جامعة الملك سعود
King Saud University

"اللَّهُمَّ لا سَهْلَ إلاَّ ما جَعَلْتَهُ سَهْلاً، وأنْتَ تَجْعَلُ الحَزْنَ إذَا شِئْتَ سَهْلاً "

Biochemistry437

Biochemical aspects of bile acids and salts

Biochemistry Team 437

Color index:
Doctors slides
Doctor's notes
Extra information
Highlights

GNT block

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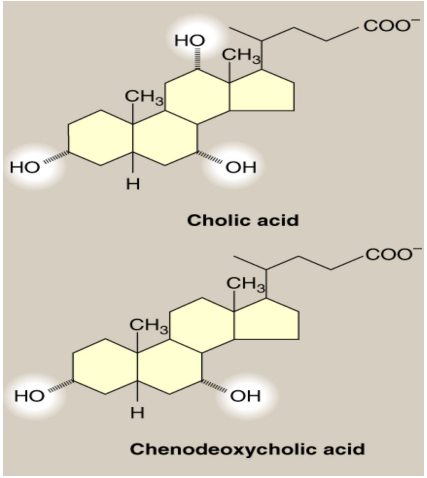
Objectives:

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

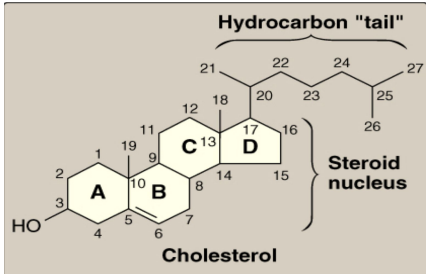
Primary Bile Acids

- Primary bile acids (24 C):
  - Amphipathic
  - -COOH at side chain "carboxylic acid"
  - Cholic acid: 3 OH
  - Chenodeoxycholic: 2 OH



Cholesterol (27 C) is the:
-Parent steroid compound
-Precursor of bile acids and salts

Cholesterol



- When we make primary bile acid from the **cholesterol** what we usually do is **remove 3 carbons** (the hydrocarbon tail is reduced) it becomes 24C molecule with carboxylic acid group at the end. Then we **add hydroxyl** group to It.
- if we add:
  - One hydroxyl group it becomes chenodeoxycholic acid.
  - two hydroxyl group it becomes cholic acid.
- Those bile acids are ionized in nature shown as (COO-) ,but in the body they are not ionized, so they will have (COOH) instead that's why we call them bile acid. (if they were ionized, they interact with sodium making salts)

Cholesterol "27 carbon molecule" is the parent compound for bile acids and salts.
Bile salt is a watery mixture of organic and inorganic molecules that's secreted and produced by the liver, it has to go to the intestine ultimately but if not required, it will be stored in the gallbladder.

Hepatic Synthesis of Bile Acids

The rate-limiting step is catalyzed by: **Cholesterol 7-α-hydroxylase**

Regulation:

Down-regulated by:

end products[1] (bile acids) "Enzyme repression[2]"

1-cholic acid or chenodeoxycholic acid.

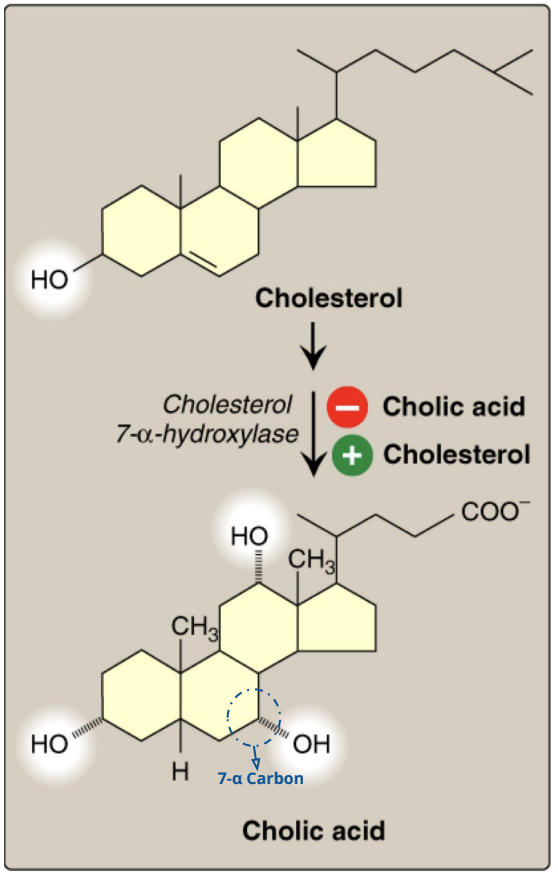
2-If we have a lot of primary bile acid it will be repress the synthesis of the enzyme.

