BCHM 270: MODULE 5

Lipid Metabolism

Content Outline

Section 1..... Introduction to Lipids: Structure and Function

Section 2..... Digestion of Dietary Lipids

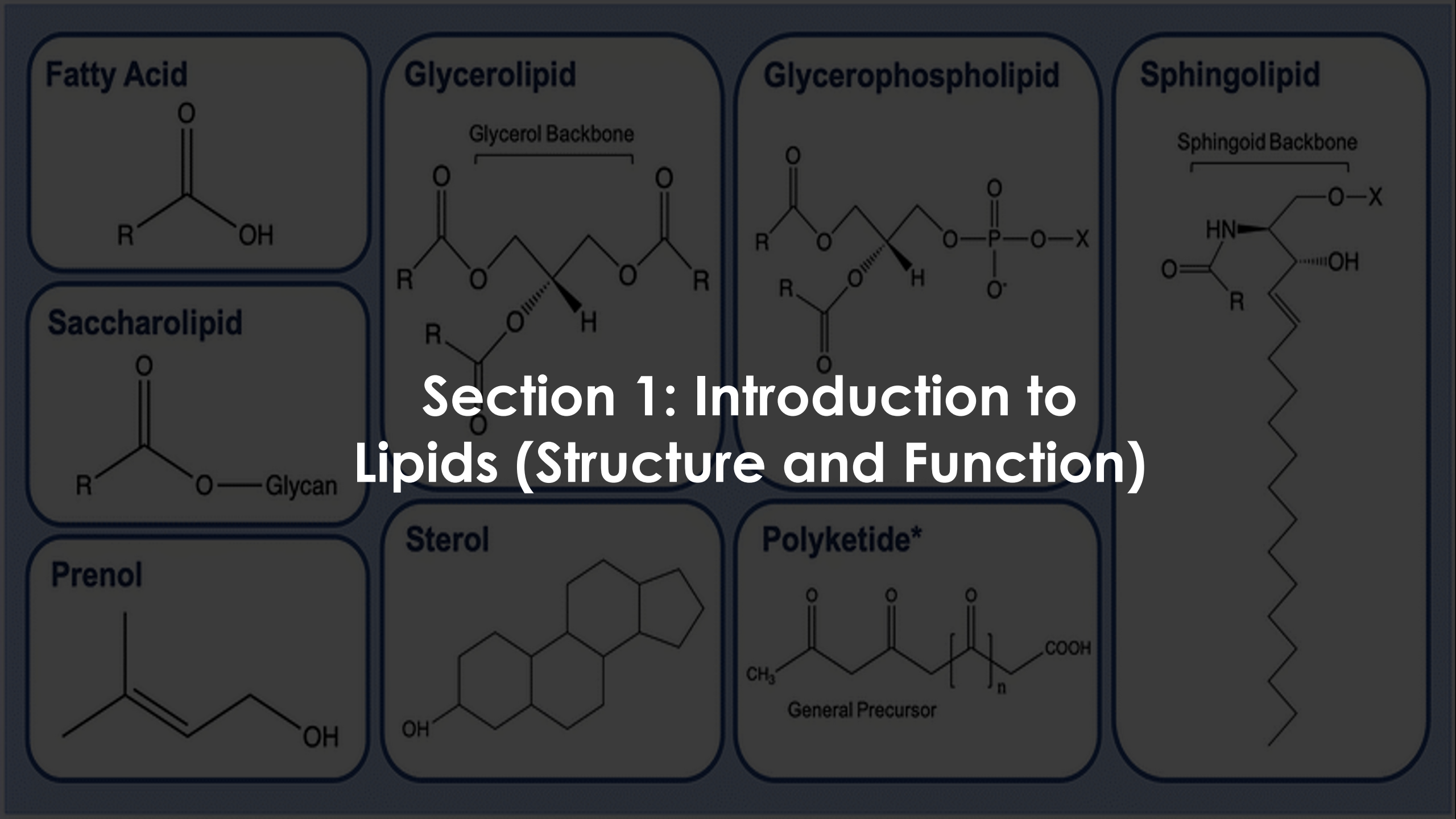
Section 3..... Fatty Acid Degradation

Section 4..... Fatty Acid Synthesis

Section 5..... Ketone Bodies as an Alternative Fuel

Section 6..... Cholesterol, Bile Salts, and Enterohepatic Circulation

Section 7..... Plasma lipoproteins



Section 1: Introduction to Lipids (Structure and Function)

Concept 1.1: General physical and chemical properties of lipids

Lipids:

- Hydrophobic organic molecules
  - Require specialized proteins (lipoproteins) for lipid transport
- Essential for homeostasis
- Stored in adipocytes as fat
  - Energy source
  - Allow for storage of fat-soluble vitamins (A,D,E,K)

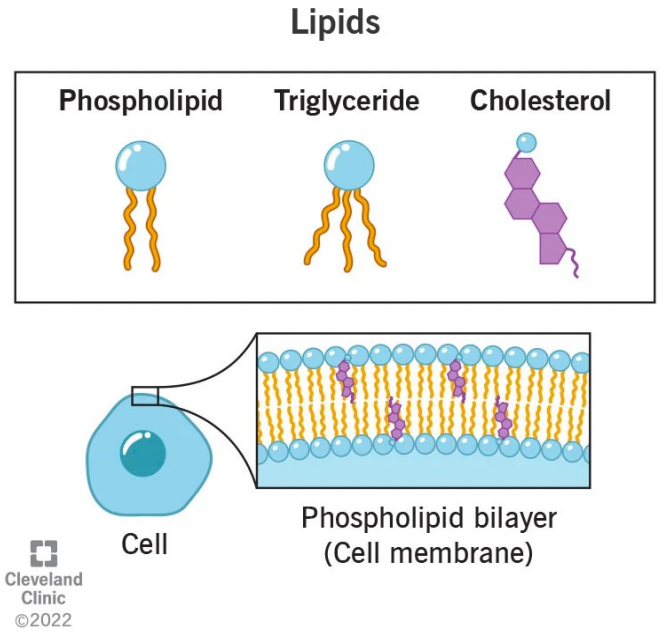


Figure 1: Types of Lipids.

Concept 1.2: Structure and nomenclature of fatty acids (include a description of cis and trans fatty acids)

Structure

- Hydrophobic hydrocarbon chain with carboxyl at end
- At physiological pH, carboxyl group ionized, so carboxylic end is hydrophilic and molecule is amphipathic

Size

- Short: < 6 carbons, Medium: 6-12 carbons. Long: 13-21 carbons, Very long: > 22 carbons
- Increasing carbon chain length increases melting point

Saturation

- Saturated- without double bonds. Double bond introduces unsaturation and lowers melting point
- Most unsaturated fatty acids are cis rather than trans.
- Cis -> 2 H on the same side, Trans -> 2 H on opposite sides
- Trans are avoided due to negative impact on cardiovascular health

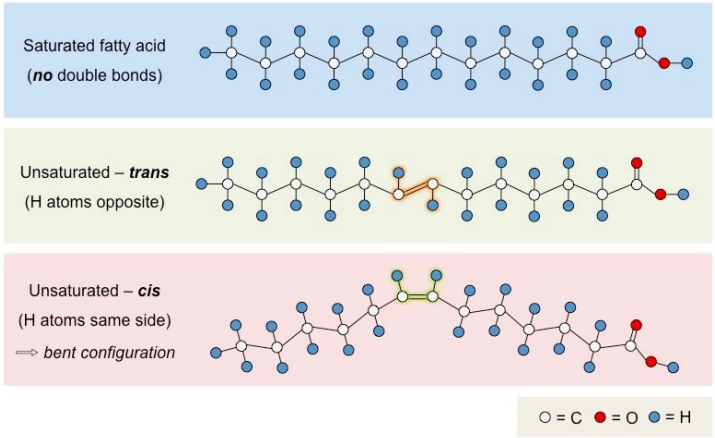


Figure 2: Saturated and unsaturated fatty acids.

Concept 1.3: Nomenclature of fatty acids (from C1 and omega end) example

Nomenclature:

- Naming convention: number of carbons, number of double bonds, position of double bonds
- Fatty acids can be numbered from alpha carbon at the carboxyl end or omega carbon at the methyl end
- C1 is carboxyl carbon, C2 is the alpha-carbon, C3 is beta-carbon, etc.

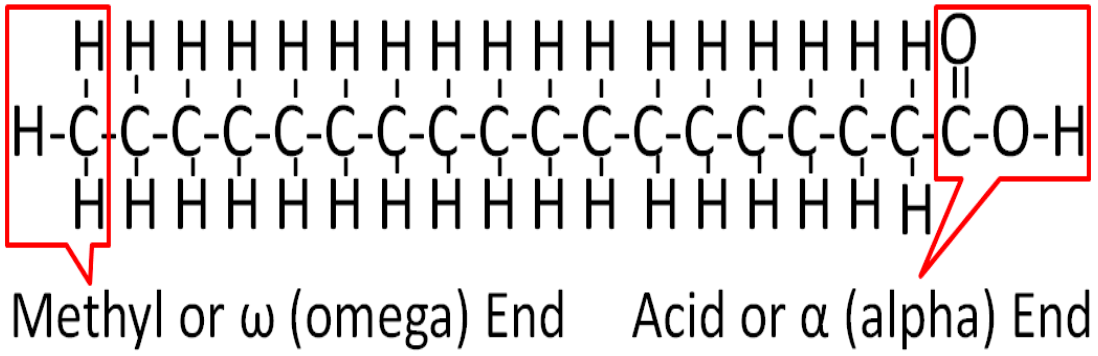


Figure 3: Fatty acid.

Section 1 Quiz: Nomenclature of fatty acids (from C1 and omega end example)- Short Answer

Q1. Name this fatty acid

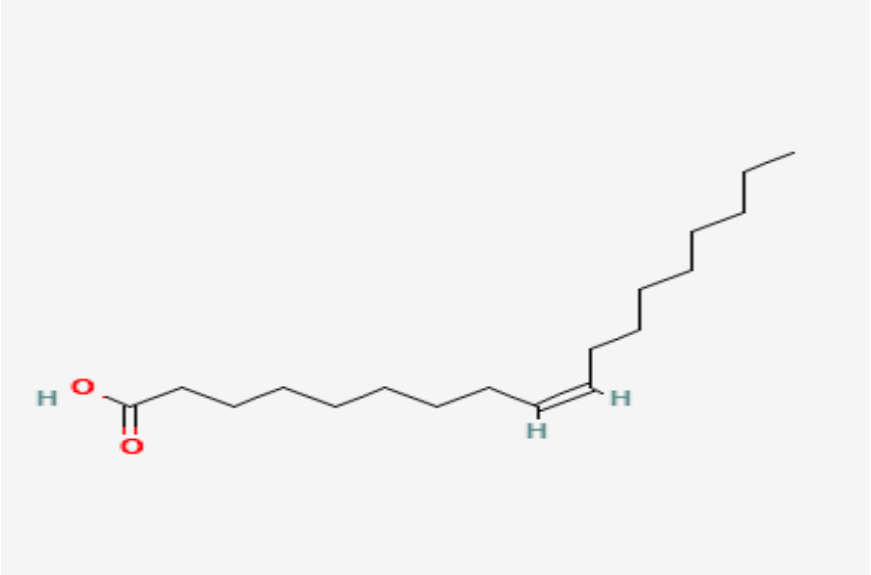
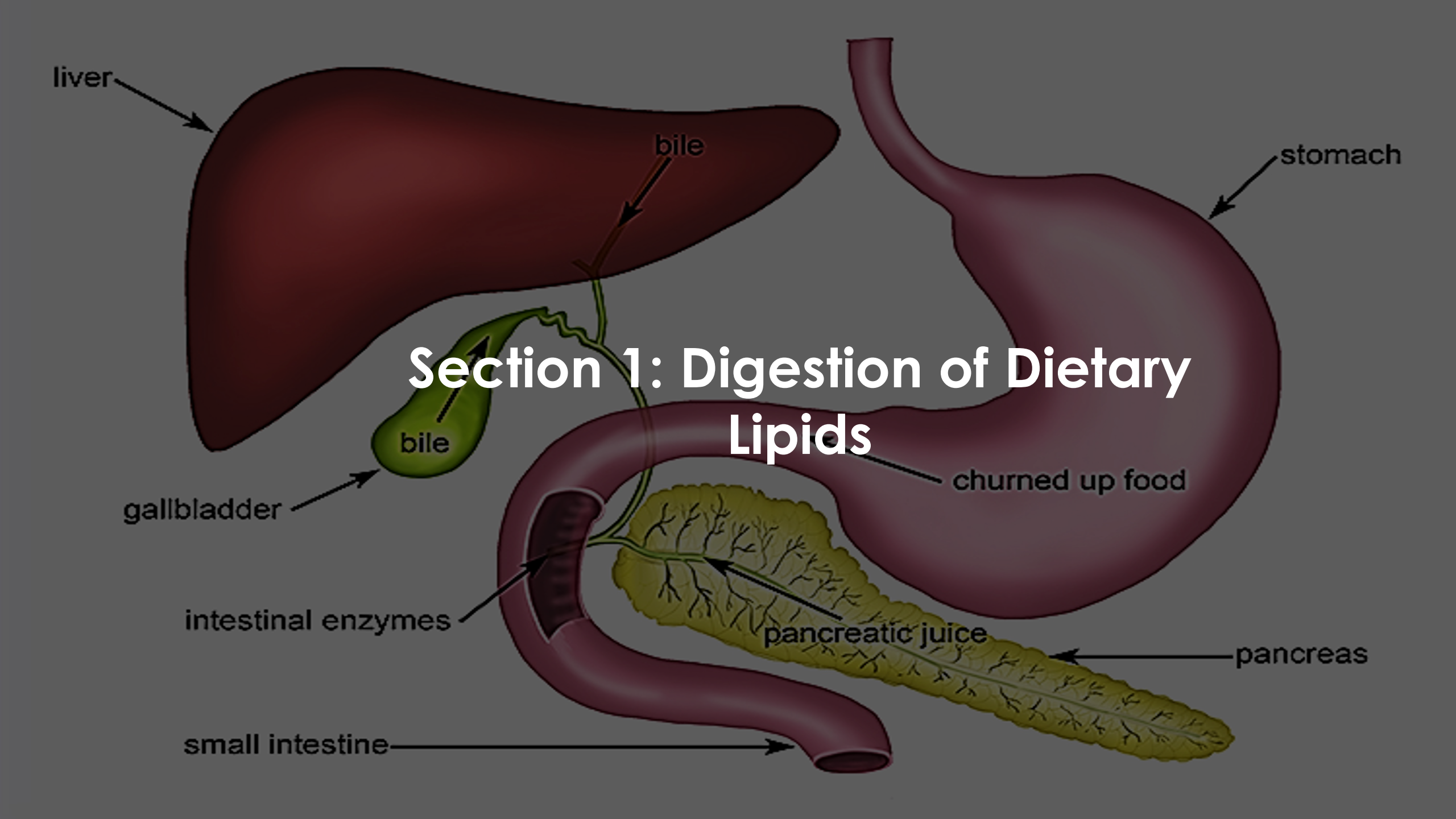


