L9:

Biochemical aspects of bile acids and salts

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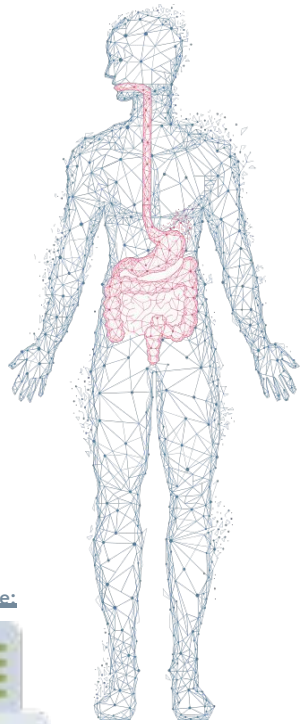

Color Index:

- Main text
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Editing file:

Objectives:

- Structure of primary bile acids and salts, and secondary bile acids and salts.
- Functions of bile salts.
- Enterohepatic circulation.
- Malabsorption syndrome.
- Cholelithiasis.

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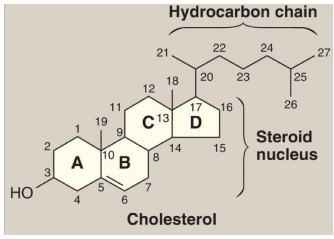
Cholesterol and Primary Bile Acids

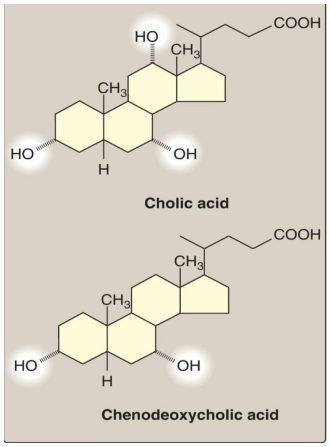
Cholesterol

- Cholesterol has 27 Carbon atoms.
- Parent steroid compound.
- Precursor of bile acids and salts.



Primary Bile Acids

- Amphipathic (both hydrophilic and hydrophobic).
- Has 24 carbon atoms and COOH at sidechain.
- They are synthesized from Cholesterol by removing 3C, and adding Hydroxyl groups. (cholesterol has only one hydroxyl group)
- Cholic acid → Has 3 OH (2 were added)
- Chenodeoxycholic→ Has 2 OH (1 was added)

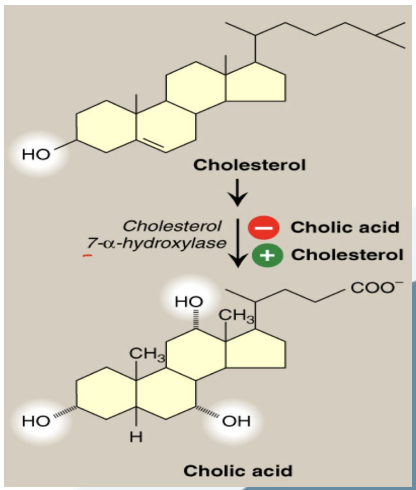


Hepatic Synthesis of Bile Acids

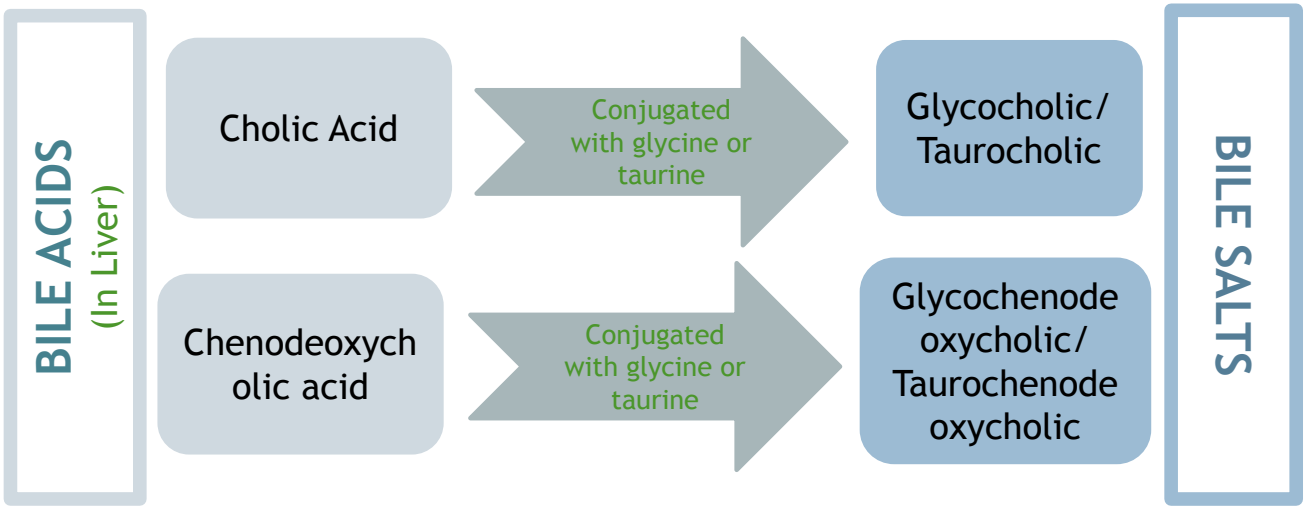
The rate-limiting step is catalyzed by: Cholesterol 7-α-hydroxylase (adds hydroxyl group to C7)

