METABOLISM

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ARKAN ACADEMY

❖ Sphingolipids

- Sphingolipids consist of a sphingosine backbone with FA and head group
  - **Sphingosine:** it is an amino alcohol with an amino group on C2 which binds FA and an alkene on the 4th carbon, and can bind a head group (R group) on C1
  - **Ceramide:** Sphingosine + FA
  - **Sphingomyelin:** Sphingosine + FA + Phosphorylcholine
  - **Glycolipid:** Sphingosine + FA + Sugar

H	Ceramides
Phosphocholine	Sphingomyelins
Sugar (s) - Single sugar (glucose or galactose) - Lactose (disaccharide) - Oligosaccharide - Sugar + sulfate	Glycosphingolipids - Cerebrosides - Lactosylceramides - Gangliosides - Sulfatides

- Synthesis of sphingomyelin:
  - ***Palmitoyl CoA*** condenses with ***serine*** producing **sphinganine** and releasing CoA and CO_2
    - ✓ The reaction requires *pyridoxalphosphate (PLP)* and *NADPH*
    - ✓ The needed energy comes from decarboxylation and the release of CoA
  - Sphinganine is **acylated at the amino group** with a long-chain fatty acid and then ***desaturated*** (producing $FADH_2$) to produce a ***ceramide*** (precursor of all sphingolipids)
  - Phosphorylcholine from ***phosphatidylcholine*** is transferred to the ceramide, producing *sphingomyelin* and *DAG*

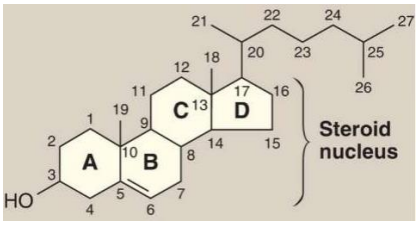
- Ceramidase: the enzyme that cuts the amide bond between sphingosine and FA
- Sphingomyelinase: the enzyme that cuts the amide bond between sphingosine and Phosphorylcholine
  - **Neimann-Pick disease** (common among Jews) results from the **deficiency of sphingomyelinase**
  - It can be either type A or B (according to severity)
  - It causes *enlarged liver and spleen*, severe *intellectual disability* and *neurodegeneration* (type A)
  - Type A can cause death in early childhood

- **Glycosphingolipids** (glycolipids) are made of ceramide with sugars attached to it by ***O-glycosidic bond***
  - They are localized in the **outer leaflet** of the plasma membrane and exposed extracellularly (adhesion, recognition, and signaling)
  - Their hydrophobic ceramide tail inserts into the outer phospholipid leaflet, while the glycan headgroup extends outwardly
- Glycolipids are classified into:
  - ***Neutral glycosphingolipids***
    - ✓ ***Cerebrosides:*** contain 1 simple sugar so it is the simplest (such as galactocerebrosides)
    - ✓ ***Globoside:*** contain oligosaccharide (such as lactosylceramide which contains lactose)
  - ***Acidic glycosphingolipids:*** They are negatively charged at physiologic pH
    - ✓ ***Gangliosides:*** attached to Nacetylneuraminic acid (NANA, a **sialic acid**)
      - They are designated as G plus a subscript (M, D, T or Q) to indicate the number of sialic acid molecules, and then a number that indicates indirectly the number of sugar residues (5 – #)
      - Sialidase (Neuraminidase) is the enzyme that removes sialic acid
    - ✓ ***Sulfatides:*** are galactocerebrosides that have a **sulfate** group on galactose molecule

- Synthesis of glycosphingolipids occurs primarily in the **Golgi apparatus** by sequential addition of glycosyl monomers transferred from **UDP-sugars** to the acceptor molecule by ***glycosyltransferases***
- **Sulfatide** (galactocerebroside sulfate) is formed by adding a sulfate to a galactose in galactocerebroside from the sulfate carrier 3′phosphoadenosine-5′-phosphosulfate (**PAPS**) by a ***sulfotransferase***
- For the synthesis of gangliosides, ***NANA (sialic acid)*** must be activated by **CDP** then added to the globoside

