# LIPID METABOLISM-1

# DIGESTION OF LIPIDS

- More than 90% of the daily consumed dietary lipids are triacylglycerols (TAGs, triglycerides).
- The remainder of the dietary lipids consist of cholesterol, cholesteryl esters, phospholipids, and free fatty acids.

- The digestion of lipids begins in the stomach, carried out by an acid stable lipase (lingual lipase) that originates from back of the tongue.
- TAG molecules, especially containing short- or medium-chain length fatty acids (less than 12 carbons, as in milk fat), are the primary target of lingual lipase.

- These same TAGs are also degraded by another lipase (gastric lipase, secreted by gastric mucosa).
- Both enzymes are relatively acid-stable (pH optimums are between 4 – 6).
- These “acid lipases” are especially important in neonates’ lipid digestion. (milk fat is the primary source of energy in neonates)

- They are also important for individuals with pancreatic insufficiency (for examle; cystic fibrosis).
- Lingual and gastric lipases help these patients in digesting TAG molecules (especially the ones containing short- to medium-chain fatty acids) in (almost complete) absence of pancreatic lipase.

# Cystic Fibrosis (CF)

- The most common lethal genetic disease in Caucasians of Northern European ancestry (prevalence; 1:3,000 births).
- This is an autosomal recessive disorder caused by mutations to the gene for the CF transmembrane conductance regulator (CFTR) protein.
- CFTR protein functions as a chloride channel on epithelium.

- Defective CFTR results in decreased secretion of chloride and increased reabsorption of sodium and water.
- In the pancreas, secretions become thickened so that, pancreatic enzymes can not reach the intestine, which leads to pancreatic insufficiency.

# Emulsification of Dietary Lipids

- Emulsification of dietary lipids occurs in the duodenum.
- The surface area of the hydrophobic lipid droplets increases by emulsification so that the digestive enzymes can act effectively.

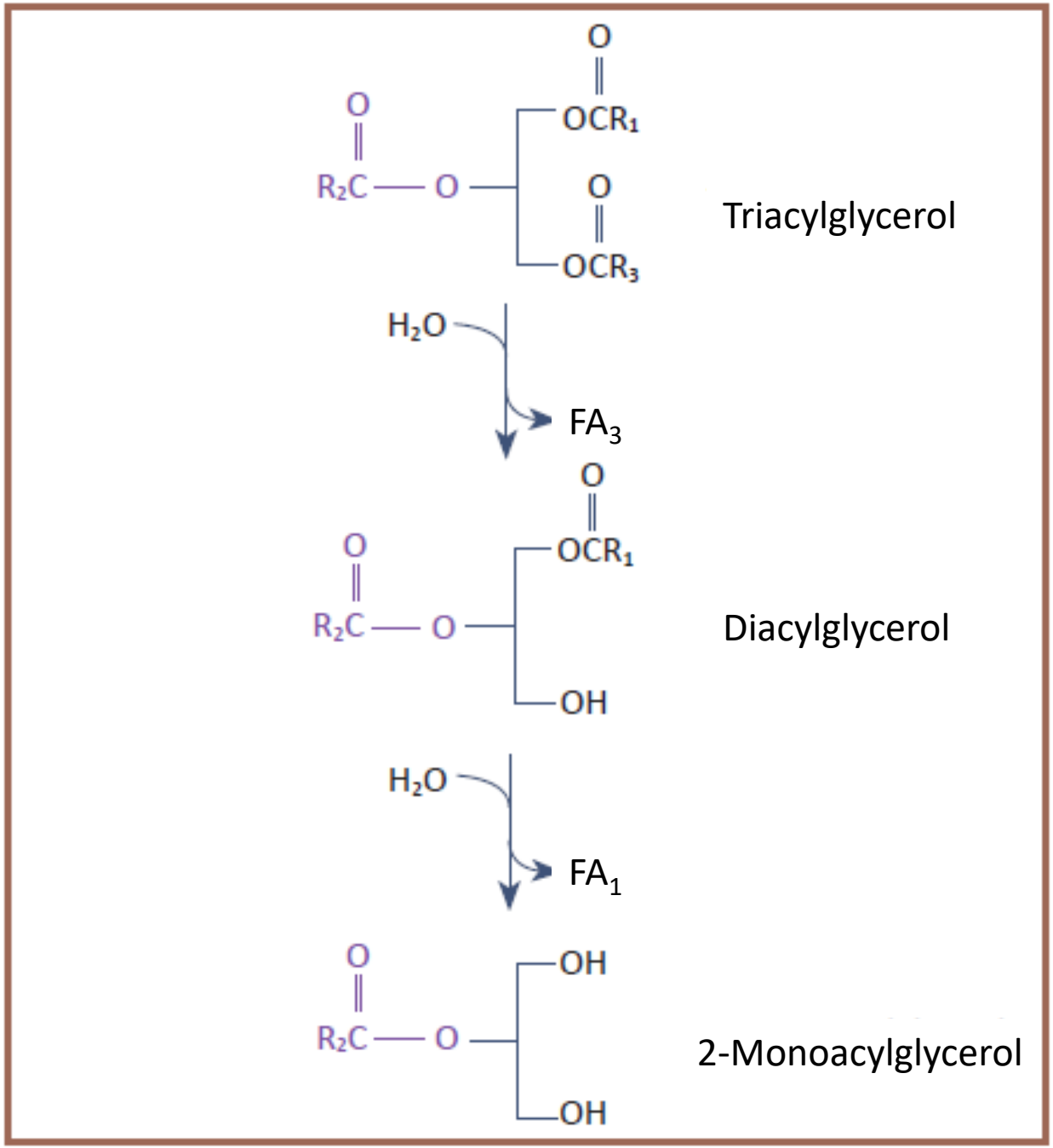
- Emulsification is accomplished by two complementary mechanisms:
  i. Detergent properties of the bile salts,
  ii. Mechanical mixing due to peristalsis.

