"Dietary Lipid Metabolism"

I. Overview

- Lipids are a heterogeneous group of water-insoluble (hydrophobic) organic molecules.

- Due to their insolubility in aqueous solutions:

    - Body lipids are generally found compartmentalized, such as:
        - Membrane-associated lipids
        - Droplets of triacylglycerol (TAG) in adipocytes
    - Or transported in blood in association with protein:
        - In lipoprotein particles
        - On albumin

- Lipids are a major source of energy for the body.

- Lipids also provide the hydrophobic barrier that permits partitioning of the aqueous contents of:

    - Cells
    - Subcellular structures

- Additional functions of lipids in the body include:
    - Some fat-soluble vitamins have regulatory or coenzyme functions
    - Prostaglandins and steroid hormones play major roles in control of the body's homeostasis
- Deficiencies or imbalances of lipid metabolism can lead to some of the major clinical problems encountered by physicians, such as:
    - Atherosclerosis
    - Diabetes
    - Obesity

II. Digestion, Absorption, Secretion, And Utilization

- The average daily intake of lipids by U.S. adults is 78 g, of which:
    - >90% is TAG (triglyceride or TG)
        - TAG consists of three fatty acids (FA) esterified to a glycerol backbone.

- The remainder of the dietary lipids consists primarily of:
  - Cholesterol
  - Cholesteryl esters
  - Phospholipids
  - Nonesterified (free) FA (FFA)

- The digestion of dietary lipids:

  - Begins in the stomach
  - Is completed in the small intestine

A. Digestion in the Stomach

- Lipid digestion in the stomach is limited.

- It is catalyzed by:

  - Lingual lipase (originates from glands at the back of the tongue)
  - Gastric lipase (secreted by the gastric mucosa)

- Both enzymes are relatively acid stable, with optimal pH values of 4 to 6.

- These acid lipases hydrolyze FA from TAG molecules, particularly:
    - Short- or medium-chain-length FA (⩽12 carbons)
    - Such as are found in milk fat
- Consequently, these lipases:
    - Play a particularly important role in lipid digestion in infants, for whom milk fat is the primary source of calories
    - Become important digestive enzymes in individuals with pancreatic insufficiency, such as:
        - Those with cystic fibrosis (CF)
- Lingual and gastric lipases aid these patients in degrading TAG molecules (especially those with short- to medium-chain FA) despite:
    - A near or complete absence of pancreatic lipase

B. Cystic Fibrosis

- CF is the most common lethal genetic disease in Caucasians of Northern European ancestry.

- It has a prevalence of 1:3,300 births in the United States.

- CF is an autosomal-recessive disorder caused by:
    - Mutations to the gene for the CF transmembrane conductance regulator (CFTR) protein

- CFTR functions as a chloride channel on epithelium in:

    - Pancreas
    - Lungs
    - Testes
    - Sweat glands

- Defective CFTR results in:

    - Decreased secretion of chloride
    - Increased uptake of sodium and water

- In the pancreas, the depletion of water on the cell surface results in:

    - Thickened mucus that clogs the pancreatic ducts
    - Prevents pancreatic enzymes from reaching the intestine
    - Leads to pancreatic insufficiency

- Treatment includes:
    - Replacement of pancreatic enzymes
    - Supplementation with fat-soluble vitamins
- Note: CF also causes:
    - Chronic lung infections with progressive pulmonary disease
    - Male infertility

C. Emulsification in the Small Intestine

- The critical process of dietary lipid emulsification occurs in the duodenum.
- Emulsification increases the surface area of the hydrophobic lipid droplets so that:
    - Digestive enzymes, which work at the interface of the droplet and the surrounding aqueous solution, can act effectively.