Figure 4: Oleic Acid (18:1 cis-Δ9) an omega-9 fatty acid.



Section 1: Digestion of Dietary Lipids

Concept 2.1: Chemical & Physical Digestion in mouth and stomach

Mouth and Stomach

- Lipid digestion begins in stomach by grinding/mixing
- Lingual and gastric lipases begin to work
- Lipases degrade triacylglycerols (TAGs) into diacylglycerol and free fatty acids (FFA)

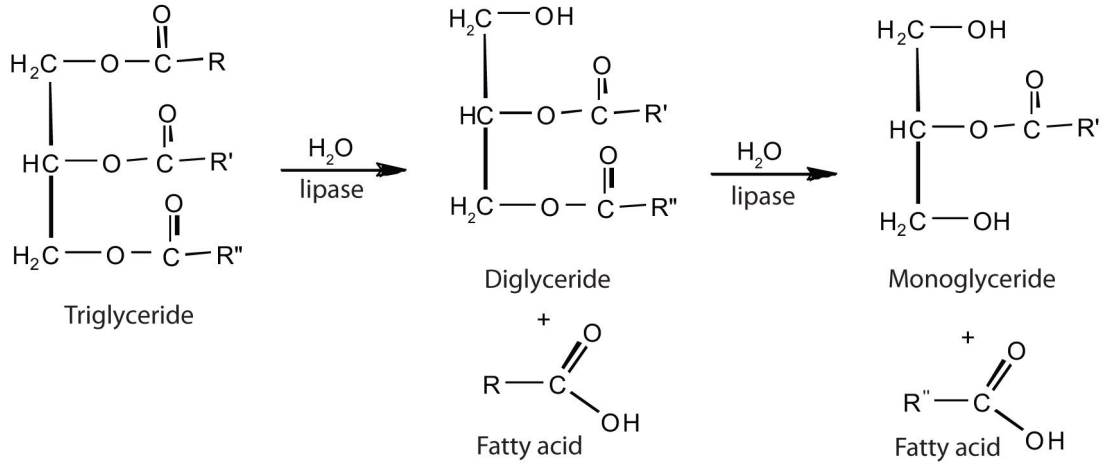


Figure 5: Digestion of Lipids.

Concept 2.2: Chemical & Physical Digestion in the intestines

Intestinal processes:

1. Emulsification of lipids - mixture of 2+ liquids that do not mix normally, one is in form of very small globules (lipids) throughout the other (bile salts).
    - An emulsifier is an agent used to make emulsion (e.g., soap, bile salts).
    - Dietary lipids emulsification by 2 mechanisms:
        - Bile salts: emulsifier (released by gallbladder after fatty meal)
        - Peristalsis: mechanical mixing
            - Lipases work in aqueous solution, emulsified lipid droplets and mixing increases surface area of fats to allow lipases to work more efficiently

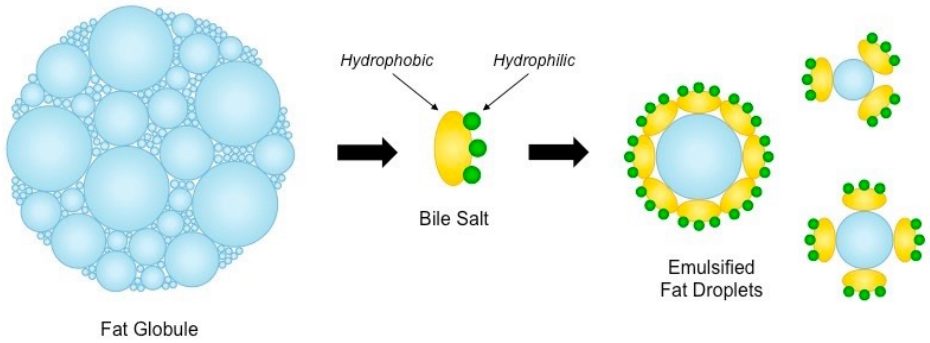


Figure 6: Emulsification by fats.

2. Absorption of lipids
3. Resynthesis of TAG and cholesterol esters by enterocytes
4. Chylomicron assembly/release

Pancreas:

- Produces digestive enzymes for lipids and releases them in the small intestine in response to hormones
    - Pancreatic lipase converts TAG into monoacylglycerol + FFA, cholesteryl esterase converts cholesterols into esters, to allow absorption in intestine

Concept 2.3: Lipid absorption by the small intestine

Absorption of Lipids by Enterocytes

- FFA and monoacylglycerol can form micelles, which are absorbed by enterocytes
- Cholesterol and other lipids also enter enterocytes
- Short/medium FA easily digested since micelles not needed for absorption

Chylomicron Assembly/Release

- FFAs and monoacylglycerols reassembled into TAGs
- Newly synthesized TAGs and cholesterol esters packaged with other lipids into chylomicron
- Chylomicrons released into bloodstream via lymphatic system

Destinations for Dietary Lipids in the Body

- FFAs directly absorbed by peripheral cells or circulate with serum albumin until absorbed by cells
- Glycerol released from TAG eventually absorbed and enters glycolysis or gluconeogenesis
- Chylomicron components circulated to other tissues, TAG absorbed by cells and chylomicron remnants absorbed by liver

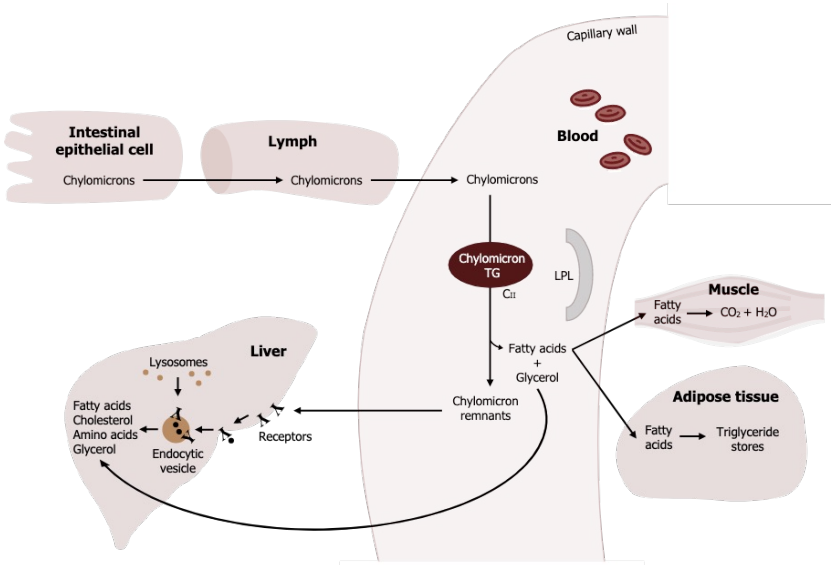


Figure 7: Movement of lipids in the body.

Spotlight on Disease: Lipid Malabsorption

- Steatorrhea - increased presence of lipids in feces, results from lipid malabsorption can lead to nutritional deficiencies because of excretion
    - Cystic fibrosis (CF) - loss in pancreatic enzymes due to mucosal thickening which blocks pancreatic ducts
        - Recessive genetic disorder affecting body systematically
        - Cause: 2 faulty copies of CFTR gene encoding for a chloride ion channel
        - CFTR is Important in formation of sweat, digestive juices, mucus and is normally located on outer membrane of exocrine glands
        - Malfunctioning CFTR leads to buildup of thick sticky mucus
        - Symptoms: salty-tasting skin, poor growth, food malabsorption
- Liver disease: production of bile salts decrease, micelles do not form, fats cannot be broken down by lipases