- Bile salts are derivatives of cholesterol.
- They consist of a sterol ring structure with a side chain to which a molecule of glycine or taurine is attached.
- Emulsifying agents interact with the dietary lipid particles and the aqueous duodenal contents.
- Through this, they stabilize the particles and prevent them from coalescing.

- The dietary TAGs, cholesteryl esters, and phospholipids are enzymically digested by the help of pancreatic enzymes.
- Secretion of those enzymes are controlled hormonally.

# Degradation of TAGs

- TAG molecules are too large to be taken up efficiently by the mucosal cells of the intestinal villi.
- Therefore, they are acted upon pancreatic lipase, which removes the fatty acids at carbons 1 and 3.
- The products of the hydrolysis are a mixture of 2-monoacylglycerols and free fatty acids.




The effect of pancreatic lipase

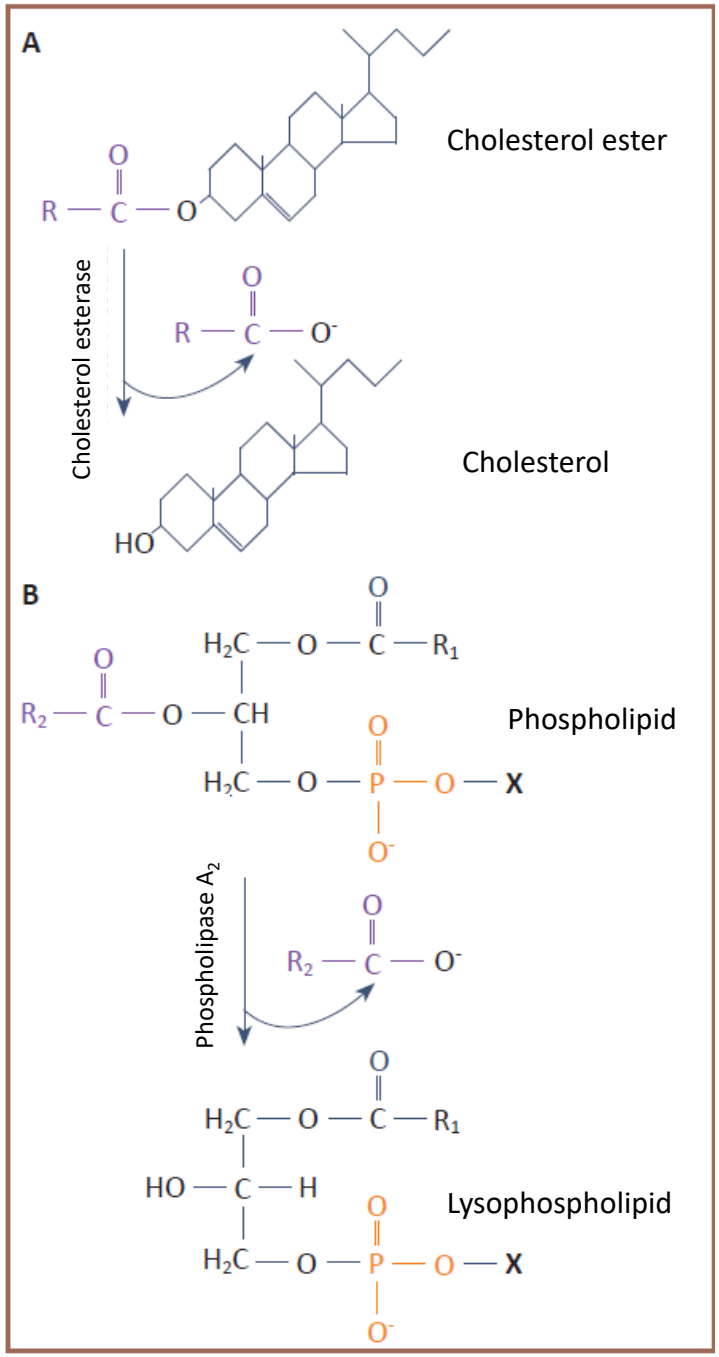
- Another protein, colipase, also secreted by the pancreas, binds the lipase and anchors it at the lipid-aqueous interface.
- Colipase restores activity to lipase in the presence of inhibitory substances (like bile acids which bind the micelles).
- Colipase is secreted in the form of procolipase and then activated in the intestine by trypsin.

