Bile salt

Objectives :

- Functions of the bile and stages of its secretion.
- Characteristics and main constituents of bile.
- Functions of gallbladder.
- Absorption, uptake and functions of bile acids.
- Enterohepatic circulation of bile salts.
- Control of biliary system.

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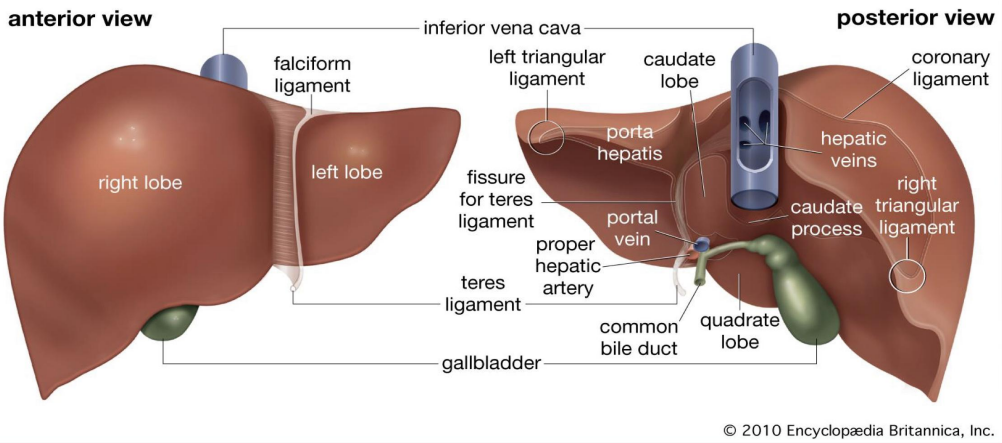
Colour index:
- Important
- Numbers
- Extra

وَأَن لَّيْسَ لِلْإِنسَانِ إِلَّا مَا سَعَىٰ

The liver

- The liver is the largest internal organ in the body, constituting about 2.5% of an adult's body weight.
- Receives 25% of the cardiac output via the portal vein and hepatic artery. Double blood supply
- Takes up, stores, and distributes nutrients and vitamins.
- Plays an important role in maintaining blood glucose levels.
    - Stores the excess glucose in the form of glycogen in hyperglycemia, and release it in hypoglycemia.
- Regulates the circulating blood lipids by the amount of very low–density lipoproteins (VLDL) it secretes.
- Synthesizes many of the circulating plasma proteins.
- Takes up numerous toxic compounds and drugs from the portal circulation.
- Performs important endocrine functions. Secrete: Angiotensinogen, Thrombopoietin, Hepcidin.
- Serves as an excretory organ for bile pigments, cholesterol, and drugs.

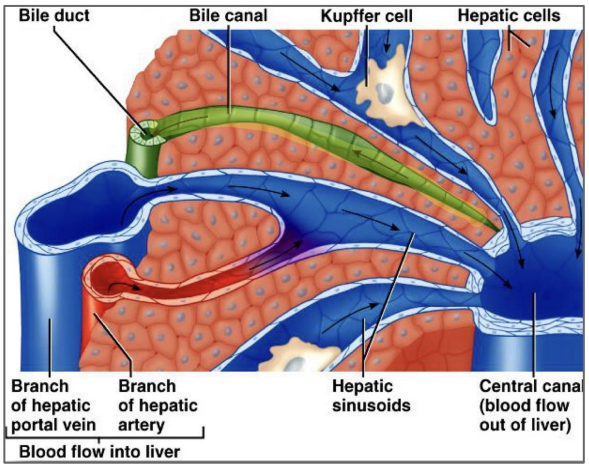


The main digestive function of the liver

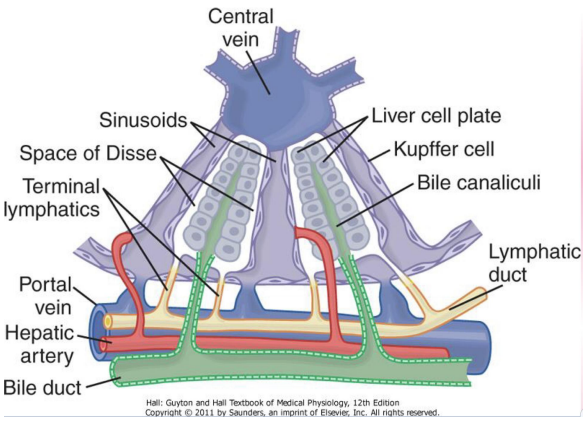
- The main digestive function of the liver is the secretion of bile.
- Bile serves two important functions:
    a. It plays an important role in fat digestion and absorption by its contents of bile salts.
    b. Bile serves as a means for excretion of waste products from the blood. These include especially bilirubin, end product of hemoglobin destruction.