- Glycosphingolipids are degraded in the lysosomes by ***lysosomal hydrolases*** which remove the sugars sequentially (from the last one added, ending with the first one added)
  - Defect in the degradation of glycosphingolipid, glycosaminoglycans, and glycoproteins causes lysosomal storage diseases
- **Sphingolipidoses:** disorders related to defective degradation of sphingolipids
  - Usually, only a single sphingolipid (the substrate for the deficient enzyme) accumulates in the involved organs, and the disorders are progressive becoming more severe with aging and can be fatal
  - There is extensive phenotypic variability due to
    - ✓ ***Allele heterogeneity:*** different mutations within the same gene (different alleles)
    - ✓ ***Locus heterogeneity:*** different genes are defective
  - They are autosomal-recessive disorders, except for **Fabry disease**, which is **X linked**
  - The incidence of sphingolipidoses is low in most populations, except for *Gaucher* and *Tay-Sachs* diseases, which, like *Niemann-Pick disease*, show a high frequency in the Ashkenazi Jewish people
  - **Tay-Sachs disease:** causes accumulation of GM2, which can cause neurodegeneration, blindness, seizure, muscle weakness and cherry-red macula
    - ✓ *β-Hexoseaminidase* is the deficient enzyme
  - **Gaucher disease:** (the most common lysosomal storage disease) causes the accumulation of glucocerebroside, hepatosplenomegaly, osteoporosis, CNS disorders, mental retardation and can be treated by **ERT** (Enzyme replacement therapy)
    - ✓ *β-Glucosidase (glucocerebrosidase)* is the deficient enzyme
  - **Farber disease:** causes accumulation of ceramide, painful and progressive joint deformity, subcutaneous nodules, hoarse cry, tissue granuloma and cherry-red macula
    - ✓ *Ceramidase* is the deficient enzyme
- The diagnosis involves measurement of enzyme activity in cultured fibroblasts or peripheral leukocytes and DNA analysis (which more cost effective)
- Treatment involves recombinant *human enzyme replacement* therapy for Gaucher and Fabry disease (which is expensive), and *bone marrow transplantation* for Gaucher disease and *Substrate reduction therapy* for Gaucher disease (Pharmacologic reduction of glucosylceramide)

❖ Cholesterol



- Cholesterol is a very hydrophobic compound
  - It is a 27-carbon molecule that consists of 4 fused hydrocarbon rings (A–D) of 17 carbons called the **steroid nucleus**, 2 methyl groups (C18 and 19) and 8C branched hydrocarbon chain attached to carbon 17 of the D ring
  - where ring A has a hydroxyl group at carbon 3 (which make it amphipathic)
  - Ring B has a double bond between C5 and c6
  - Most plasma cholesterol is esterified with a FA attached at carbon 3 making it **more hydrophobic**
- Cholesterol is absorbed in the intestines by ***NPC1L1*** transporter which is inhibited by ezetimibe
- Cholesterol is pumped out (back into the intestine) by ***ABCG5/8*** transported
  - If ABCG5/8 is defective, ***sitosterolemia*** (cholesterol accumulation) occurs increasing the risk of MI
- Plant sterols (**phytosterols**) are poorly absorbed by humans (5% in comparison of cholesterol by 40%), and actively transported back into intestines lumen
  - Phytosterols decrease the absorption of cholesterol by competing it on its transporter

- Cholesterol synthesis occurs in many steps in the *cytosol*, *SER* and *peroxisomes*
- This endergonic pathway takes its energy by the hydrolysis of *thioester bond of acetyl CoA* and *ATP*
  - It requires *NADPH* as a reducing agent
- Steps of Cholesterol synthesis:

> HMG CoA synthase has 2 isozymes:
> Cytosolic (cholesterol)
> Mitochondrial (ketone bodies)

Cytosol

  - ***2 acetyl CoA*** condenses into ***acetoacetyl CoA*** by thiolase
  - HMG CoA synthase (**cytosolic** isozyme) produces ***HMG CoA***

SER

  - HMG CoA is reduced to ***mevalonate*** by ***HMG CoA reductase***
    - ✓ HMG CoA reductase is an integral protein in the **SER** membrane
    - ✓ A **rate-limiting reaction** and a committed step
    - ✓ **2 NADPH** are oxidized
    - ✓ CoA is released making the reaction **irreversible**

Peroxisome

  - Mevalonate is activated by transferring 2 Phosphate from 2 ATP forming ***pyrophosphomevalonate***
  - Pyrophosphomevalonate is decarboxylated into ***IPP*** (isopentenyl pyrophosphate) which is a 5-C isoprene unit (isoprenoid family)
    - ✓ This step requires 1 ATP

> Nonsterol isoprenoids include ubiquinone (CoQ)

  - IPP is isomerized by isomerase into ***DPP*** (3,3-dimethylallyl phosphate)
  - Addition of IPP into DPP forming 10-C molecule is ***GPP*** (geranyl pyrophosphate) by synthase
  - Addition of IPP into GPP forming 15-C molecule is ***FPP*** (farnesyl pyrophosphate) by synthase

