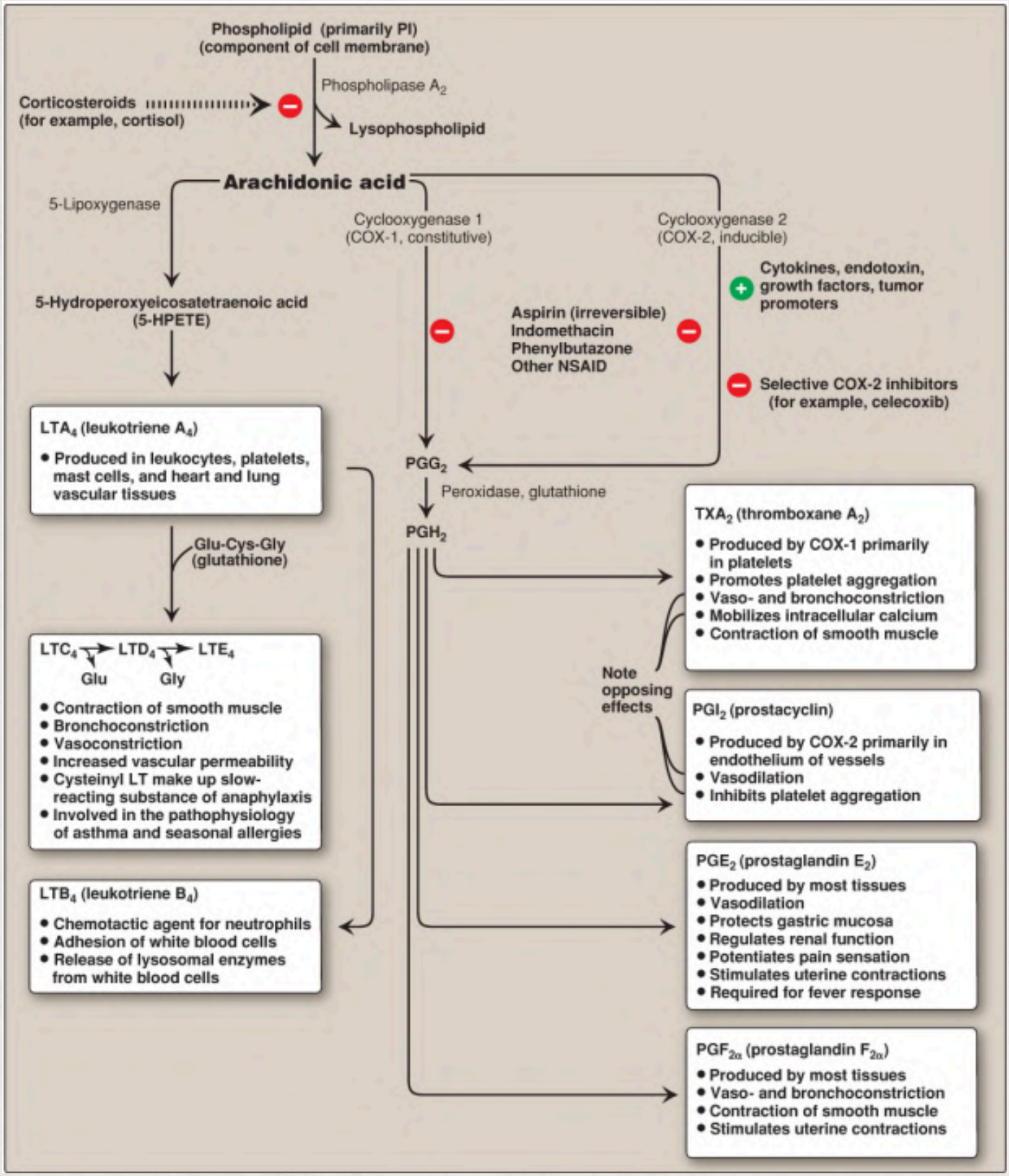
Overview of Eicosanoid Synthesis



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