Up-regulated by:

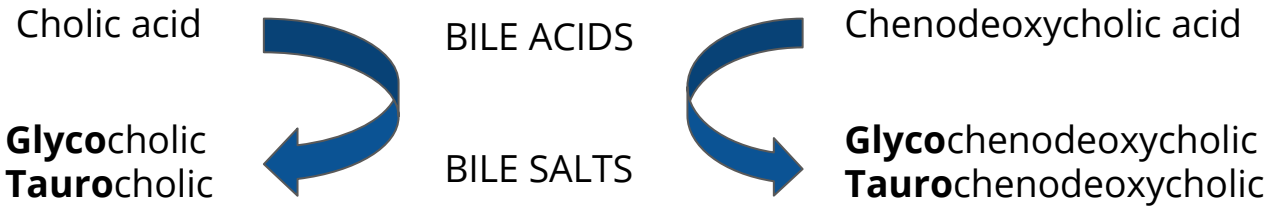
cholesterol "Enzyme induction"

1-If we have a lot of cholesterol and less primary bile acid it will make more of the enzyme.

- Formation of bile acid is a multi step process but we're going to focus on the rate limiting step for the synthesis of both primary bile acid,which is:
- the addition of the 1st hydroxyl group to the carbon at the 7 α position.
- This reaction is catalyzed by the enzyme : Cholesterol 7-α-hydroxylase.
- What happens is: Hydroxylation (adding a hydroxyl group) of cholesterol at carbon No.7.



Primary Bile Acids and Salts



-the primary bile acid (the cholic acid and Chenodeoxycholic acid) interact with glycine or taurine to form the **Conjugated bile acids.**
-When we add glycine to cholic acid it becomes Glycocholic, if we add taurine it becomes Taurocholic and so on, now they can also be called **bile salts.**
-the majority of the molecules are glycine that's why the ratio is 3:1

Bile salts (Conjugated bile acids): **amide-linked** with glycine or taurine
The ratio of glycine to taurine forms in the bile is 3:1

- Glycocholic & Glycochenodeoxycholic 75%.
- Taurocholic & Taurochenodeoxycholic 25%.

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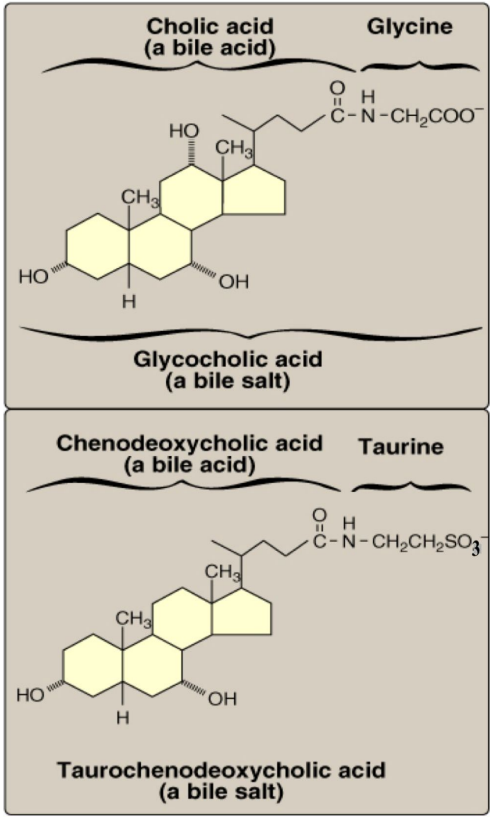
Bile Salts