- Emulsification is accomplished by two complementary mechanisms:
    - Use of the detergent properties of the conjugated bile salts
    - Mechanical mixing due to peristalsis
- Bile salts:
    - Are made in the liver
    - Stored in the gallbladder
    - Are amphipathic derivatives of cholesterol
- Conjugated bile salts consist of:
    - A hydroxylated sterol ring structure
    - A side chain to which a molecule of glycine or taurine is covalently attached by an amide linkage
- These emulsifying agents:
    - Interact with the dietary lipid droplets and the aqueous duodenal contents
    - Stabilize the droplets as they become smaller from peristalsis
    - Prevent the droplets from coalescing

D. Degradation by Pancreatic Enzymes

- The dietary TAG, cholesteryl esters, and phospholipids are enzymatically degraded (digested) in the small intestine by pancreatic enzymes, whose secretion is hormonally controlled.

1. Triacylglycerol Degradation

- TAG molecules are too large to be taken up efficiently by the mucosal cells (enterocytes) of the intestinal villi.
- Therefore, they are hydrolyzed by an esterase, pancreatic lipase, which:
    - Preferentially removes the FA at carbons 1 and 3
- The primary products of hydrolysis are a mixture of:
    - 2-monoacylglycerol (2-MAG)
    - FFA

- (Note: Pancreatic lipase is found in high concentrations in pancreatic secretions [2% to 3% of the total protein present], and it is highly efficient catalytically, thus ensuring that only severe pancreatic deficiency, such as that seen in CF, results in significant malabsorption of fat.)

- A second protein, colipase, also secreted by the pancreas:

    - Binds the lipase at a ratio of 1:1
    - Anchors it at the lipid–aqueous interface
    - Restores activity to lipase in the presence of inhibitory substances like bile salts that bind the micelles

- (Note: Colipase is secreted as the zymogen, procolipase, which is activated in the intestine by trypsin.)

- Orlistat, an antiobesity drug, inhibits gastric and pancreatic lipases, thereby:

    - Decreasing fat absorption
    - Resulting in weight loss

2. Cholesteryl Ester Degradation

- Most dietary cholesterol is present in the free (nonesterified) form.
- 10% to 15% is present in the esterified form.
- Cholesteryl esters are hydrolyzed by:
    - Pancreatic cholesteryl ester hydrolase (cholesterol esterase)
- The reaction produces:
    - Cholesterol
    - FFA
- Activity of this enzyme is greatly increased in the presence of bile salts.

3. Phospholipid Degradation

- Pancreatic juice is rich in the proenzyme of phospholipase A2, which:
    - Like procolipase, is activated by trypsin

    - Like cholesteryl ester hydrolase, requires bile salts for optimum activity

- Phospholipase A2:

    - Removes one FA from carbon 2 of a phospholipid
    - Leaves a lysophospholipid

- Example:

    - Phosphatidylcholine (the predominant phospholipid of digestion) becomes:
        - Lysophosphatidylcholine

- The remaining FA at carbon 1 can be removed by lysophospholipase, leaving a:

    - Glycerylphosphoryl base (e.g., glycerylphosphorylcholine)

- The glycerylphosphoryl base may be:

    - Excreted in the feces
    - Further degraded
    - Absorbed

4. Control

- Pancreatic secretion of the hydrolytic enzymes that degrade dietary lipids in the small intestine is hormonally controlled.

- Enteroendocrine cells found throughout the small intestine secrete several hormones, such as:

    - Cholecystokinin (CCK)
    - Secretin

- Enteroendocrine I cells, located in the mucosa of the lower duodenum and jejunum, produce:

    - The peptide hormone CCK, in response to:
        - Presence of lipids
        - Partially digested proteins entering these regions of the upper small intestine

- CCK acts on:

    - The gallbladder:
        - Causing it to contract and release bile
        - Bile is a mixture of bile salts, phospholipids, and free cholesterol

    - The exocrine cells of the pancreas:
        - Causing them to release digestive enzymes

- CCK also decreases gastric motility, resulting in:

    - A slower release of gastric contents into the small intestine

- Enteroendocrine S cells produce another peptide hormone, secretin, in response to:

    - The low pH of the chyme entering the intestine from the stomach

- Secretin causes the pancreas to release:

    - A solution rich in bicarbonate, which:
        - Helps neutralize the pH of the intestinal contents
        - Brings them to the appropriate pH for digestive activity by pancreatic enzymes

E. Absorption by Enterocytes

- FFA, free cholesterol, and 2-MAG are the primary products of lipid digestion in the jejunum.
- These, plus:
    - Bile salts
    - Fat-soluble vitamins (A, D, E, and K)
    - → Form mixed micelles
- Mixed micelles are:
    - Disc-shaped clusters of a mixture of amphipathic lipids
    - Coalesce with:
        - Hydrophobic groups on the inside
        - Hydrophilic groups on the outside
- Therefore, mixed micelles are soluble in the aqueous environment of the intestinal lumen
- These particles approach the primary site of lipid absorption, the:
    - Brush border membrane of the enterocytes

- This microvilli-rich apical membrane is:
    - Separated from the liquid contents of the intestinal lumen by an:
        - Unstirred water layer
    - This layer mixes poorly with the bulk fluid
- The hydrophilic surface of the micelles:
    - Facilitates the transport of the hydrophobic lipids through the unstirred water layer
    - To the brush border membrane, where they are absorbed
- Bile salts are:
    - Absorbed in the terminal ileum
    - With <5% being lost in the feces
- Note: Cholesterol and plant sterols are taken up by the enterocytes through the Niemann-Pick C1-like 1 (NPC1L1) protein in the brush border cells.
- Ezetimibe, a cholesterol-lowering drug, inhibits NPC1L1, reducing cholesterol absorption in the small intestine.

- Because short- and medium-chain FA are water soluble, they:
    - Do not require the assistance of mixed micelles for absorption by the intestinal mucosa

F. Triacylglycerol and Cholesteryl Ester Resynthesis

- The mixture of lipids absorbed by the enterocytes migrates to the smooth endoplasmic reticulum (SER), where:
    - Biosynthesis of complex lipids takes place
- The long-chain FA are first converted into their activated form by:
    - Fatty acyl coenzyme A (CoA) synthetase (thiokinase)

- Using the fatty acyl CoA derivatives, the:
    - 2-MAG absorbed by the enterocytes are converted to TAG through:
        - Sequential reacylations by two acyltransferases:
            1. Acyl CoA:MAG acyltransferase
            2. Acyl CoA:diacylglycerol acyltransferase
- Lysophospholipids are reacylated to form phospholipids by:
    - A family of acyltransferases
- Cholesterol is acylated primarily by:
    - Acyl CoA:cholesterol acyltransferase
- (Note: Virtually all long-chain FA entering the enterocytes are used in this fashion to form TAG, phospholipids, and cholesteryl esters.)

- Short- and medium-chain FA:
    - Are not converted to their CoA derivatives
    - Are not reesterified to 2-MAG
    - Instead, they are:
        - Released into the portal circulation
        - Carried by serum albumin to the liver

G. Secretion from Enterocytes

- The newly resynthesized TAG and cholesteryl esters are:
    - Very hydrophobic
    - Aggregate in an aqueous environment
- Therefore, they must be packaged as particles of lipid droplets, which are:
    - Surrounded by a thin layer composed of:
        - Phospholipids
        - Nonesterified cholesterol
        - A molecule of the protein apolipoprotein (apo) B-48

- This layer stabilizes the particle and:
    - Increases its solubility
    - Prevents multiple particles from coalescing
- (Note: Microsomal TG transfer protein is essential for the assembly of all TAG-rich apo B-containing particles in the ER.)
- The lipoprotein particles are:
    - Released by exocytosis from enterocytes into the lacteals
    - (lymphatic vessels in the villi of the small intestine)
- The presence of these particles in the lymph after a lipid-rich meal:
    - Gives it a milky appearance
- This lymph is called chyle
- (as opposed to chyme, the semifluid mass of partially digested food that passes from the stomach to the duodenum)

- The particles are named chylomicrons

- Chylomicrons:

    - Follow the lymphatic system to the thoracic duct
    - Are then conveyed to the left subclavian vein
    - Enter the blood

- (Note: Once released into blood, the nascent [immature] chylomicrons pick up apolipoproteins E and C-II from high-density lipoproteins and mature.