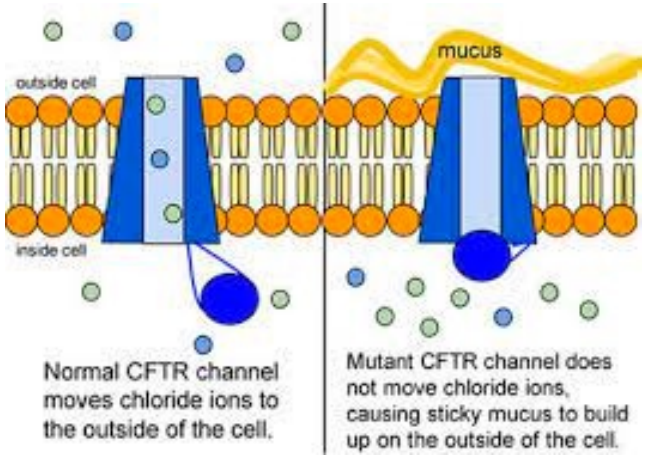


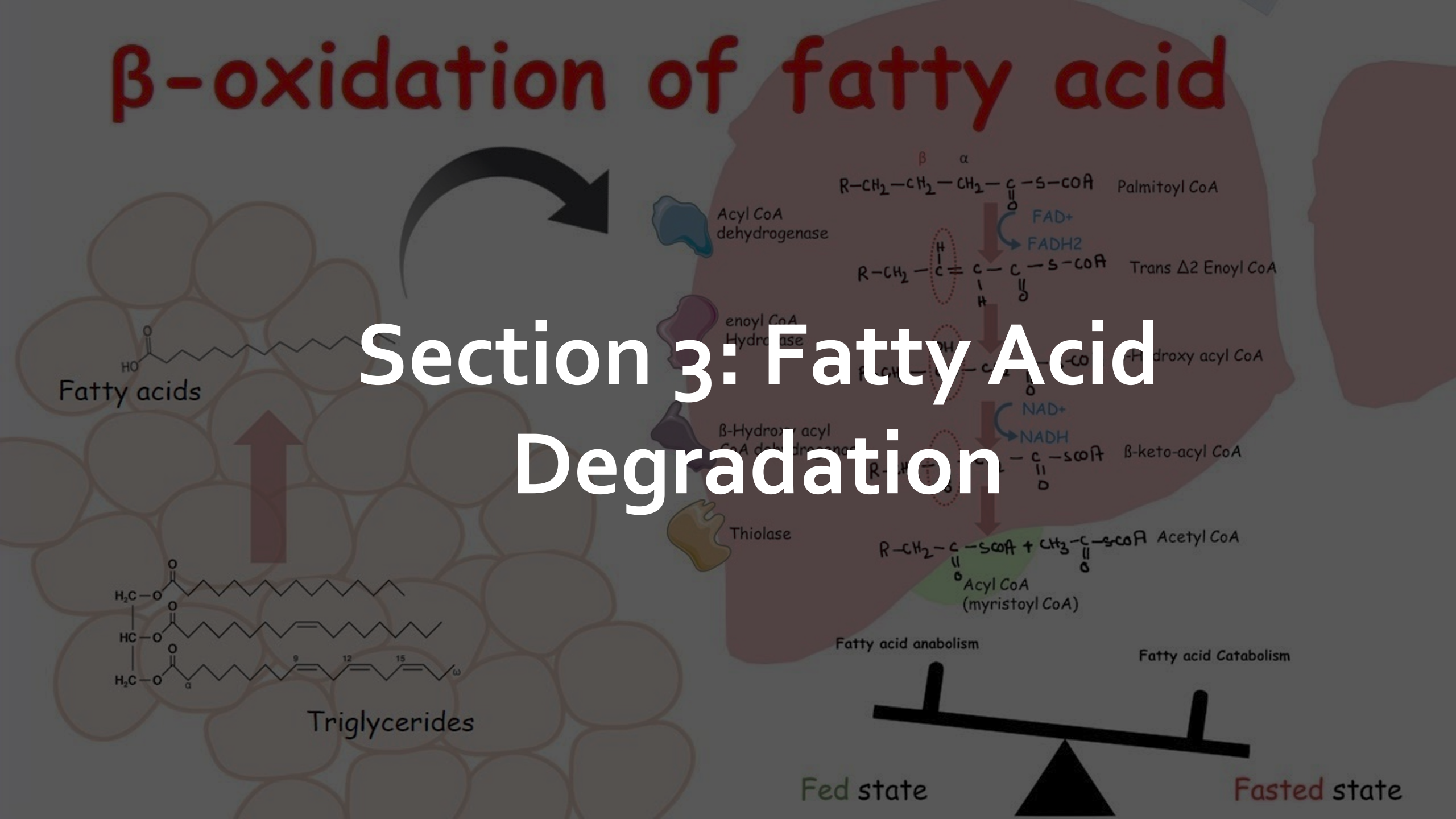
Figure 8: Pathogenesis of Cystic Fibrosis.

Section 2 Quiz: Multiple Choice

Q2. Triacylglycerols when broken down form what products?

a. Cholesterol and Free Fatty Acid
b. Monoglyceride & Cholesterol
c. Cholesterol & Diglyceride
d. Monoglyceride & Free Fatty Acid

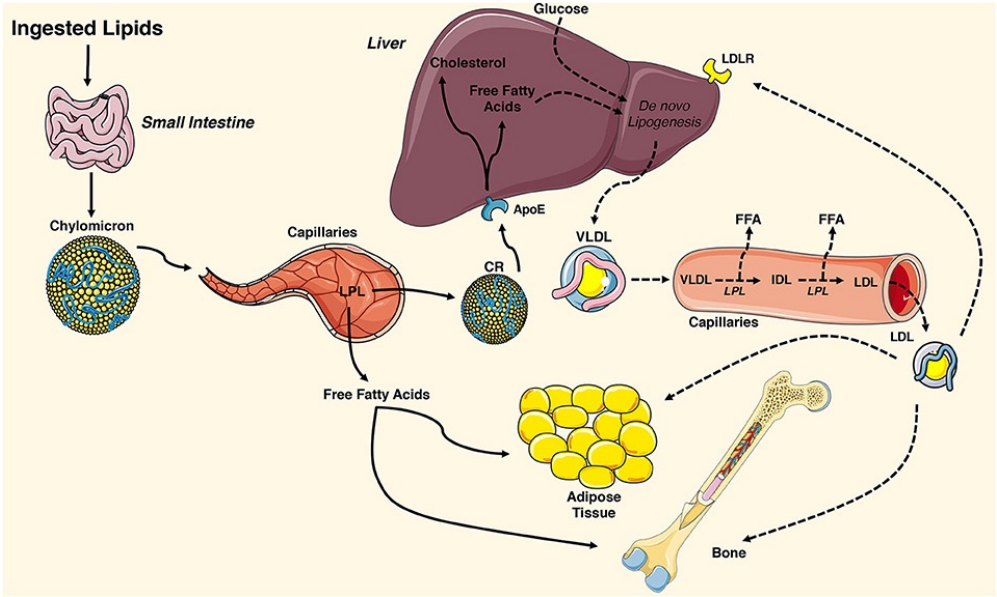
Answer: D



Section 3: Fatty Acid Degradation

Concept 3.1: General overview

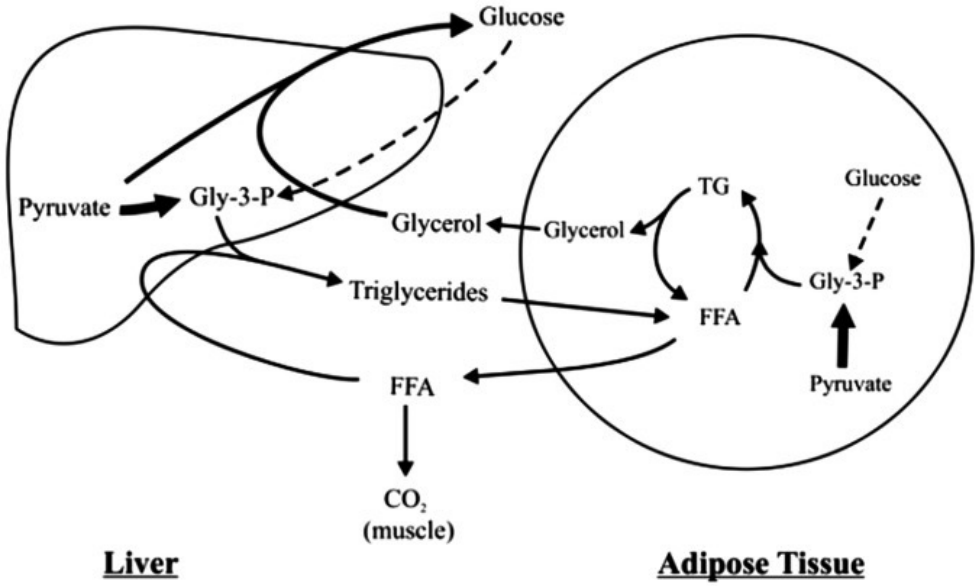
- TAGs are stored forms of fatty acids in adipose tissues and are released into circulation as FFA when energy is needed
- FFA bind to albumin and are transported to target tissues
- Hormone-sensitive lipase (HSL) hydrolyzes TAG in adipose tissues
- Fatty acids are activated in the cytoplasm to form fatty acyl-CoA
- Fatty acyl-CoA is transported into the mitochondrial matrix for β-oxidation
- Beta-oxidation breaks down fatty acids to generate ATP and occurs in the mitochondrial matrix
- Beta-oxidation involves a series of four reactions that remove two carbons at a time
- Key regulatory enzymes include CPT1 and ACAD



https://www.frontiersin.org/articles/10.3389/fendo.2020.578194/full

Concept 3.2: Release of fatty acids from Triacylglycerol

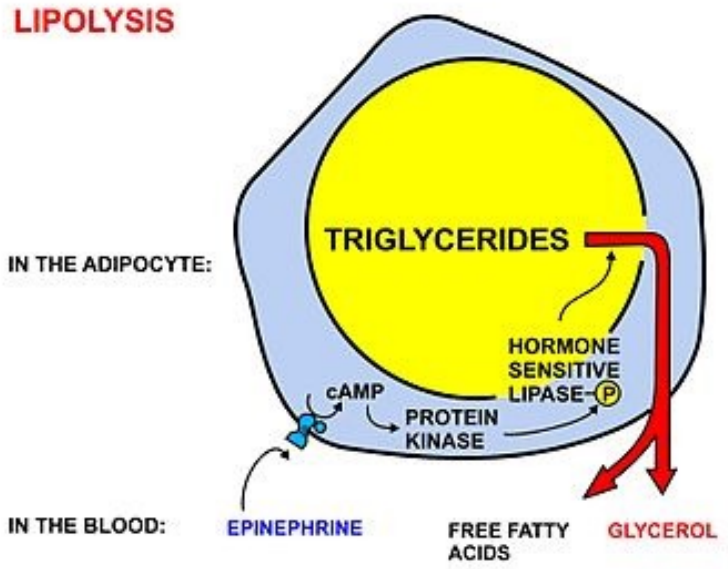
- Hormone-sensitive lipase (HSL) is a key enzyme involved in the hydrolysis of triacylglycerols (TAGs) in adipose tissue.
  - Green activators: Glucagon, epinephrine, norepinephrine, and growth hormone stimulate HSL activity.
  - Red inhibitors: Insulin, high levels of glucose, and high levels of fatty acids inhibit HSL activity.
- HSL catalyzes the rate-limiting step in the breakdown of TAGs into free fatty acids (FFA) and glycerol.
  - Specifically, HSL hydrolyzes the ester bond between the first and second carbon of the glycerol backbone of TAGs.
  - This results in the release of one FFA and diacylglycerol (DAG), which can be further hydrolyzed to release another FFA.



https://www.jbc.org/article/S0021-9258%2820%2984065-4/fulltext

Concept 3.3: Glycerol Release into the Blood

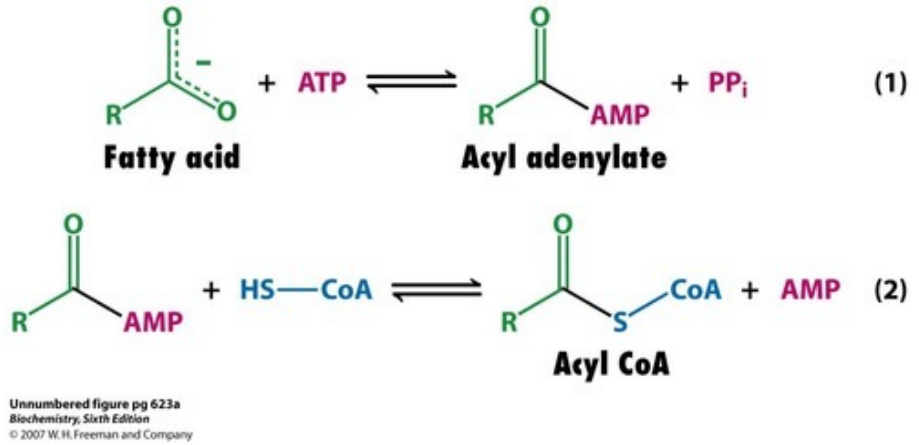
- TAGs are hydrolyzed in adipose tissue, releasing glycerol.
- Glycerol can be transported to the liver via the bloodstream due to its water solubility and ability to diffuse across cell membranes.
- In the liver, glycerol is converted to glucose through gluconeogenesis.
- Glycerol is phosphorylated to G3P by glycerol kinase.
- G3P is oxidized to DHAP by glycerol-3-phosphate dehydrogenase.
- DHAP can be converted to glucose via gluconeogenesis.
- Conversion of glycerol to glucose is important for maintaining blood glucose levels during fasting or low carbohydrate intake.
- Gluconeogenesis is stimulated by glucagon and cortisol, which promote glycogen breakdown and glucose synthesis from non-carbohydrate sources.



https://en.wikipedia.org/wiki/Lipolysis

Concept 3.4: Activation of fatty acids

- Fatty acids must be activated before they can enter the mitochondria for beta-oxidation.
- Activation occurs in the cytosol of the cell, where fatty acids are attached to coenzyme A (CoA) to form fatty acyl-CoA.
- The enzyme responsible for this attachment is fatty acyl-CoA synthetase, which requires ATP to drive the reaction.
- The resulting fatty acyl-CoA molecule can then be transported into the mitochondria by a protein transporter called carnitine palmitoyltransferase I (CPT-I).
- Once inside the mitochondria, the fatty acyl-CoA can undergo beta-oxidation to produce ATP.