- Addition of glycine or taurine results in the presence of fully ionized groups at pH 7.0:
  - COO- of glycine &
  - SO3- of taurine

(hence, its name as bile salts e.g., Sodium or potassium glycocholate)

Na or K Glycocholate



Characteristics:

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

-how does this formation of bile salts happen on a chemical level? COOH of Cholic or chenodeoxycholic acids interact with amine group of glycine or taurine forming an amide linkage. The added amino acid has an ionized group at the end “COO of glycine or SO3 of taurine” that attaches to a metal, becoming a salt “bile salts”

Na or K Taurochenodeoxycholate

Secondary Bile Acids

"explained more in the next slide"

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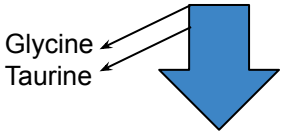
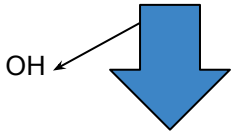
Bile salts	Glycol- or Taurocholate	-Chenodeoxycholate



Intestinal bacteria (Deconjugation)

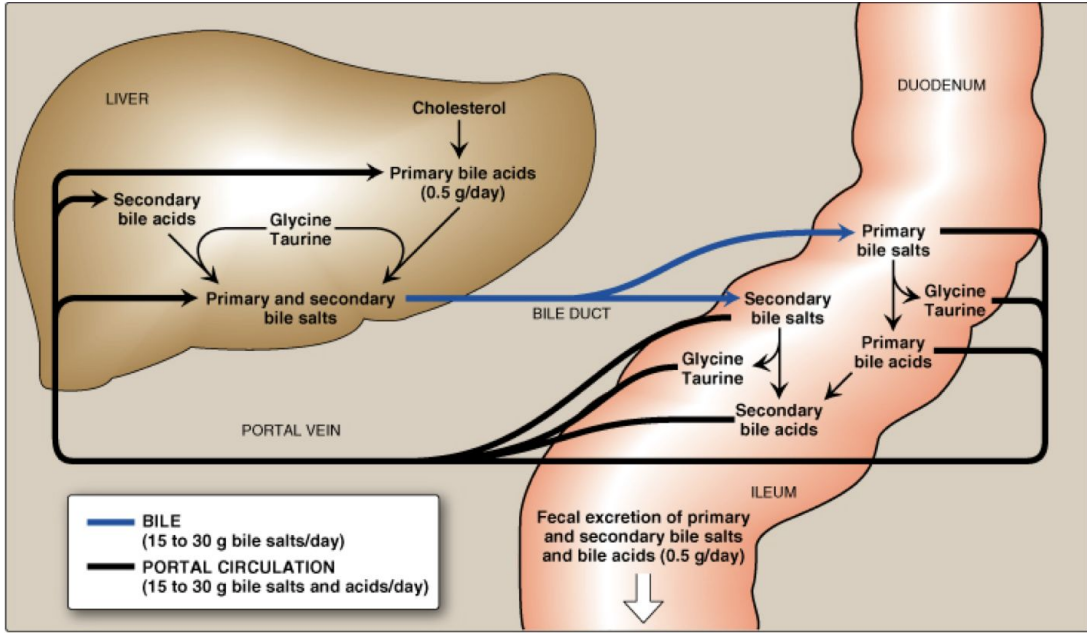
1° Bile acids	Cholic acid	Chenodeoxycholic



Intestinal bacteria (remove hydroxyl group at C7)