> ***Farnesyl*** is used to anchor proteins to the inner face of the plasma membrane by **prenylation** (covalent bond with proteins such as Ras)

SER

  - 2 FPP combine releasing pyrophosphates and get reduced, forming the 30-C molecule called ***squalene***
    - ✓ Squalene is formed from six isoprenoid units each mevalonate to be converted into IPP requires hydrolysis of 3 ATP, so the **18 ATP** are required to make the polyisoprene squalene
    - ✓ Squalene is hydrophobic requiring an **intracellular protein carrier** to remain soluble
  - Squalene is converted to ***lanosterol*** by SER-associated enzymes that use O_2 and NADPH
    - ✓ These enzymes include monooxygenase and synthase
    - ✓ The hydroxylation of linear squalene triggers the cyclization of the structure to lanosterol
  - Modification of the side chain of lanosterol (shortening by removing methyl groups, double bond is re-located) to form ***cholesterol***

- Regulation of cholesterol metabolism:
  - Gene expression: ***SREBP*** transcription factor can bind the promoter element of specific genes such as the gene of HMG CoA reductase activating its synthesis
    - ✓ SREBP is activated by ***SCAP*** and inhibited by ***INSIG*** (trap it in the ER)
    - ✓ INSIG can also bind HMG CoA reductase and trap it inside the ER (inhibit it)
  - Post-translational and hormonal regulation:
    - ✓ ***AMP*** and ***Glucagon*** activates AMPK & PKA phosphorylates HMG CoA reductase, inhibiting it
    - ✓ ***Insulin*** activates phosphatase, which activates HMG CoA reductase
  - Pharmacological regulation: ***Statin*** works as a **competitive inhibitor** to HMG CoA reductase because it is similar to the structure of HMG

- The intact **steroid nucleus is eliminated** from the body by:
  - Conversion to *bile acids* (protonated) and *bile salts* (unprotonated), a small percentage of which is excreted in the *feces*
  - secretion of cholesterol into the bile, which transports it to the intestine for elimination

- **Bile** consists of a watery mixture of organic and inorganic compounds
  - *Phosphatidylcholine* (PC) & conjugated *bile salts* are the most important organic components of bile
  - Bile can either pass directly from the **liver**, where it is synthesized, into the duodenum through the common bile duct, or be stored in the gallbladder
- The bile acids contain 24 carbons, with two or three hydroxyl groups and a side chain that terminates in a carboxyl group (pKa ~ 6), where the duodenum (pH ~6), 50% exist as bile acids (protonated) and 50% exists as bile salts (deprotonated), but in the jejunum (pH ~8) it is mainly deprotonated
- **Primary bile acids** (*cholic acid* and *Chenodeoxycholic acid*) are synthesized by modifying cholesterol:
  - Cholesterol is hydroxylated by ***7-α-hydroxylase*** (require **NADPH**)
    - ✓ This enzyme is SER-associated cytochrome P450 monooxygenase found only in liver where its expression is **downregulated** by *bile*
    - ✓ It is the rate limiting and committed step

    Cholic acid = triol
    Chenodeoxycholic = diol
  - The double bond in B ring is removed
  - The hydrocarbon chain is shortened by 3 carbons
  - Introducing a carboxyl group at the end of the chain
  - In the liver, primary bile acids can be *conjugated* by **glycine** or **taurine** on the carboxyl group making them more amphipathic and better emulsifiers
    - ✓ The ratio of the glycine to taurine forms in the bile is ~3/1
    - ✓ Taurine is an end product of *cysteine metabolism*
- Intestinal bacteria modify and deconjugate the primary bile acids forming ***secondary bile acids*** such as *deoxycholic acid* and *lithocholic acid*
- After lipid absorption, 95% of bile is recycles and reabsorbed into the liver by the ***portal vein*** (enterohepatic circulation), via *Apical Sodium-Bile salt Cotransporter* in the intestinal walls
  - 5% of bile is excreted
  - Bile acid **sequestrants**, such as *cholestyramine*, bind bile salts in the gut and prevent their reabsorption, thereby promoting their excretion which consequently reduces plasma cholesterol
- Bile salt deficiency (**Cholelithiasis**)
  - ↑ Cholesterol or ↓ bile acids = insolubility which causes ***gallbladder stones*** (cholelithiasis)
  - Treatment: *cholecystectomy* or oral *administration of chenodeoxycholic acid* results in a gradual (months to years) dissolution of the gallstones