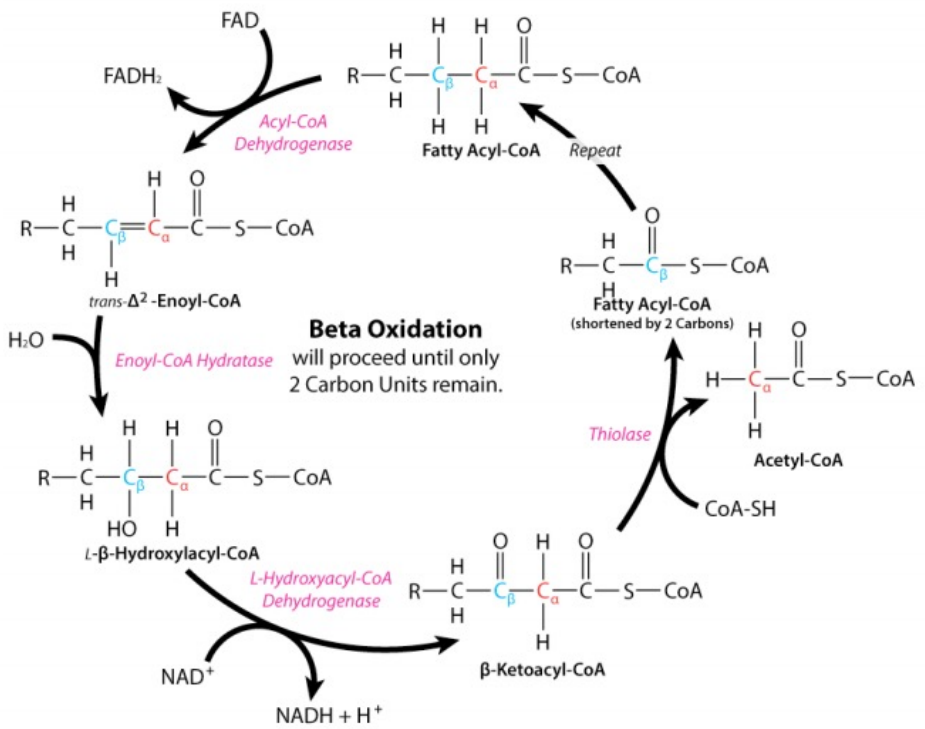


Unnumbered figure pg 623a
Biochemistry, Sixth Edition

https://quizlet.com/539769296/beta-oxidation-of-fatty-acids-flash-cards/

Concept 3.5: Beta-Oxidation

- Beta-oxidation is the process of breaking down fatty acids to produce ATP.
- The process takes place in the mitochondria and involves four main steps: oxidation, hydration, oxidation, and thiolysis.
- Each cycle of beta-oxidation produces one molecule of acetyl-CoA, one molecule of NADH, and one molecule of FADH2.
- The number of cycles that can occur for a given fatty acid is dependent on the length of its carbon chain, with longer chains producing more cycles.
- Once acetyl-CoA is produced through beta-oxidation, it can enter the Krebs Cycle (also known as the citric acid cycle or the tricarboxylic acid cycle) to produce more ATP.
- The Krebs Cycle takes place in the mitochondria and involves a series of chemical reactions that convert acetyl-CoA into carbon dioxide and high energy products such as ATP, NADH, and FADH2.

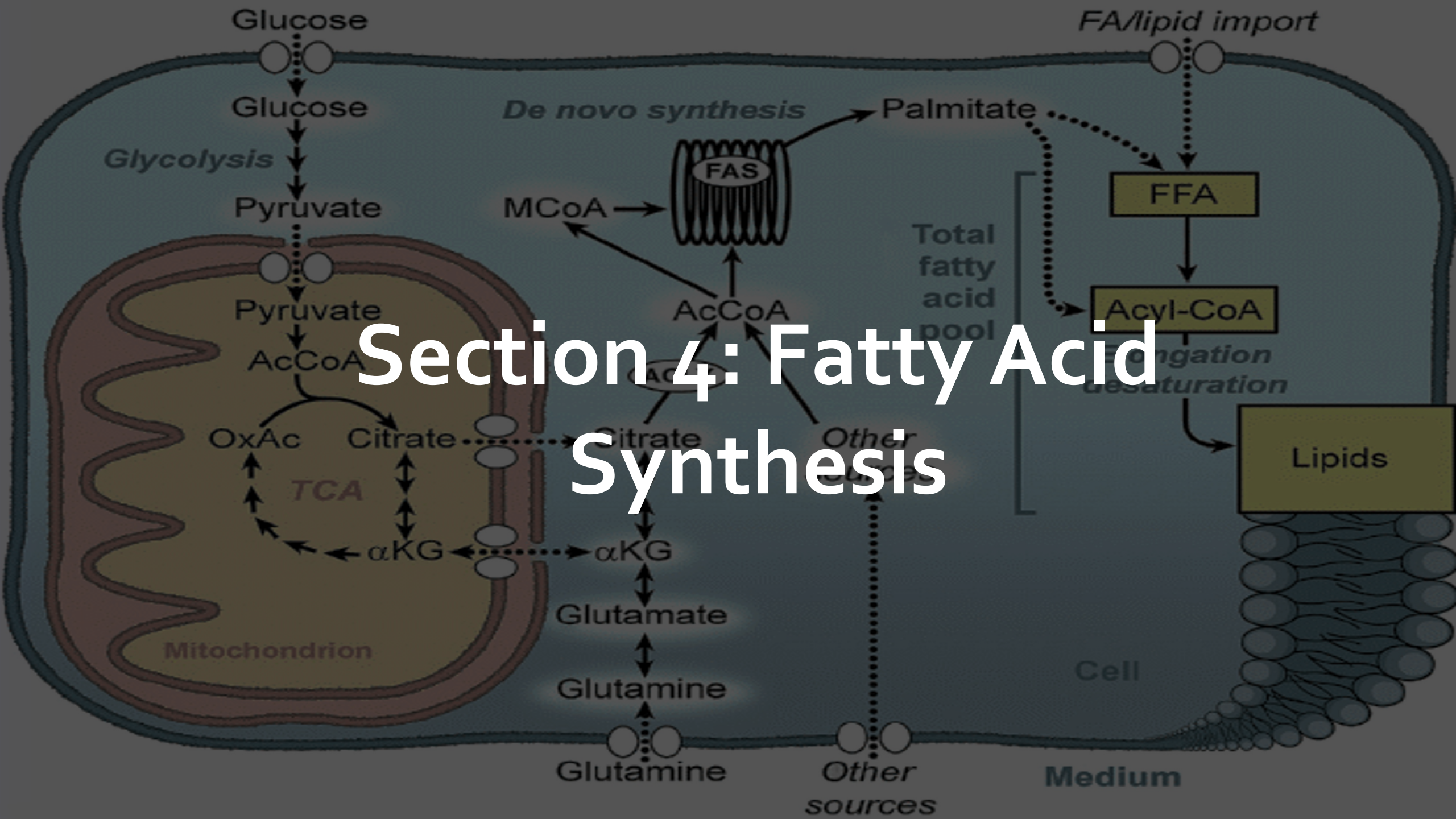


https://bio.libretexts.org/Bookshelves/Biochemistry/Book%3A_Biochemistry_Free_and_Easy_%28Ahern_and_Rajagopal%29/06%3A_Metabolism_I_-_Oxidative_Reductive_Processes/6.11%3A_Fatty_Acid_Oxidation

Section 3 Quiz: Beta-Oxidation Calculation

If an 8-carbon fatty acid undergoes beta-oxidation, how many ATP molecules can be generated from its complete oxidation?

- Energy yield from beta-oxidation of even-chained fatty acids:
  - Each cycle of beta-oxidation generates 1 $FADH_2$, 1 NADH, and 1 acetyl-CoA molecule.
  - Each $FADH_2$ molecule generates 1.5 ATP through oxidative phosphorylation.
  - Each NADH molecule generates 2.5 ATP through oxidative phosphorylation.
  - Each acetyl-CoA molecule generates 10 ATP through the citric acid cycle.
- Energy yield from complete oxidation of an 8-carbon fatty acid:
  - The 8-carbon fatty acid will undergo 4 cycles of beta-oxidation, generating 4 $FADH_2$, 4 NADH, and 4 acetyl-CoA molecules.
  - Energy yield: (4 x 1.5 ATP) + (4 x 2.5 ATP) + (4 x 10 ATP) = 42 ATP
- Answer: 42 ATP



Section 4: Fatty Acid Synthesis

Concept 4.1: General overview

Overview:

- Involves the conversion of acetyl-CoA into palmitate (16:0) through 3 key steps
  1. Cytoplasmic acetyl-CoA production
  2. Decarboxylation of acetyl-CoA to form malonyl-CoA
  3. Catalysis by fatty acid synthase

Location:

- Process begins in the mitochondrial matrix and ends in the cytoplasm

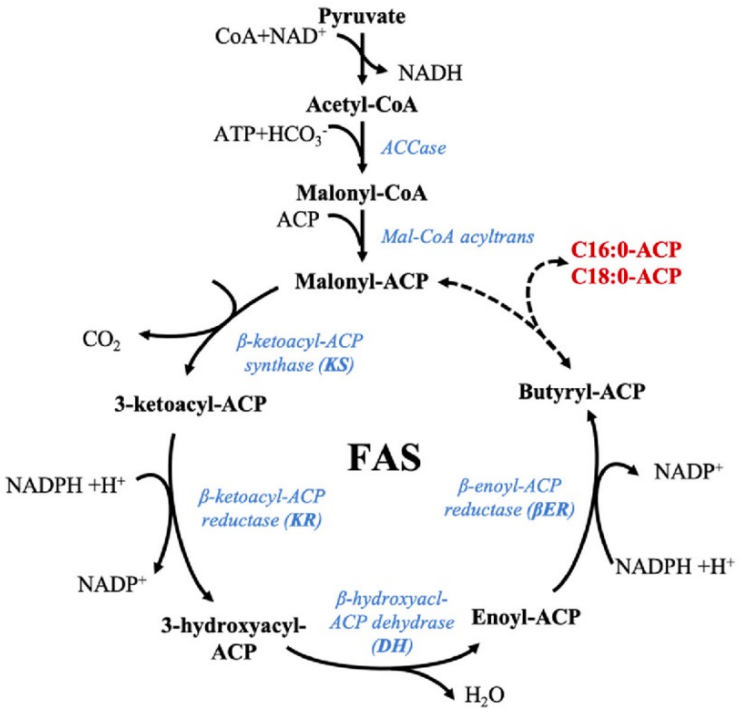


Figure 1. Overall fatty acid synthesis cycle

Concept 4.2: Production of Cytoplasmic Acetyl-CoA

Why this step occurs:

- Fatty acid synthesis must occur in the cytoplasm
- Acetyl-CoA from the TCA cycle is found in the mitochondrial matrix
  - Cannot cross the mitochondrial membrane to enter cytoplasm

Step 1:

- *Citrate synthase* converts mitochondrial acetyl-CoA into citrate
- Citrate passes through the mitochondrial matrix to enter the cytoplasm
- *ATP citrate lyase* cleaves citrate to form acetyl-CoA and oxaloacetate
  - This step requires 1 ATP

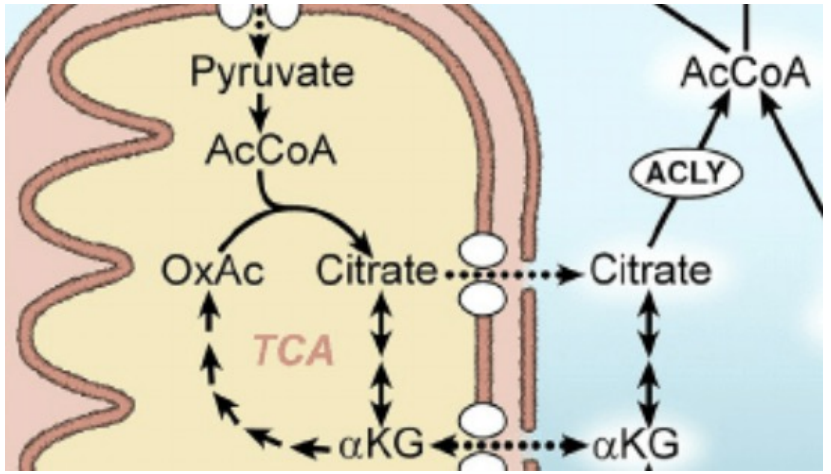


Figure 2. Conversion of acetyl-CoA into citrate.