2° Bile acids	Deoxycholic acid	Lithocholic

Enterohepatic Circulation



- Both primary and secondary bile salts are present in the bile duct
- All Bile salts & bile acid "go by the portal vein to the liver".
- Bile released from the liver ***does not*** contain bile acids, only salts

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- In the liver the **primary** bile **acid** is formed from cholesterol. then glycine or taurine are added to the primary bile acid to make them primary bile salt.
- Through the common bile duct, the bile salts reach the intestine.
- In the intestine, the intestinal bacteria acts on this primary salt and removes the of glycine and taurine making the primary bile acid again.
  The intestinal bacteria further acts on the primary bile acid by removing the hydroxyl group which produces the secondary bile acid.
- Through the portal vein, the secondary bile acid is take to the liver, where it is conjugated with taurine or glycine, making a secondary bile salt.
- The secondary bile salt, along with the primary bile salts present already in the liver, go through the bile duct to the intestine and the circle continues.

Hormonal Control of Bile Secretion

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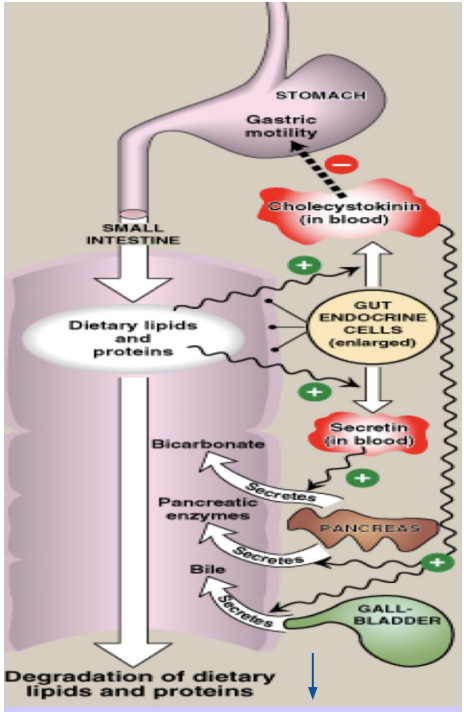
Stimulus:	Undigested lipids and partially digested proteins in duodenum
Hormone from gut cells:	Cholecystokinin (CCK) Secreted by the I cells of the intestines, A hormone that functions to enhance digestion.
Responses:	1. Secretion of pancreatic enzymes 2. Bile Secretion 3. Slow release of gastric contents

All the various responses work to cause the same effect, to help in the digestion of lipids



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As shown in the picture dietary lipids and proteins stimulates Gut endocrine cells .. (In this case I cells for CCK secretion and S cells for secretin secretion) Cholecystokinin (CCK) has two functions: 1. Decreases Gastric motility 2. Stimulates Pancreatic enzymes and bile secretion and release into small intestine (relaxes sphincter of oddi) Secretin Stimulates the release of bicarbonate into duodenum to neutralize the acidity of the chyme that is coming from the stomach

Functions of Bile Salts

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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

1-Bile salts are made from cholesterol
2-phospholipase A2

Emulsification of Dietary Lipids in Duodenum: Role of Bile Salts

• 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 "forming a mass"

What do we require for Emulsification?
1- The molecule must be amphipathic
2-Mechanical mixing (peristalsis)

Absorption of Lipids by Intestinal Mucosal Cells: Role of Bile salts

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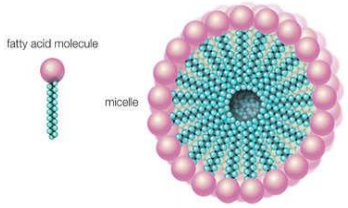
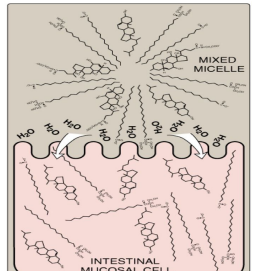
Mixed Micelles

They are disc-shaped clusters of amphipathic lipids.
What is their function? They have a role in lipid digestions.
Structure: Arranged with their hydrophobic groups on the inside and their hydrophilic groups on the outside.
Because the environment is hydrophilic and lipids are hydrophobic so they
Keep the lipids deep within away from the surrounding hydrophilic environment.