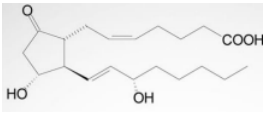
❖ Eicosanoids

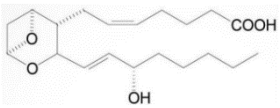
- They are derived from ω-3 and ω-6 polyunsaturated FA with **20-C** especially *arachidonic acid*, and they include prostaglandins (PGI), prostacyclins (PGI), thromboxanes (TX), leukotrienes (LT) and lipoxins (LX)
  - They are *not hormones*
  - They have *short half-life* (*rapidly metabolized* to inactive products) and *aren't stored*
  - ***Prostanoid:*** Prostaglandin, prostacyclin, thromboxane

Arachidonic acid is an eicosatetraenoic FA
- It is synthesized by the elongation (by 2C) and desaturation (from 2 to 4 double bonds) of ***linoleic acid***
- It is usually incorporated to the **C-2** of **PI** in the plasma and ER membranes
- PLA2 is inhibited by corticosteroids

- Eicosanoids elicit physiologic (*inflammatory*) and pathologic (*hypersensitivity*) responses affecting:
  - gastric integrity, renal function, smooth muscle contraction (intestine and uterus), blood vessel diameter (dilation and constriction), and platelet homeostasis

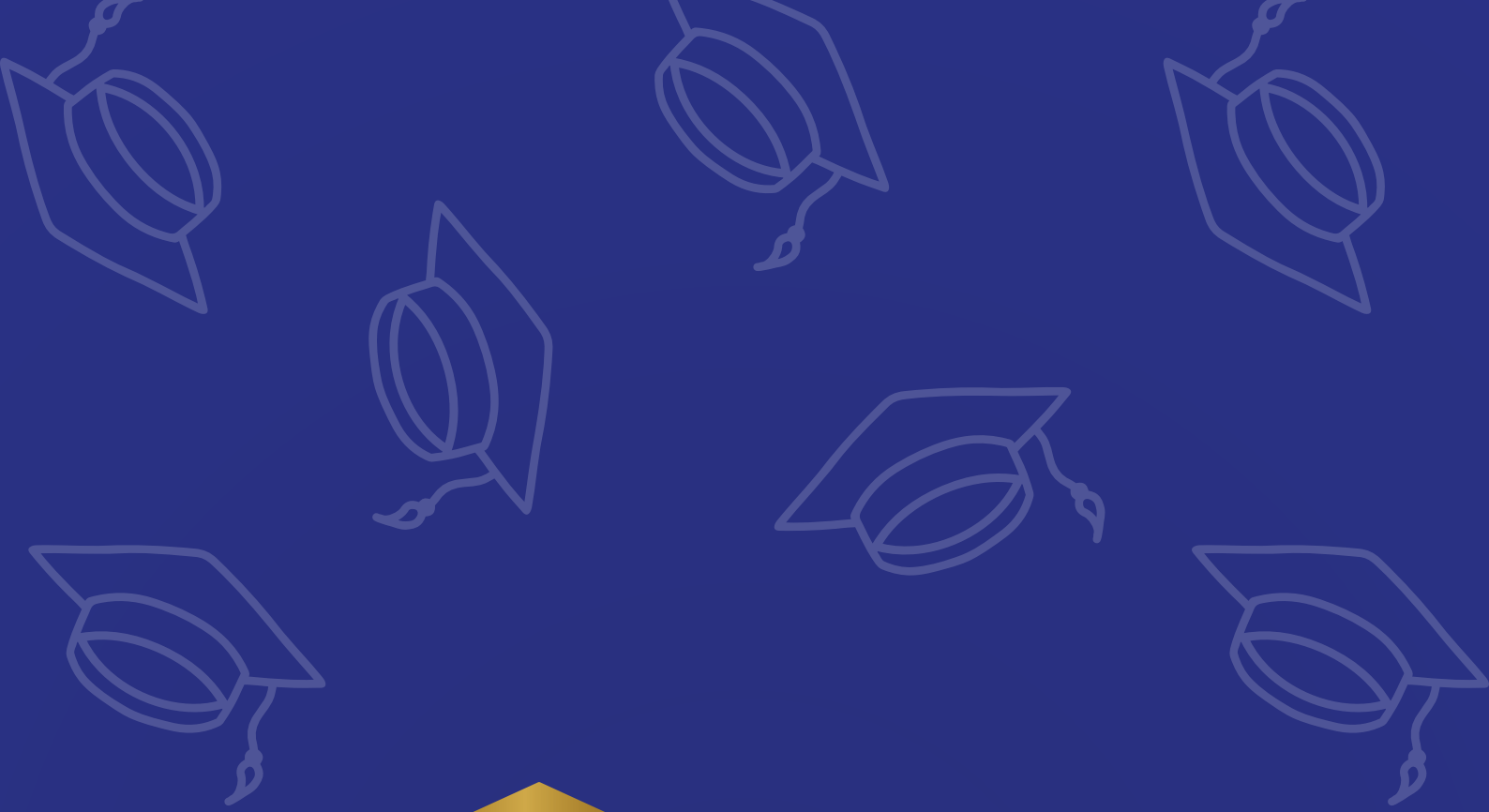
- **Prostaglandins** are produced by almost all nucleated cells in most tissues
  - They have a *cyclopentane ring* (5-membered ring)
  - They are designated by a letter that describes the *ring modification* followed by a number that indicates the *number of double bonds*