Regulation:
1- Down-regulated by end products (bile acids) "Enzyme repression"
2- Up-regulated by cholesterol "Enzyme induction"

Enzyme repression/induction refers to gene regulation.
For example Cholesterol, when it is activating cholesterol 7 alpha hydroxylase, It is increasing the expression of the genes for this enzyme.



Primary Bile Acids and Salts



Bile Salts (Conjugated Bile Acids)

-Amide-linked with glycine or taurine. Before the bile acids leave the liver, they are conjugated to a molecule of either glycine or taurine (an end product of cysteine metabolism) by an amide bond between the carboxyl group of the bile acid and the amino group of the added compound.

-The ratio of glycine to taurine forms in the bile is 3:1

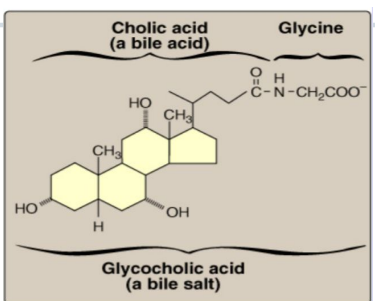
Addition of glycine or taurine results in the presence of fully ionized groups at pH 7.0:
1. COOH- of glycine, 2. SO3- of taurine

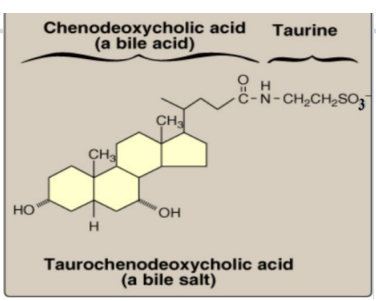
Glycine adds a carboxyl group with a lower pKa, while taurine adds a sulfonate group. This lower pKa makes these groups more prone to losing a proton (H+) and becoming negatively charged (COO- for glycine, SO3- for taurine) at the alkaline pH of bile. The resulting ionized groups enhance the amphipathic nature of bile salts.

Hence, its name as bile salts e.g, Sodium or potassium glycocholate. The name “bile salts” is used because these compounds, formed by conjugating bile acids with glycine or taurine, can combine with sodium or potassium ions.

-More effective detergent than bile acids.
-Only bile salts, but not acids, found in bile

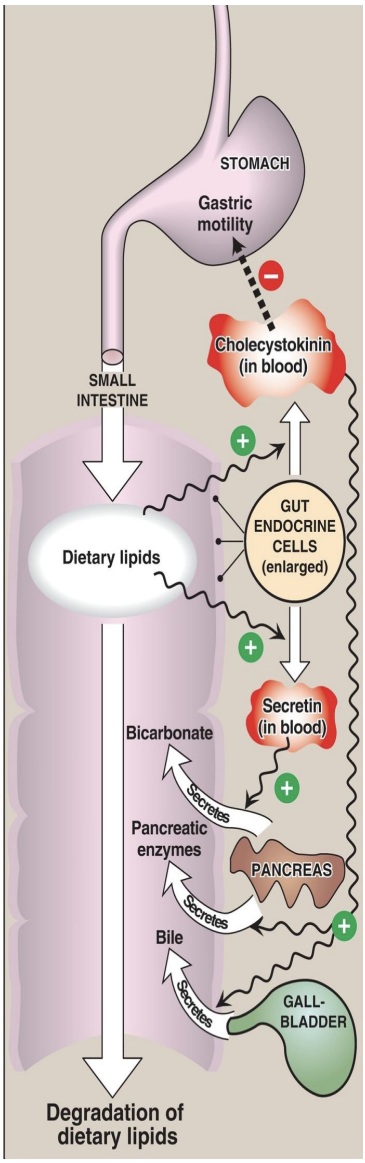
Bile salts combined with Na or K to give:
1- Na or K Glycocholate 2- Na or K Taurochenodeoxycholate





Hormonal Control of Bile Secretion

Stimulus:	Undigested lipids and partially digested proteins in duodenum
Hormone from gut cells:	Cholecystokinin (CCK)
Responses:	1- Secretion of pancreatic enzymes. 2- Bile secretion 3- Slow release of gastric contents.