H. Lipid Malabsorption

- Lipid malabsorption results in:

    - Increased lipid (including fat-soluble vitamins and essential FA, see Chapter 16) in the feces
    - A condition known as steatorrhea

- Steatorrhea can be caused by disturbances in lipid digestion and/or absorption

- Such disturbances can result from several conditions, including:
    - Cystic fibrosis (CF) → Causing poor digestion
    - Short bowel syndrome → Causing decreased absorption
    - Bariatric surgery → Insufficient secretion of pancreatic enzymes
- The ability of short- and medium-chain FA to be:
    - Taken up by enterocytes without the aid of mixed micelles
    - → Has made them important in medical nutrition therapy for individuals with malabsorption disorders

I. Use by the Tissues

- Most of the TAG contained in chylomicrons is broken down in the capillary beds of:
    - Skeletal muscle
    - Cardiac muscle
    - Adipose tissue

- TAG is degraded to:
    - FFA
    - Glycerol
- This reaction is catalyzed by:
    - Lipoprotein lipase (LPL)
- LPL is synthesized and secreted primarily by:
    - Adipocytes
    - Muscle cells
- Secreted LPL is anchored to the luminal surface of endothelial cells in the capillaries of:
    - Muscle
    - Adipose tissues
- LPL is activated when bound to its cofactor:
    - ApoCII, which resides on the circulating lipoprotein particles

- Note: Familial chylomicronemia [type I Hyperlipoproteinemia] is a rare, autosomal-recessive disorder caused by a deficiency of:
    - LPL or
    - Its coenzyme apo C-II [see Chapter 18].
    - The result is fasting chylomicronemia and severe hypertriacylglycerolemia, which can cause pancreatitis.

I. Fate of Free Fatty Acids (FFA)

- The FFA derived from the hydrolysis of TAG may:
    - Directly enter adjacent muscle cells and adipocytes, or
    - Be transported in the blood in association with serum albumin, until they are taken up by cells

- Note: Human serum albumin is a large protein secreted by the liver.

- It transports a number of primarily hydrophobic compounds in the circulation, including:
    - FFA
    - Some drugs

- Most cells can:
    - Oxidize FA to produce energy
- Adipocytes can also:
    - Reesterify FFA to produce TAG molecules, which are:
        - Stored until the FA are needed by the body

2. Fate of Glycerol

- Glycerol released from TAG is:
    - Taken up from the blood
    - Phosphorylated by hepatic glycerol kinase to produce:
        - Glycerol 3-phosphate
- Glycerol 3-phosphate can:
    - Enter glycolysis
    - Enter gluconeogenesis by oxidation to dihydroxyacetone phosphate
    - Be used in TAG synthesis

3. Fate of Chylomicron Remnants

- After most of the TAG has been removed, the chylomicron remnants (which contain):
    - Cholesteryl esters
    - Phospholipids
    - Apolipoproteins
    - Fat-soluble vitamins
    - A small amount of TAG