Concept 4.3: Carboxylation of Acetyl-CoA to Malonyl-CoA

Step 2:

- Acetyl-CoA is carboxylated by *acetyl-CoA carboxylase* to form malonyl-CoA
  - Reaction uses 1 ATP

Importance of this step:

- *Acetyl-CoA carboxylase* is the rate-limiting enzyme of fatty acid synthesis
  - This reaction commits the substrate to fatty acid synthesis

Acetyl-CoA carboxylase regulation:

- Activators
  - Insulin
    - Activates phosphatases that dephosphorylate the enzyme
  - Citrate

- Inhibitors
  - Glucagon and epinephrine
    - Activate kinases that phosphorylate the enzyme
  - Long-chain fatty acyl-CoA

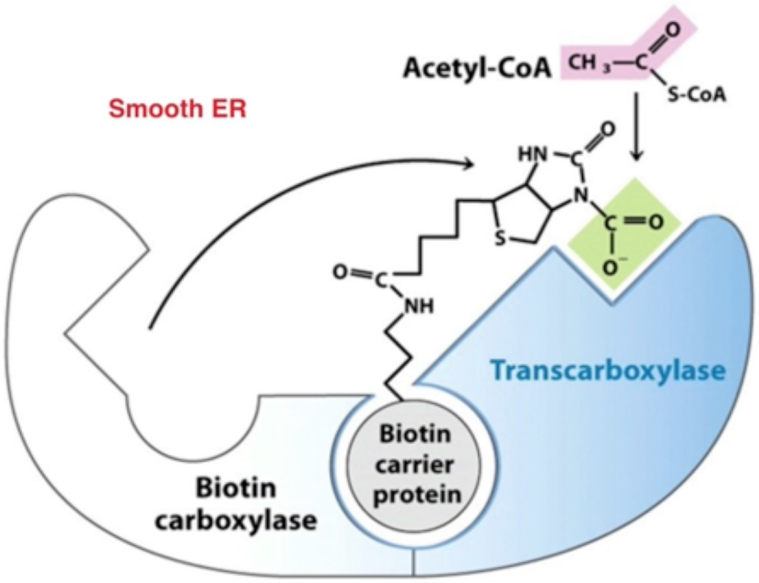


Figure 3. Diagram of acetyl-CoA carboxylase.

Concept 4.4: Fatty Acid Synthase

Step 3:

- A cycle begins
  - *Fatty acid synthase* catalyzes the formation of a fatty acid from malonyl-CoA and acetyl-CoA from steps 1 and 2
  - Each cycle adds 2 carbons to the end of the fatty acyl-CoA away from the 2 carbons from the initial acetyl-CoA
    - Added to the omega end
  - Cycle continues until palmitate (16:0) is formed (7 total cycles)

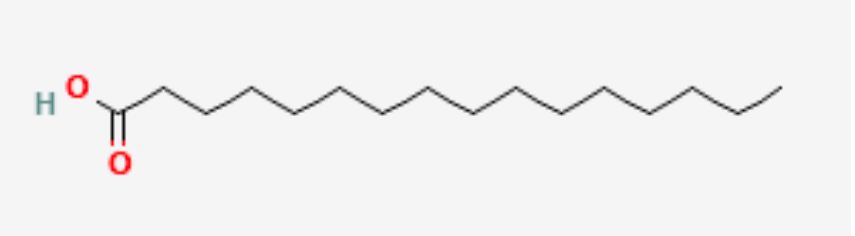


Figure 4. Palmitate (16:0)

Cycle reagents and products:

- Each cycle uses 1 fatty acyl-CoA (fatty acid chain), 1 malonyl-CoA (carbons added to chain), and 2 NADPH (energy source for *fatty acid synthase*)
- Each cycle produces 1 elongated fatty acyl-CoA, 2 $NADP^+$, 1 CO_2, and 1 H_2O

Overall reaction:

1 fatty acyl-CoA + 1 malonyl CoA + 2 NADPH --> 1 elongated fatty-acyl-CoA + 2 $NADP^+$ + 1 CO_2 + 1 H_2O

Summary of Fatty Acid Synthesis

Step 1:

- Acetyl-CoA moves from mitochondrial matrix to cytoplasm

Step 2:

- Acetyl-CoA is converted to malonyl-CoA by *acetyl-CoA carboxylase*
  - Rate-limiting enzyme

Step 3:

- *Fatty acid* synthase cycles and adds a malonyl-CoA to the fatty acyl-CoA until palmitate (16:0) forms

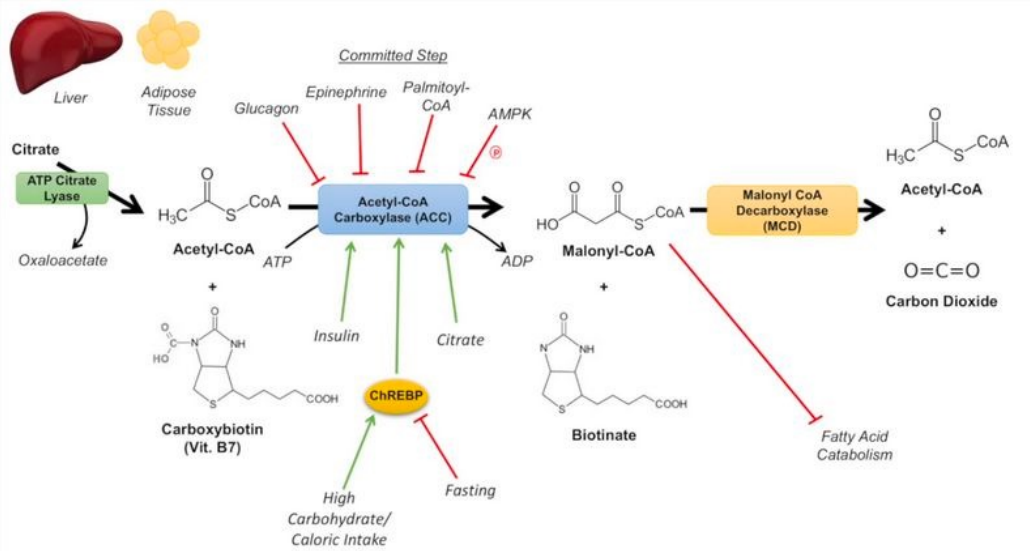


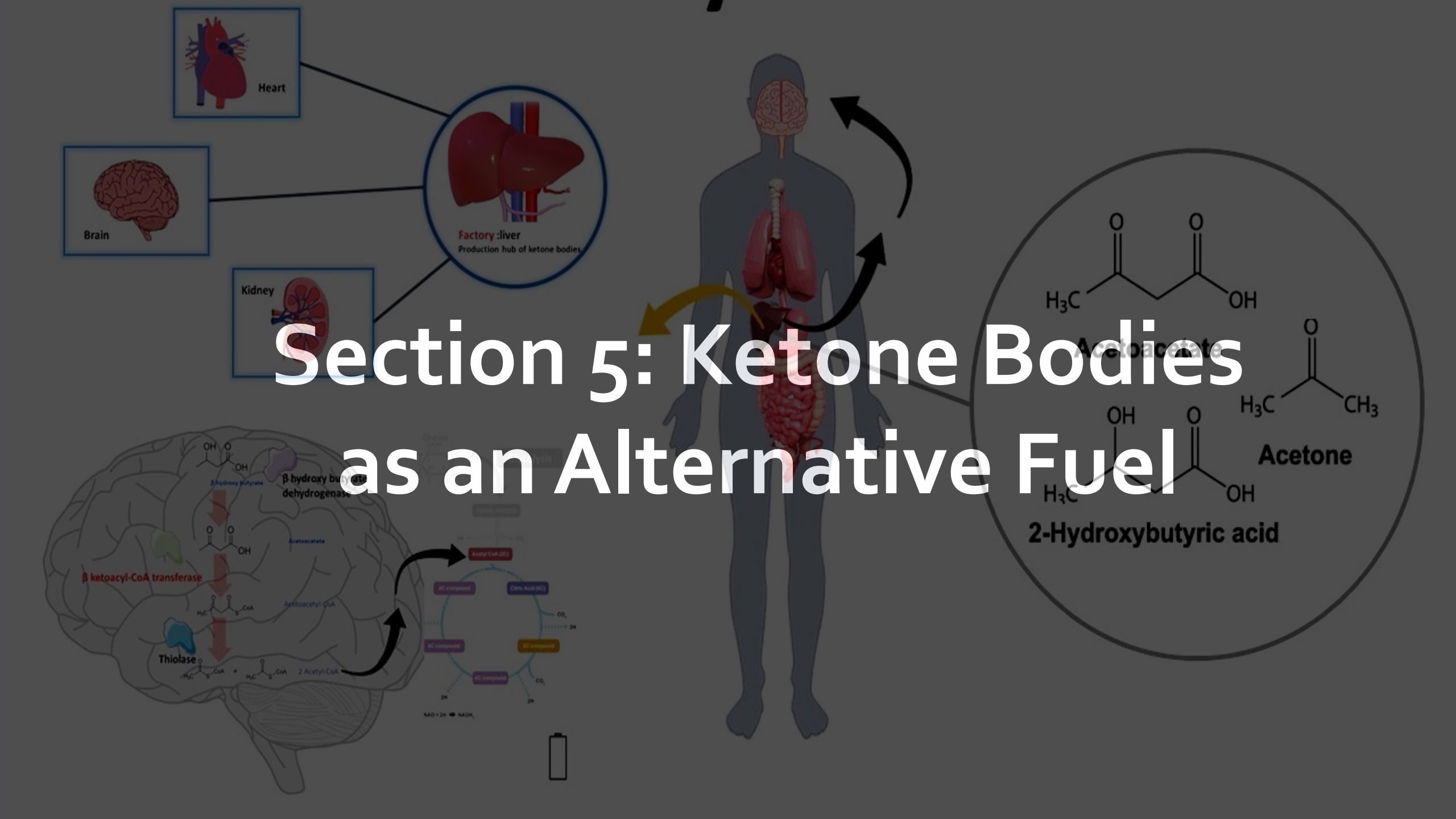
Figure 5. Overall fatty acid synthesis reaction

Section 4 Quiz: Multiple Choice

Which of the following is not involved in the regulation of *acetyl-CoA carboxylase*?

a) Epinephrine
b) Citrate
c) ADP
d) Insulin

Answer: C



Section 5: Ketone Bodies as an Alternative Fuel

Concept 5.1: Overview of Ketone Bodies and their energy use in peripheral tissues

Function:

- Ketone bodies are used by peripheral tissues as an alternative fuel source during fasting states

Location of production:

- Mitochondria of hepatic cells forms ketone bodies using acetyl-CoA from FA oxidation

How it's used for energy:

- Peripheral tissues convert ketone bodies into acetyl-CoA
  - Is then used for energy production

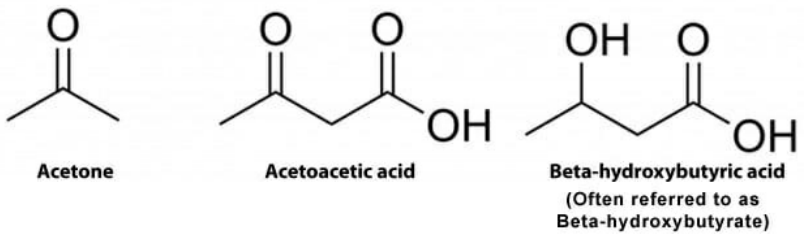


Figure 1. The 3 types of ketone bodies

Concept 5.2: Ketone Body Synthesis

Conditions necessary:

- Fasting state (low insulin and high glucagon levels)
  - Causes FA oxidation and ketogenic amino acid degradation that produce acetyl-CoA as a substrate

Synthesis:

- Involves 4 reactions that convert acetyl-CoA into acetone and CO_2
- Rate limiting enzyme is *HMG-CoA synthase*
  - Activated by glucagon
  - Inhibited by insulin

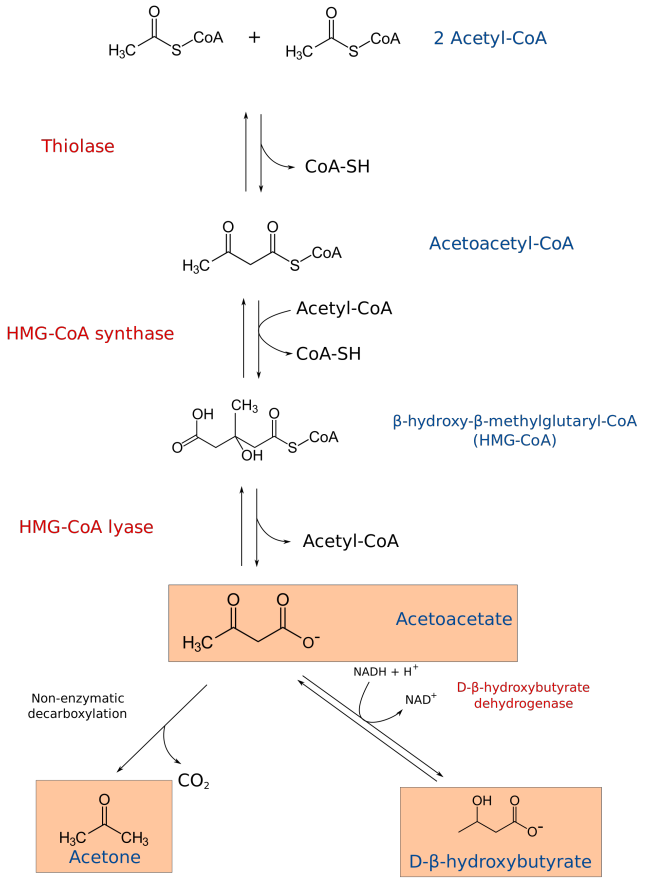


Figure 2. The ketone synthesis pathway.