Extra note: Explanation from 438 team:
Cells in the mucosa of the lower duodenum and jejunum produce a small peptide hormone, cholecystokinin (CCK), in response to the presence of lipids and partially digested proteins entering these regions of the upper small intestine. CCK acts on the gallbladder (causing it to contract and release bile) and on the exocrine cells of the pancreas (causing them to release digestive enzymes) it also decreases gastric motility, resulting in a slower release of gastric contents into the small intestine. Other intestinal cells produce another small peptide hormone, secretin, in response to lower pH of the chyme entering the intestine. Secretin cause the pancreas and liver to release a solution rich in bicarbonate that helps neutralize the pH of the intestinal contents, bringing them to the appropriate pH for digestive activity by pancreatic enzymes.

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Functions of bile salts

Functions of bile salts

Important for cholesterol excretion :
1-As metabolic products of cholesterol
2- Solubilizer of cholesterol in bile

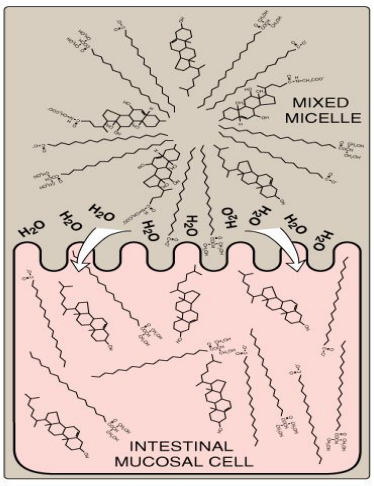
Emulsifying factors for dietary lipids a prerequisite step for efficient lipid digestion.

Cofactor for pancreatic lipase and PLA2

Facilitate intestinal lipid absorption by formation of mixed micelle

Role of Bile Salts

Emulsification of Dietary Lipids in Duodenum	**Emulsification** increases the surface area of lipid droplets, therefore the digestive enzymes can effectively act. **Mechanisms:** **1.Mechanical mixing by peristalsis** **2.Detergent effect of bile salts:** Bile salts interact with lipid particles and aqueous duodenal contents, stabilizing the particles as they become smaller, and **preventing them from coalescing.**
Absorption of Lipids by Intestinal Mucosal Cells	**Mixed micelles:** Disc-shaped clusters of amphipathic lipids. Arranged with their hydrophobic groups on the inside and their hydrophilic groups on the outside. **Micelle** includes end products of lipid digestion, bile salts and fat-soluble vitamins **Note**: Short- and medium-chain fatty acids do not require mixed micelle for absorption by intestinal cells



Mixed Micelle Formation:
-Bile salts
-End products of lipid digestion
-Fat-soluble vitamins

Secondary Bile Acids formation

Bile salts	Glyco- or Tauro-cholate	Chenodeoxycholate

"Deconjugation Reaction"

Removal of glycine / taurine

Intestinal bacteria

We want to synthesize bile salt and it doesn't have Glycine/Taurine

Bile acids	Cholic acid	Chenodeoxycholic acid

"Dehydroxylation Reaction"

Removal of hydroxyl group (OH)

Intestinal bacteria

Secondary Bile acid is only synthesised outside the liver by Intestinal bacteria.

Secondary Bile acids	Deoxycholic acid	Lithocholic

Enterohepatic Circulation

Male Slides

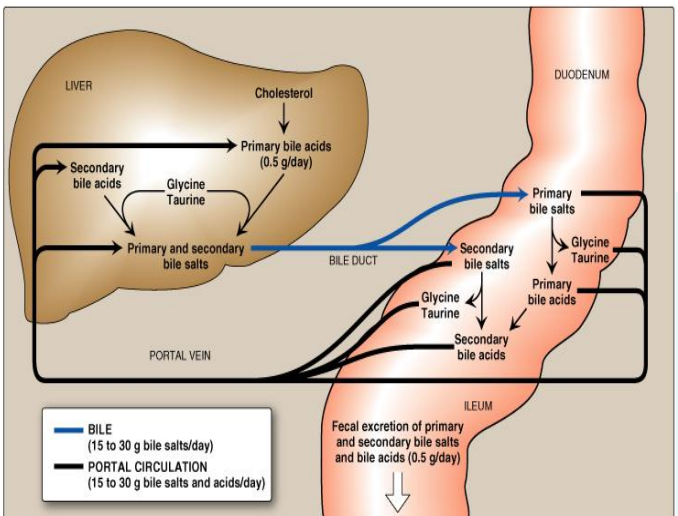
Cholestyramine:

Bile acid sequestrants ,It binds to bile acids in the gut, preventing their reabsorption & Promoting their excretion ,It is used for treatment of hypercholesterolemia

Dietary fiber:

It binds to bile acids, increasing their excretion.

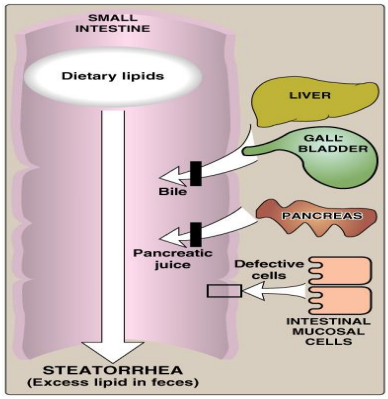
Extra note: Bile salts secreted into the intestine are efficiently reabsorbed and reused. The liver converts both primary and secondary bile acids into bile salts by conjugation with glycine or taurine, and secretes them into the bile. The bile salts is absorbed primarily in the ileum via a Na+ -bile salt cotransporter. They are actively transported out of the ileal mucosal cells into the portal blood, and are efficiently taken up by the hepatocytes via an isoform of the cotransporter. The continuous process of secretion of bile salts into the bile, their passage through the duodenum where some are converted to bile acids, their uptake in the ileum, and subsequent return to the liver as a mixture of bile acids and salts is termed the enterohepatic circulation



Maldigestion /Malabsorption of Lipids

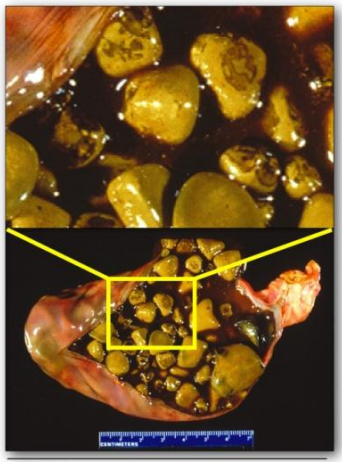
- Decreased bile secretion by:
  - **Liver diseases**: e.g. Hepatitis or cirrhosis
  - **Gallbladder diseases**: e.g. Gallstones

  both result in Malabsorption of lipids



Cholelithiasis: Cholesterol Gallstone Disease

- **↓ Bile salts in bile**:
  - **Biliary tract obstruction** → (interferes with enterohepatic circulation)
  - **Hepatic dysfunction** (↓synthesis)
- **↑ Biliary cholesterol excretion**
- **Treatment:**
  1- Bile acid replacement therapy
  2-Surgical



Quiz

MCQs

Q1: Which of the following is bile salt?
A-Cholic acid
B- Deoxycholic acid
C-Tauro-cholate
D-Lithotomic

Q2:Which of the following cause of Cholelithiasis?
A- Increased biliary cholesterol excretion
B- Decreased Bile salts in bile
C-Increased Bile salts in bile
D-A&B

Q3:Which of the following enzymes is responsible for the formation of Primary Bile acids?
A-Cholesterol 7-a- hydroxylase
B-7-a- Dehydroxylase
C-7-a- carboxylase
D-amylase

Q4: Which of the following is found in bile?
A-Bile acids
B-Carbohydrates
C-Bile salts
D-Hemoglobin

Q5:Which of the following is the precursor for Primary bile acids?
A-Proteins
B-Cholesterol
C-Carbohydrates
D-Bilirubin

Q6:Which of the following is a secondary bile acid?
A-Glycochenodeoxycholic
B-Cholic acid
C-Taurocholic
D-Lithocholic

Answers:Q1:C,Q2:D,Q3:A,Q4:C,Q5:B,Q6:D

SAQ

Q: What are the two key mechanisms by which bile salts contribute to cholesterol excretion?

A: 1-As metabolic products of cholesterol. 2- Solubilizer of cholesterol in bile

Q:What are the components of micelles?

A:Bile salts, End products of lipid digestion, Fat-soluble vitamins.

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