- **Thromboxanes** have a *6-membered ring*
- Synthesis of PGs and TXs starts by *oxidative cyclization* of arachidonic acid to yield **PGH2** by ***PGH2 synthase*** (or ***prostaglandin endoperoxide synthase***) which has two catalytic activities: a fatty acid ***cyclooxygenase*** (COX) and a ***peroxidase*** (requires reduced glutathione)
- There are two isozymes of PGH2 synthase:
  - **COX-1** is made **constitutively** in most tissues and affects *platelet aggregation* and the functions of *gastric, renal tissues*
  - **COX-2** is **inducible** in specific tissues and mediates *the pain, heat, redness, and swelling* of inflammation and the *fever* of infection
    - ✓ Induced by cytokines, endotoxin, growth factors, tumor promoter
    - ✓ **Celecoxib** is a selective inhibitor of COX2
- PGH2 can be converted by:
  - ***Thromboxane synthase:*** produces *TXA2* which produced by COX1 in platelets, and functions to promote platelet aggregation, vasoconstriction, bronchoconstriction (asthma), calcium mobilization
  - ***Prostacyclin synthase:*** produces *PGI2* which produced by COX2 in the endothelium, and functions to inhibit platelet aggregation and vasodilation
- Aspirin (irreversible) and NSAIDs are inhibitors that affects both COX 1 and 2
  - COX1 inhibition ***cannot be overcome in platelets***, but COX2 can be overcome in endothelial cells, so a low-dose aspirin lowers the risk of stroke and heart attacks by decreasing formation of thrombi
- **Bradykinin**, **epinephrine** and **thrombin** can induce the release of arachidonic acid from PI by PLA2 by binding to a GPCR that activated both **Gq and Gi**, which induces the production of PGs
- LTs are mediators of allergic response and inflammation
  - 5-lipoxygenase converts arachidonic acid into 5-HPETE which is converted into LTA4 which can be converted into other LTs in the presence of glutathione (GSH)
  - *Inhibitors of 5-LOX* and *LT receptor antagonists* are used in the **treatment of asthma**
  - LT synthesis is inhibited by cortisol and not by NSAID
  - Aspirin-exacerbated respiratory disease is a response to LT overproduction with NSAID use in ~10% of individuals with asthma

- **LTC4, LTD4, LTE4** cause contraction of smooth muscles, vasoconstriction, bronchoconstriction, anaphylaxis and asthma
- **LTB4** is a chemotactic agent for neutrophils, adhesion and release lysosomal enzymes of WBCs
- Catabolism of prostanoids:
  - Prostanoids are often deactivated quickly either spontaneously or enzymatically ($t_{½}$ = 30 seconds)
  - Prostanoids are first transported from the ECF to cytoplasm by the prostaglandin transport protein (PGT) where they are converted into products that are either inactive or can inhibit cell proliferation
  - They are eliminated via the kidney into the urine
- Lipoxins: an anti-inflammatory (inhibit the actions of the leukotrienes)
- Synthetic pathways of lipoxins:
  - Classic pathway: 5-lipoxygenase (*5-LOX*) in leukocytes followed by *12-LOX* in platelets
  - *15-LOX* in epithelial cell (such as airway cells) followed by *5-LOX* action in leukocytes
  - Aspirin-mediated *acetylation of COX-2* which alters the enzyme to convert arachidonic acid to biologically active LXs (15R-HETE) in monocytes and leukocytes by 5-lipoxygenase (*5-LOX*)
- Lipoxins can regulate the actions of histamine leading to a reduction in edema
- *Resolvins (Rv)*, *protectins (PD)*, and *maresins (MaR)* are ***anti-inflammatory*** lipids that are derived from the omega-3 EPA- and DHA by lipoxygenases
  - Aspirin triggers their synthesis
  - They stimulate the resolution of the inflammatory responses through GPCR via diverse action such as limiting neutrophil recruitment to the site of inflammation and promoting macrophage clearance of debris, apoptotic cells and bacteria



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