Spotlight on Disease: Diabetic Ketoacidosis

Biochemical basis

- Occurs in individuals with uncontrolled type 1 diabetes
  - Results in inability to absorb glucose and high fatty acid degradation
- Lack of insulin production causes excess ketone body synthesis
  - Ketone bodies are acidic
    - Causes metabolic acidosis (ketoacidosis) due to decreased blood pH

Symptoms:

- Fruity odor on breath
- Dehydration due to glucose and ketone body excretion in urine
- Can cause coma or death

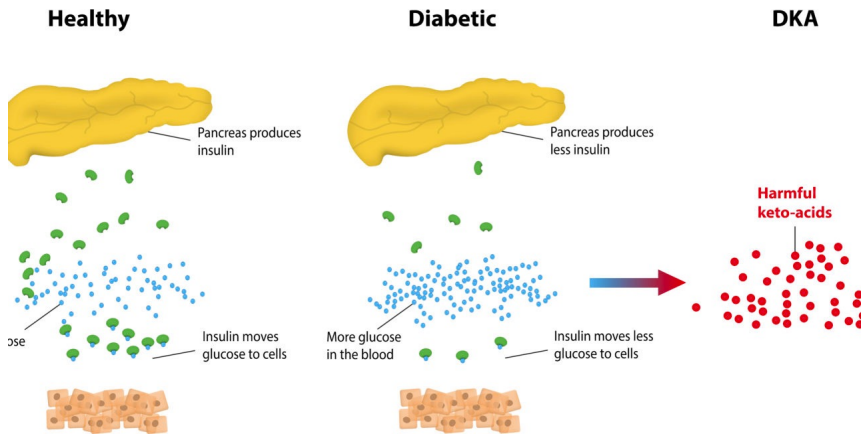


Figure 3. Function of insulin in a healthy vs. diabetic individual.

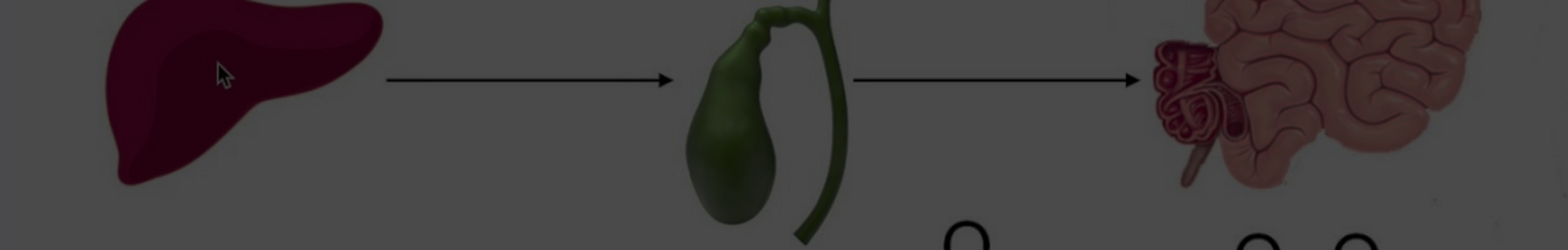
Section 5 Quiz: Short Answer

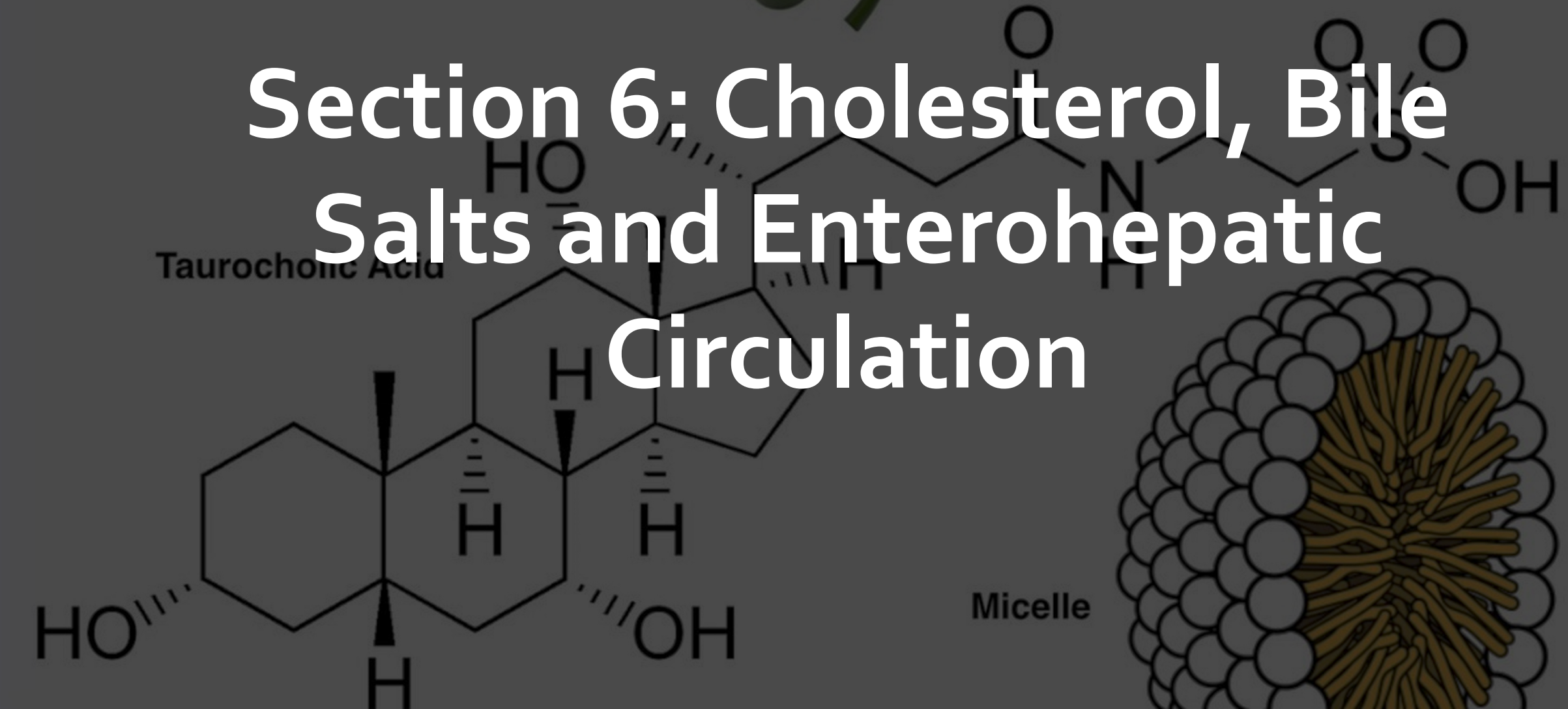
What are the conditions necessary for ketone body production and how are these conditions harmful in uncontrolled type 1 diabetes?

Answer:

- Fasting conditions are necessary (low insulin, high glucagon)
- Uncontrolled type 1 diabetes causes prolonged low insulin levels
  - Produces excess acidic ketone bodies which can cause diabetic ketoacidosis
    - Can cause coma or death

Section 6: Cholesterol, Bile Salts and Enterohepatic Circulation





Concept 6.1: Overview of Cholesterol Synthesis

- Cholesterol
  - Precursor to hormones like steroids

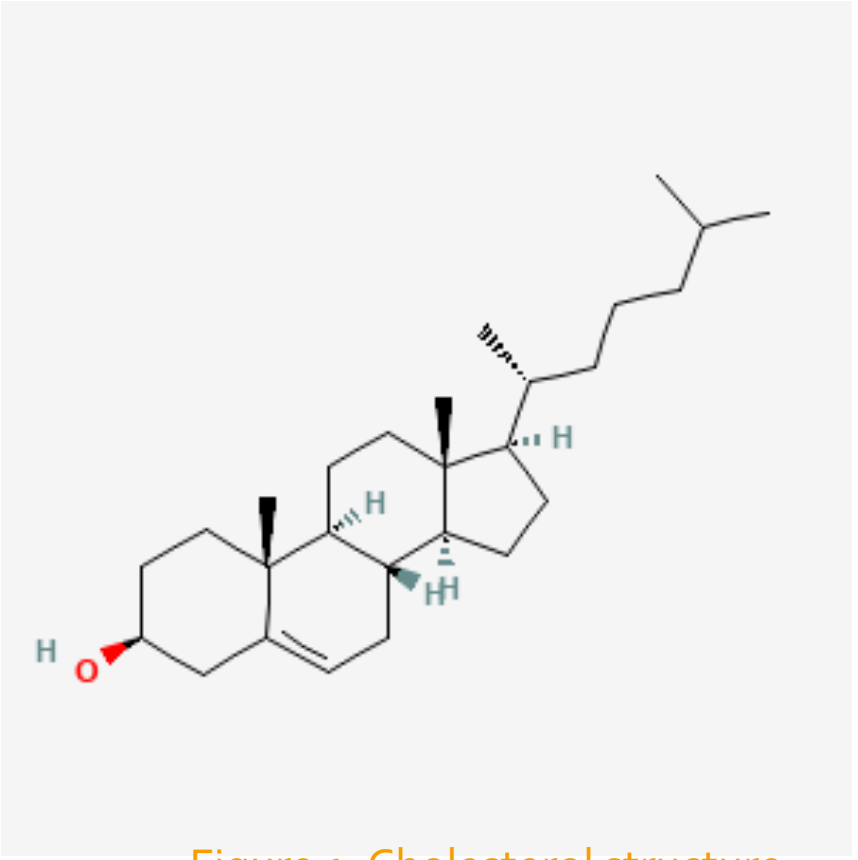


Figure 1: Cholesterol structure

Concept 6.2: HMG-CoA to Mevalonate

- Enzyme-catalyzed conversion of HMG-CoA to mevalonate is control point for cholesterol biosynthesis regulation
- Reactant: HMG-CoA
- Product: Mevalonate
- Enzyme: HMG-CoA reductase
  - Activated by: Insulin
  - Inhibited by: Glucagon, statins, cholesterol

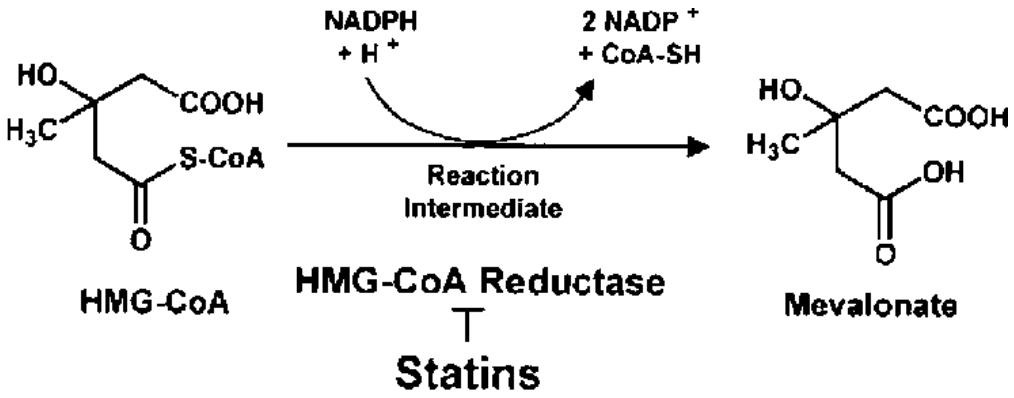


Figure 2: Conversion of HMG-CoA to Mevalonate

Concept 6.3: Regulation of Cholesterol Biosynthesis

- Sterol-mediated
  - Sterol regulatory element binding protein (SREBP) is a transcription factor
  - SREBP --> upregulates expression of HMG-CoA reductase gene
- Low cholesterol levels
  - Activates SREBP --> more HMG-CoA production
- High cholesterol levels
  - Inhibits SREBP --> less HMG-CoA production
- Hormonal regulation #1
  - Glucagon signaling --> phosphorylation --> inhibition of HMG-CoA reductase
- Hormonal regulation #2
  - Insulin signaling --> dephosphorylation --> activation of HMG-CoA reductase