Bile is secreted in two stages:

- The initial portion is continually secreted by the hepatocytes.
- It is secreted into bile canaliculi that originate between the hepatic cells.
- Hepatic Bile: Isotonic secretion, with high Na+, Cl- and HCO3 and low K+ and Ca2+.
    - **High** in comparison to the gallbladder bile, not the plasma.
- The bile flows in the canaliculi toward the hepatic duct and common bile duct.

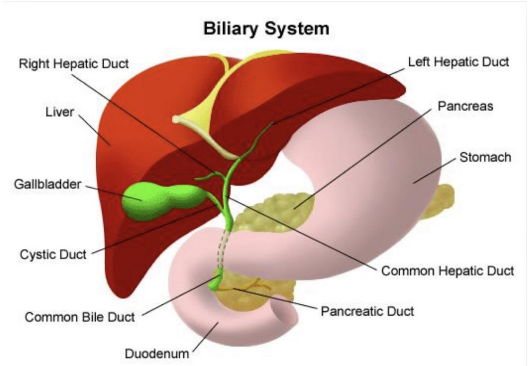


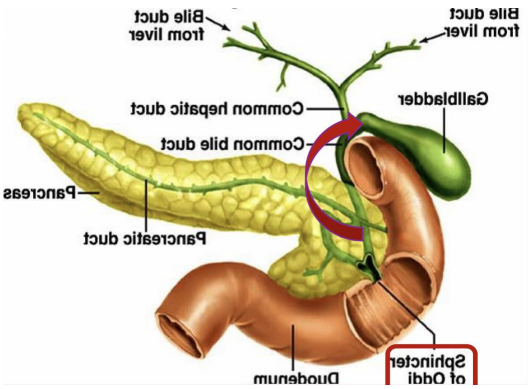
Bile canaliculi & Duts



Bile is secreted in two stage

- From the common bile duct, bile either empties directly into the duodenum or is diverted through the cystic duct into the gallbladder.
- Gallbladder bile is the second portion which is added to the initial bile secretion.
    - one of the function of gallbladder is to concentrate the bile by water active channels which also drag NaCl and others
- Gallbladder bile: high Bile acid anion and Ca2+ ; but low Na+ , Cl- , HCO3,H2O
- The common bile duct open into the duodenum in company with the pancreatic duct at the ampulla of vater.
- This opening is guarded by the sphincter of Oddi(choledochoduodenalsphincter).





*Bile is considered both secretion (bile salts) and excretion (Bilirubin, cholesterol).

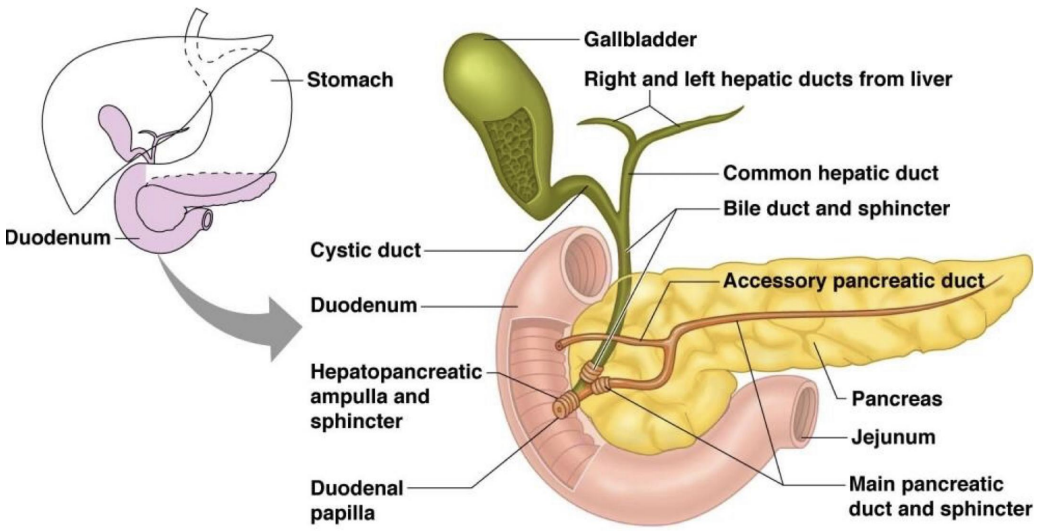
*During the meal, bile is poured directly from the liver and the gallbladder.
In between the meals, bile is stored in the gallbladder.

Differences between hepatic bile & gallbladder Bile

	Hepatic bile	Gallbladder bile
Water	98%	89%
Total solids	2-4%	11%
Bile salts	26	145
Bilirubin	0,7	5
Cholesterol	2,6	16
Phospholipids	0,5	4
Na+	145	130
HCO3	28	10
Ca++	5	23
Cl-	100	25
K+	5	12
pH	8,3	7,5

The low pH prevent the formation of gallstones, because calcium is more soluble in the acidic medium.