# Degradation of Cholesteryl Esters

- Most of the dietary cholesterol is present in nonesterified form (only 10–15% is found in esterified form).
- Cholesteryl esters are hydrolyzed by pancreatic cholesteryl ester hydrolase (cholesterol esterase), which produces cholesterol plus free fatty acids.
- The presence of bile salts increase the activity of the enzyme (cholesterol esterase).

# Degradation of Phospholipids

- Pancreatic juice is rich in the proenzyme of phospholipase A2 that, like procolipase, is activated by trypsin and, like cholesteryl ester hydrolase, requires bile salts for optimum activity.
- Phospholipase A2 removes one fatty acid from carbon 2 of a phospholipid, leaving a lysophospholipid.




Effects of cholesterol esterase and phospholipase $A_2$

- The fatty acid at carbon 1 is removed by lysophospholipase, leaving a glycerylphosphoryl base (which can be left in the lumen and excreted in the feces, further degraded, or absorbed).

# Hormonal Control of Lipid Digestion

- Pancreatic enzymes that degrade dietary lipids in the small intestine are under the control of hormones.
- Mucosal cells of the lower duodenum and jejunum produce and secrete a small peptide hormone, **cholecystokinin (CCK)**.
- Secretion of the CCK is stimulated by the presence of lipids and partially digested proteins in the upper small intestine.

- CCK cause gallbladder to contract and release bile (a mixture of bile salts, phospholipids, and free cholesterol) and cause the exocrine cells of the pancreas to release digestive enzymes.
- It also decrease gastric motility which results in slower release of gastric contents into the small intestine.

- **Secretin,** another small peptide hormone is also secreted by intestinal cells, whose secretion is stimulated by the low pH of the chyme entering the intestine.
- Secretin causes the pancreas and the liver to release a solution rich in bicarbonate (helps neutralize the pH of the intestinal contents), which brings the intestinal content to the appropriate pH for digestive activity of pancreatic enzymes.

# Absorption of Lipids

- Free fatty acids, free cholesterol, and 2-monoacylglycerol are the primary products of lipid digestion in the jejunum.
- These, plus bile salts and fat-soluble vitamins form mixed micelles (diskshaped clusters of amphipathic lipids that coalesce with their hydrophobic groups on the inside and their hydrophilic groups on the outside).
- Mixed micelles are, therefore, 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 (mucosal cells).
- This membrane is separated from the liquid contents of the intestinal lumen by an unstirred water layer.
- The hydrophilic surface of the micelles facilitates the transport of the hydrophobic lipids to the brush border membrane.

- Bile salts are absorbed in the ileum.
- Relative to other dietary lipids, cholesterol is only poorly absorbed by the enterocytes.
- Short- and medium-chain length fatty acids do not require any assistance for absorption by the intestinal mucosa.

# TAG, Cholesteryl Ester and Phospholipid Resynthesis in Enterocytes

- The mixture of lipids absorbed by the enterocytes migrates to the endoplasmic reticulum where biosynthesis of complex lipids takes place.
- Fatty acids are first converted into their activated form by fatty acyl-CoA synthetase (thiokinase).

- Using the fatty acyl CoA derivatives, the 2-monoacylglycerols absorbed by the enterocytes are converted to TAGs by the enzyme complex, TAG synthase.
- This complex has activities of both of the enzymes: acyl CoA:monoacylglycerol acyltransferase and acyl CoA:diacylglycerol acyltransferase.
- By consecutive action of these enzymes, two fatty acids are attached to the 2-monoacylglycerols.

- Lysophospholipids are reacylated to form phospholipids by a family of acyltransferases, and cholesterol is esterified to a fatty acid primarily by acyl CoA:cholesterol acyltransferase.
- All long-chain fatty acids entering the enterocytes are used in this fashion to form TAGs, phospholipids, and cholesteryl esters.

- Short- and medium-chain length fatty acids are not converted to their CoA derivatives, and are not reesterified to 2-monoacylglycerol.
- They are directly released into the portal circulation, where they are carried by serum albumin to the liver.