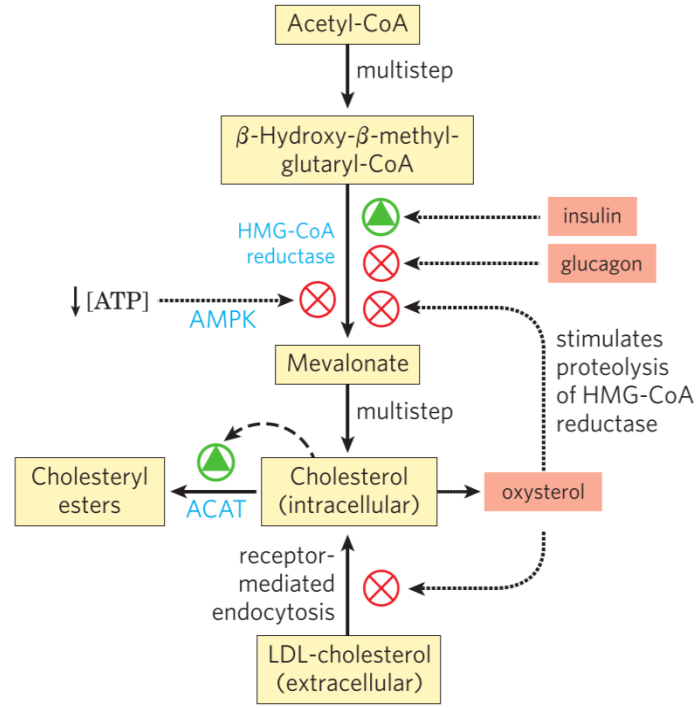


Figure 3: Insulin and glucagon regulation of cholesterol biosynthesis

Spotlight on Disease: Hypercholesteremia

- Hypercholesteremia
  - Can lead to atherosclerosis/coronary artery disease
  - Elevated cholesterol secretion into bile leads to cholesterol gallstone disease
- Statins
  - Structural analogs of HMG-CoA
  - Competitively inhibit HMG-CoA reductase
  - Hypercholesteremia treatment

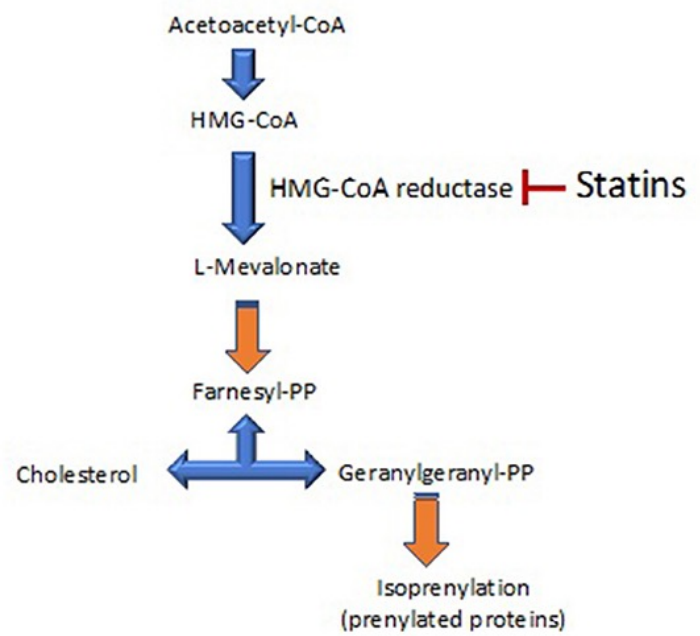


Figure 4: Role of statins

Concept 6.4: Overview of bile acid synthesis and enterohepatic circulation

- Cholesterol
  - Precursor to bile salts/acids (emulsify fats in digestion)
- Enterohepatic circulation
  - Bile synthesized in liver
  - Bile stored in gallbladder
  - Bile travels through bile ducts
  - Bile ducts release bile into duodenum
  - Eliminates heme breakdown products + excess cholesterol

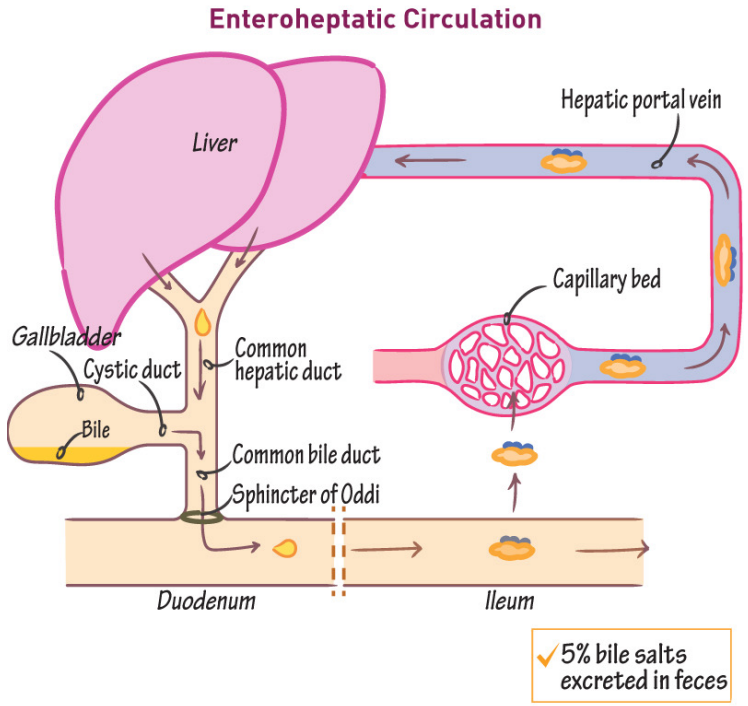


Figure 5: Enterohepatic circulation

Concept 6.5: Importance of Bile Acids

- Bile acids
  - Polar derivatives of cholesterol
  - Detergents --> have polar + nonpolar face
  - Carboxyl side chain --> pKa of approximately 6
  - Most bile acids --> cholic acid + chenodeoxycholic acid
- Bile acids vs bile salts
  - Bile salts: half protonated
  - Bile acids: deprotonated

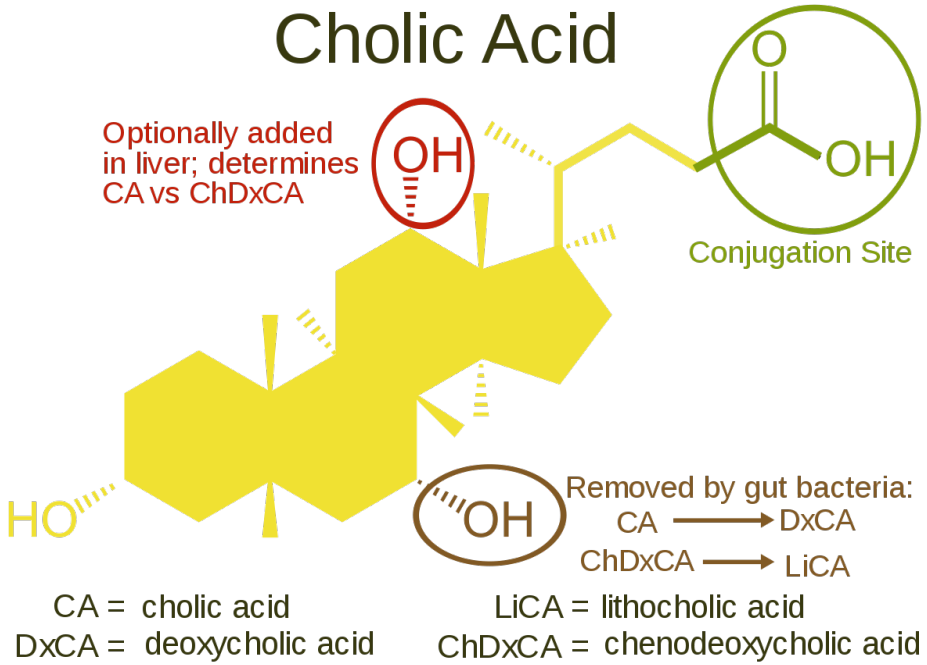


Figure 6: Cholic acid structure

Spotlight on Disease: Cholelithiasis

- Biochemical basis
  - Cholesterol excess entering bile
  - More cholesterol than can be solubilized by bile salt
  - Cholesterol precipitates --> gall stones
  - Causes
    - Bile acid malabsorption from intestine
    - Biliary tract obstruction
    - Hepatic dysfunction
    - Excessive biliary cholesterol excretion
- Treatment
  - Gall bladder removal
  - Chenodeoxycholic acid supplements
    - Dissolve gall stones