Micelle include end products of lipid digestion, bile salts and fat-soluble vitamins.
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

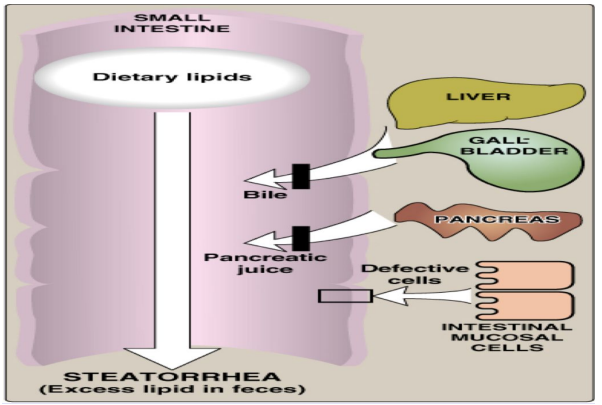
Contents of micelles: 2-monoacylglycerol, cholesterol, long chain fatty acids, phospholipids

Maldigestion/Malabsorption of Lipids

Decreased bile secretion by:

Liver Diseases	Decreases synthesis e.g., Hepatitis or cirrhosis
Gallbladder Diseases	obstruction e.g., Gallstones

That leads to Malabsorption of lipids & steatorrhea



Cholelithiasis "gallbladder stones"

- Causes:
  1. ↓Bile salts in bile:
  - Biliary tract obstruction (interferes with enterohepatic circulation)
  - Hepatic dysfunction (synthesis)

  2. ↑Biliary cholesterol excretion presence of more cholesterol in the bile that goes to the gallbladder. And reduced mobility of the gallbladder i.e electrolytes imbalance. Contribute to this problem

- Treatment :
  •Bile acid replacement therapy.
  • Surgical "cholecystectomy"

You need bile salts to solubilize cholesterol If the ratio between the cholesterol and the bile salts is disturbed due to any reason " bile salts decrease, or cholesterol increases". The bile that contains a lot of cholesterol will stay in the gallbladder, then Cholesterol will be accumulated and precipitate, Thus causing Gallstones to form.

Summary

Bile acids	Bile salts
Unconjugated Chenodeoxycholic acid: 2 OH Cholic acid : 3 OH	Conjugated
Amphipathic	Enhanced amphipathic function
Formed from cholesterol (by Cholesterol 7-α-hydroxylase)	Formed from Bile acid + glycine or Taurine
Partially ionized And Less polar	Fully ionized and More polar
NOT found in bile	Found in bile
Enzyme repression by bile acids Enzyme induction by cholesterol	**Functions** :cholesterol excretion Emulsifying factors for dietary lipids Cofactor for pancreatic lipase and PLA2 Facilitate intestinal lipid absorption

MCQs:

1 Cholecystokinin function is
A Secretion of hepatic enzymes
B Bile secretion
C fast release of gastric contents
D Stimulates the pancreas to release a watery solution

2 Which one of the following is NOT a functions of Bile Salts?
A Important for cholesterol digestion
B Emulsifying factors for dietary lipids
C Cofactor for pancreatic lipase
D Facilitate intestinal lipid absorption

3 The rate-limiting step of the synthesis of Bile Acids is catalyzed by?
A Cholesterol 6-β-hydroxylase
B Cholesterol 7-α-hydroxylase
C Cholesterol 6-α-hydroxylase
D Cholesterol 7-β-hydroxylase

4 Which one of the following is NOT a primary bile acids characteristic?
A Amphipathic
B Hydrophilic
C 24 C
D -COOH at side chain

5 Absorption of Lipids by Intestinal Mucosal Cells is a role of
A Bile salts
B Bile acid
C CCK
D microvilli

5- A
4- B
3- B
2- A
1- B