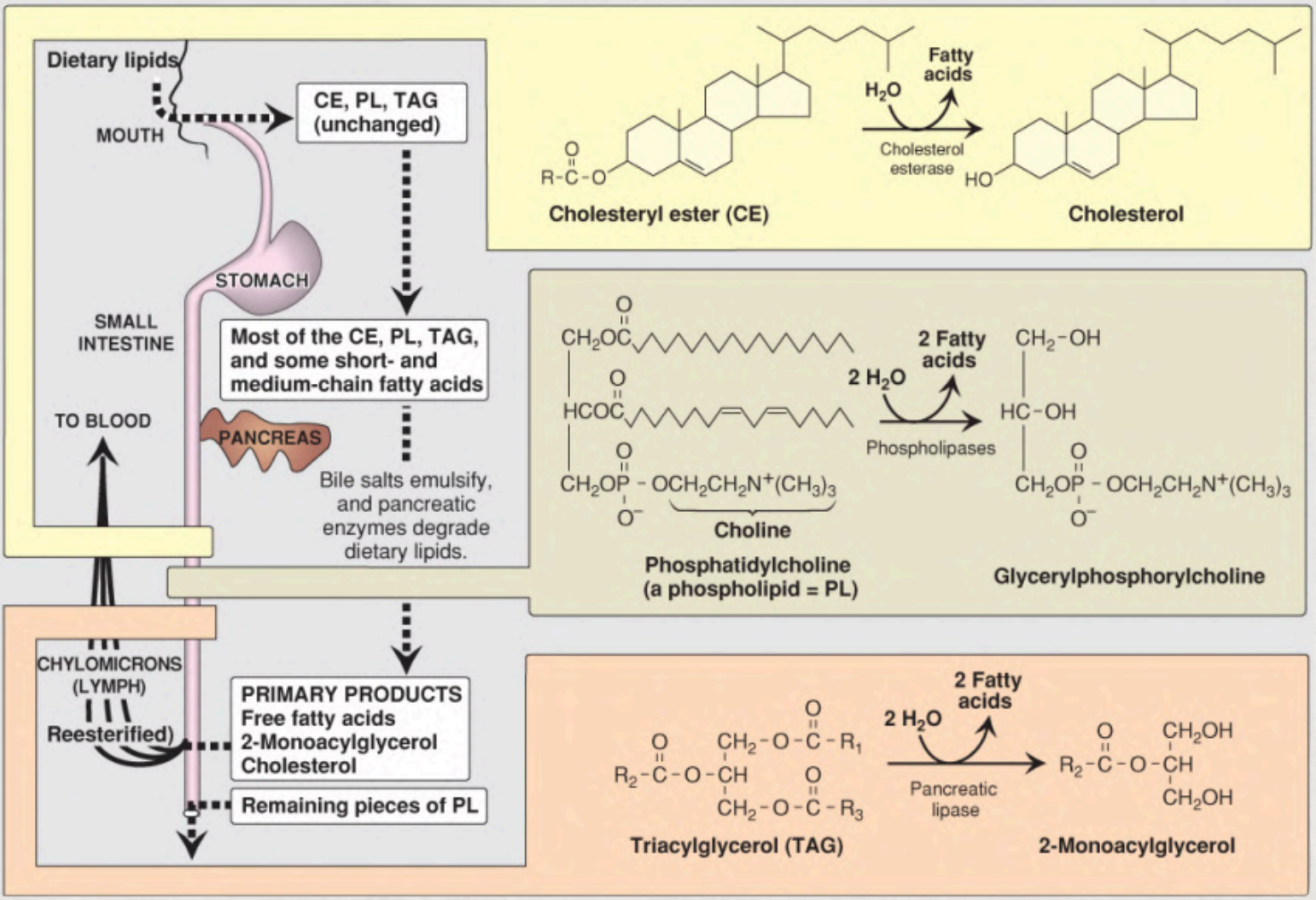
→ Bind to receptors on the liver

- Apo E is the ligand for this receptor-mediated binding
- The chylomicron remnants are endocytosed by the liver
- Intracellular remnants are:
    - Hydrolyzed to their component parts
- Cholesterol and the nitrogenous bases of phospholipids (e.g., choline) can be:
    - Recycled by the body

- Note: If removal of remnants by the liver is decreased because of impaired binding to their receptor, they accumulate in the plasma.

- This is seen in the rare:
  - Type III hyperlipoproteinemia
  - (also called familial dysbetalipoproteinemia or broad beta disease).

Overview Lipid Digestion



Assembly and Secretion of Chylomicrons by Intestinal Mucosal Cells