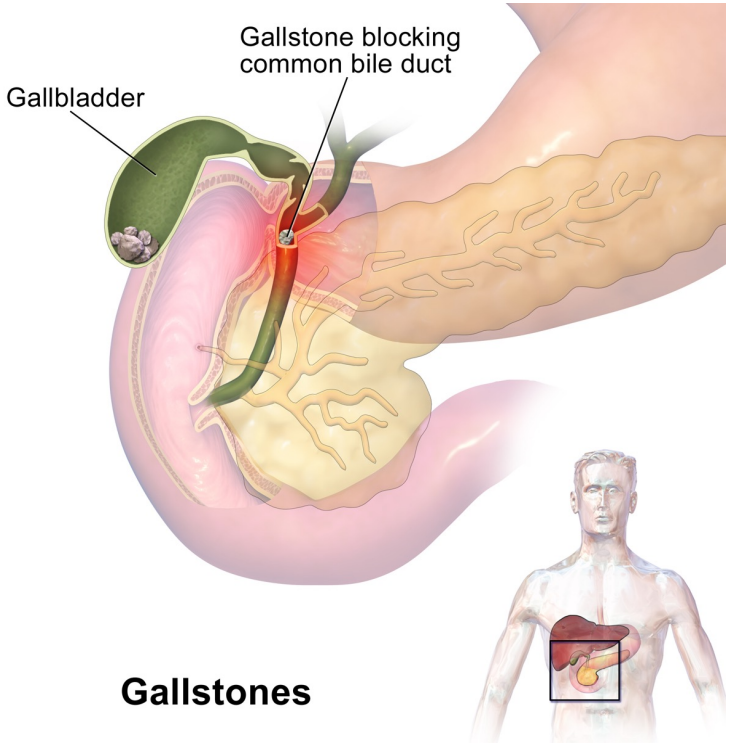


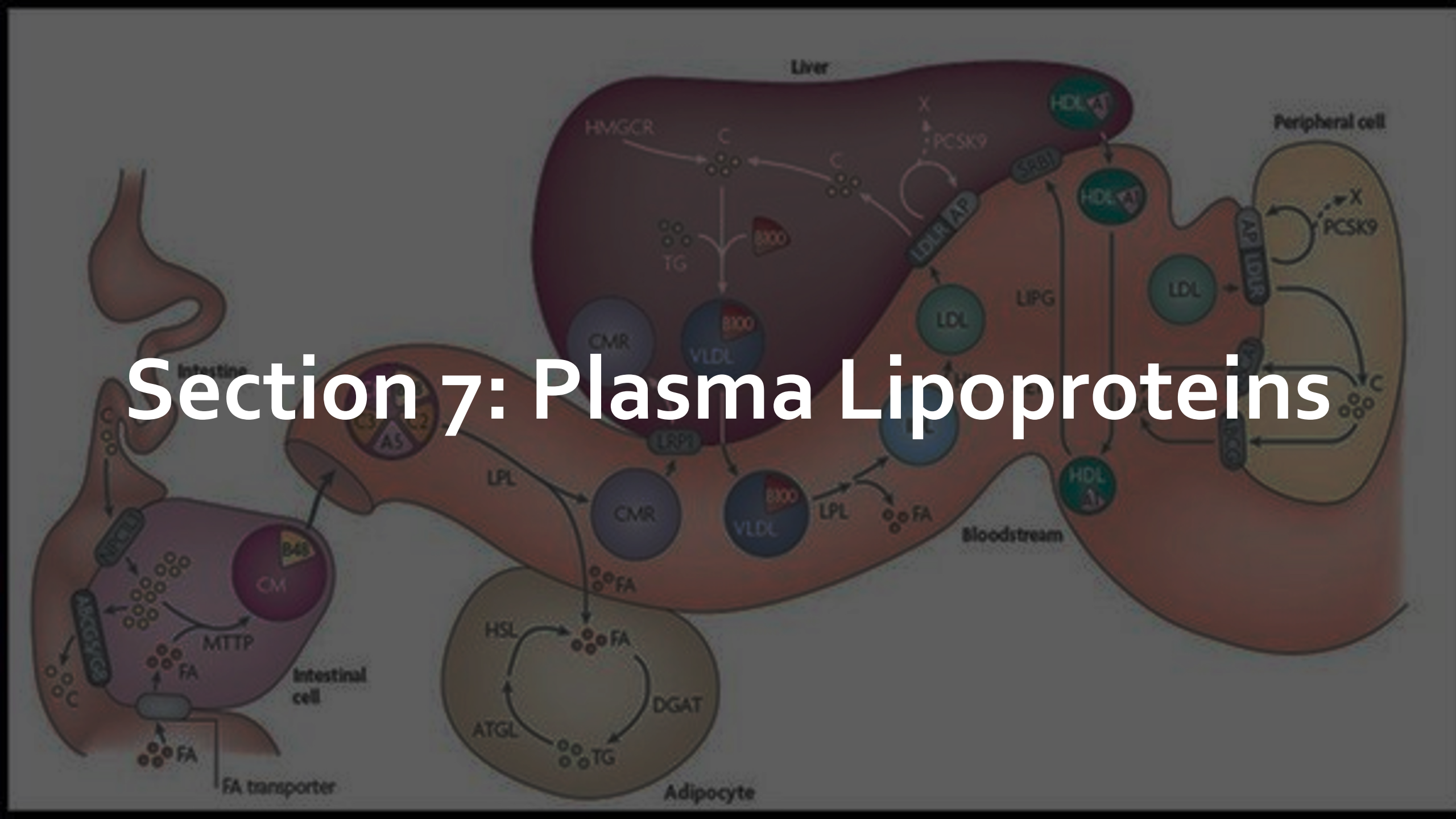
Figure 7: Gallstones

Section 6 Quiz: Short Answer

Question: Describe the role of SREBP.

Answer: SREBP stands for sterol regulatory element binding protein. It is a transcription factor that increases expression of the gene that codes for HMG-CoA reductase, the enzyme responsible for the conversion of HMG-CoA into mevalonate. This conversion serves as the checkpoint for cholesterol biosynthesis.

Section 7: Plasma Lipoproteins



Concept 7.1: Introduction to Lipoproteins

- Lipoproteins
  - Circulate lipids/cholesterols/fatty acids to targets in body
  - Found in plasma of blood

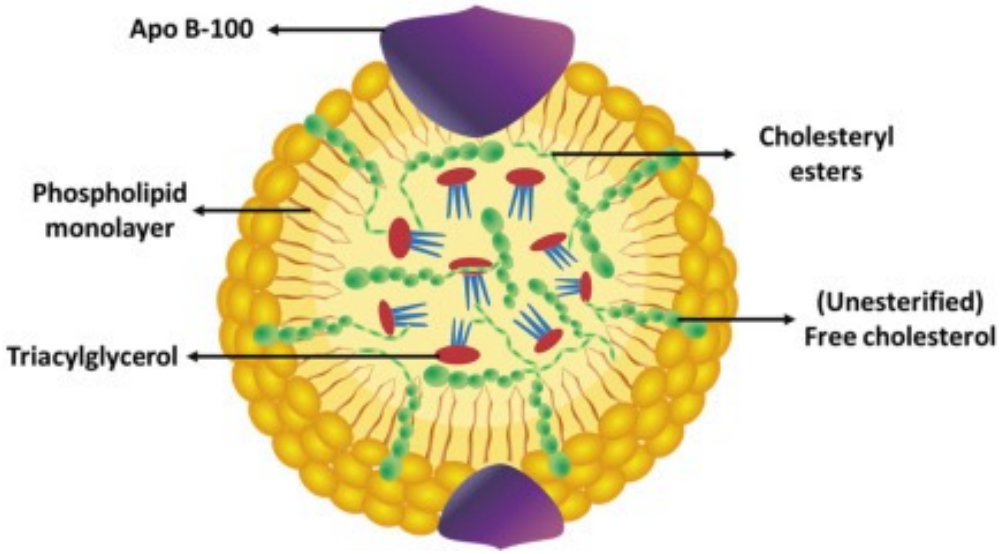


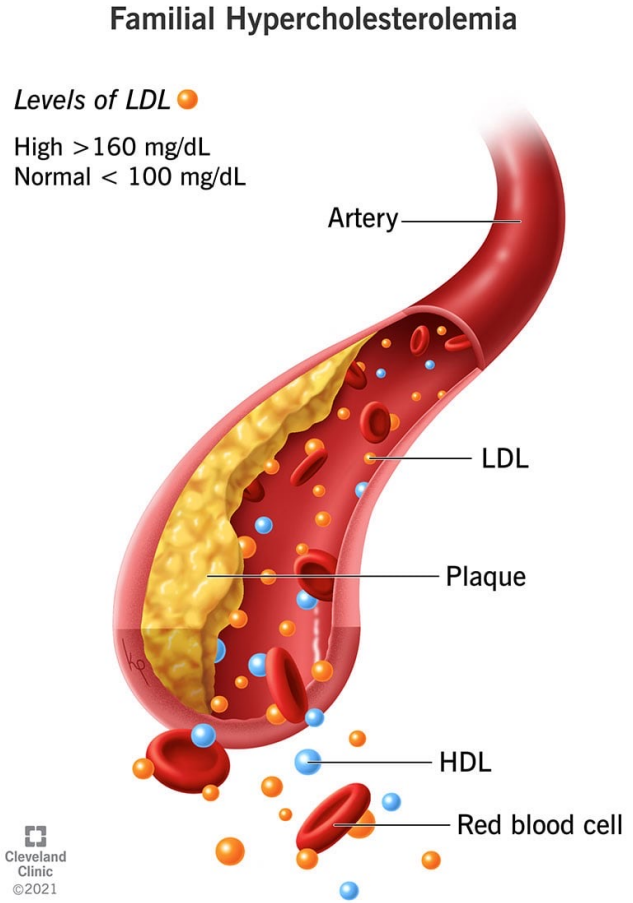
Figure 1: Example of a lipoprotein

Concept 7.2: Different types of lipoproteins

	Composition	Density (g/mL)	Diameter (nm)	Function
Chylomicrons	Highest lipid + lowest protein content	<0.95	75-1200	Dietary fat transport
VLDL	Higher protein content + lower lipid content	0.95-1.006	30-80	Endogenous fat transport
IDL	Higher protein content + lower lipid content	1.006-1.019	15-35	LDL precursor
LDL	Higher protein content + lower lipid content	1.019-1.063	18-25	Cholesterol transport
HDL	Greatest protein content + lowest lipid content	1.063-1.21	7.5-20	Reverse cholesterol transport

Spotlight on Disease: Familial Hypercholesterolemia

- Autosomal dominant disorder
- LDL receptor deficiency
  - Decreased LDL uptake
  - Greater blood LDL and cholesterol levels
  - Accelerates progression to atherosclerosis



Familial Hypercholesterolemia

Spotlight on Disease: Lipoprotein Lipase Deficiency

- Autosomal recessive disorder
- Caused by mutation that prevents lipoprotein lipase synthesis
- Prevents breakdown of TAGs in chylomicrons
- Causes hypertriacylglycerolemia (build-up of chylomicrons in blood)

Spotlight on Disease: Oxidized Lipoproteins

- Oxidized LDL --> accumulate under endothelium of blood vessels
- Macrophages --> uptake modified LDL via scavenger receptors
- Increased intracellular cholesterol levels --> cholesteryl esters accumulate inside macrophage
- Macrophages become foam cells --> atherosclerotic plaques form

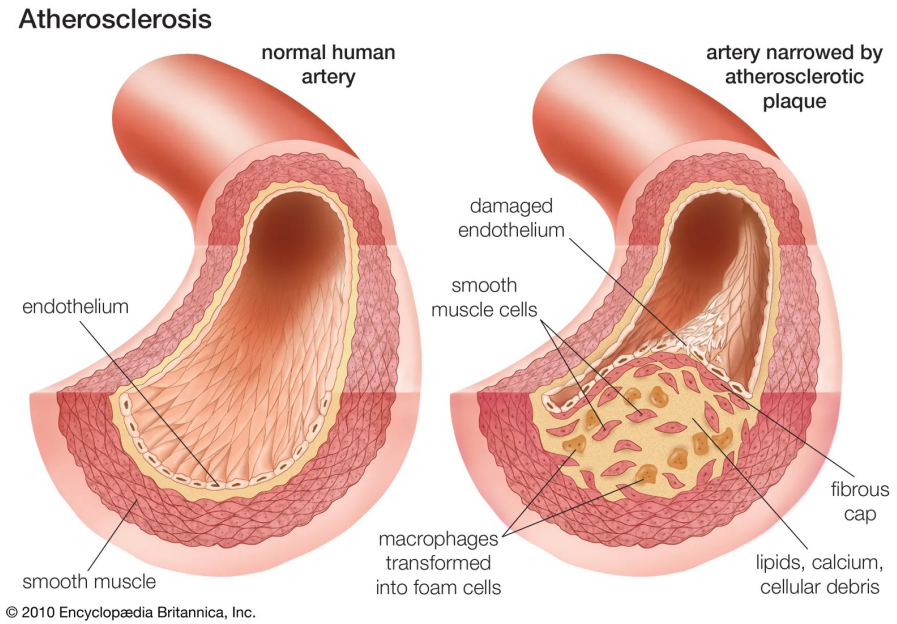


Figure 2: Normal artery versus artery with atherosclerotic plaque

Spotlight on Disease: Atherosclerosis

- Starts with inflammation in endothelial cells of vessel wall of retained LDL particles
- Leads to formation of fatty plaques
- Plaques obstruct/rupture arteries
- Causes stroke heart attack

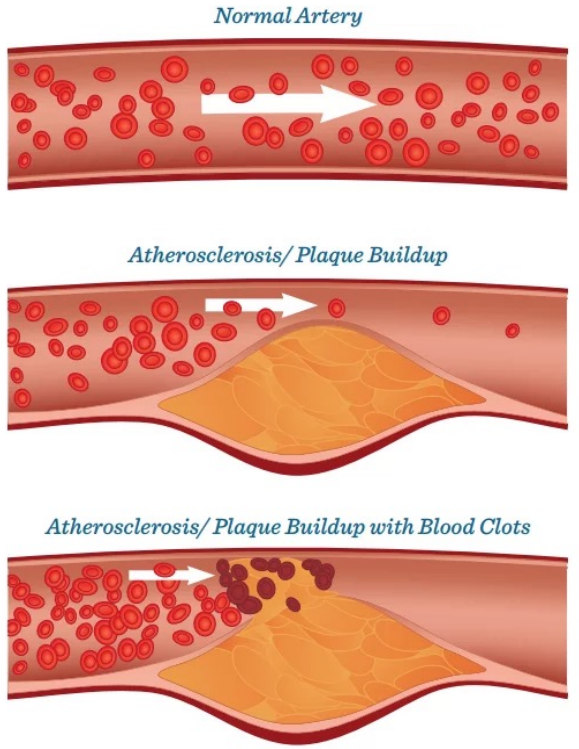


Figure 3: Impact of atherosclerosis

Section 7 Quiz: Multiple Choice

Question: Which of these conditions can lead to atherosclerosis?

a. Lipoprotein lipase deficiency
b. Familial hypercholesteremia
c. Neither a & b
d. Both a & b

Answer: b.

Section 7 Quiz: Short Answer

Question: Describe the differences between VLDL and HDL.

Answer: VLDL stands for very low density lipoproteins and HDL stands for high density lipoproteins. HDL have greater protein content and lower lipid content than VLDL. HDL are more dense and smaller than VLDL. HDLs are involved in reverse cholesterol transport whereas VLDL are involved in endogenous fat transport.