The Gallbladder



Characteristic of bile

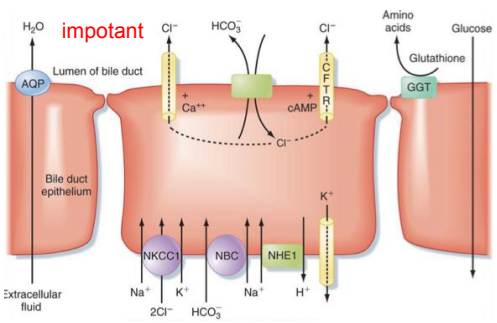
- Bile is a viscous golden yellow or greenish fluid.
- It is isotonic with plasma and slightly alkaline.
- NaHCO3 in bile is responsible for its alkaline reaction and participates with pancreatic and duodenal secretion in neutralization of acid chyme delivered from stomach.
- The liver produces about 5 L /day, but only 600- 1000 ml/day are poured into the duodenum.

What are the components of bile ?

1. Bile acids (bile salts) (65% of dry weight of bile)
2. Phospholipids (As lecithin, 20%)
3. Proteins (5%)
4. Cholesterol (4%), bile is the major route for cholesterol excretion
5. Bile pigments (as bilirubin, 0.3%)

From bile ducts epithelial cells:

- Electrolytes mainly HCO3- , in addition to H2O
- These contribute to the volume of hepatic bile.
- HCO3- aids in neutralization of acid chyme.



Composition of bile

From ducts

From hepatocytes

- Aqueous alkaline Solution (NaHCO3)
- Organic constituents
  - Bile salts(65%) Lecithin (20%). Proteins (5%) Cholesterol (4%) Bilirubin (0.3%)

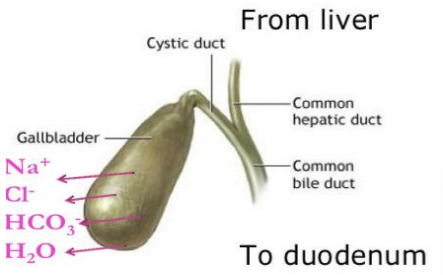
Storing and concentrating bile in the gallbladder

- Bile is secreted continually by the liver cells and then normally stored in the gallbladder until needed (gallbladder can hold 30 to 60 mL).

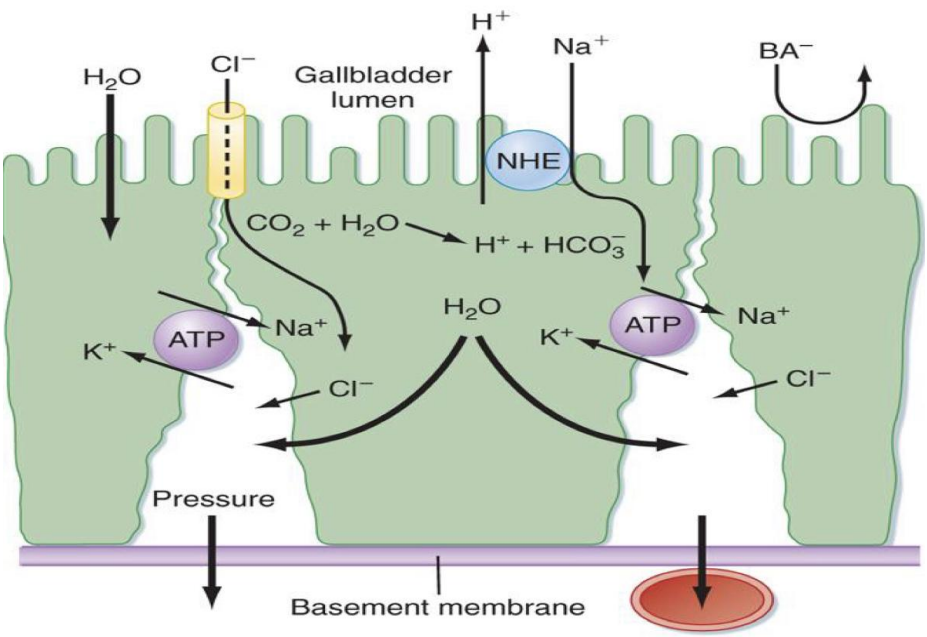
- Gallbladder concentrates the bile,during every 12 hours of bile secretion (rusually about 450 mL) because Na+ is actively transport through the gallbladder mucosa.

- Then, followed by secondary absorption of Cl-, water, and most other diffusible constituents.

- Bile is normally concentrated in this way about 5-fold, but it can be concentrated up to a maximum of 20-fold.



Concentrations of bile during storage in the gallbladder



CFTR: Cystic fibrosis transmembrane conductance regulator, chloride channel. The tight junctions have low permeability, they resist the passage of Bile Acid anions (BA) out of the lumen.

Regulation of bile secretion

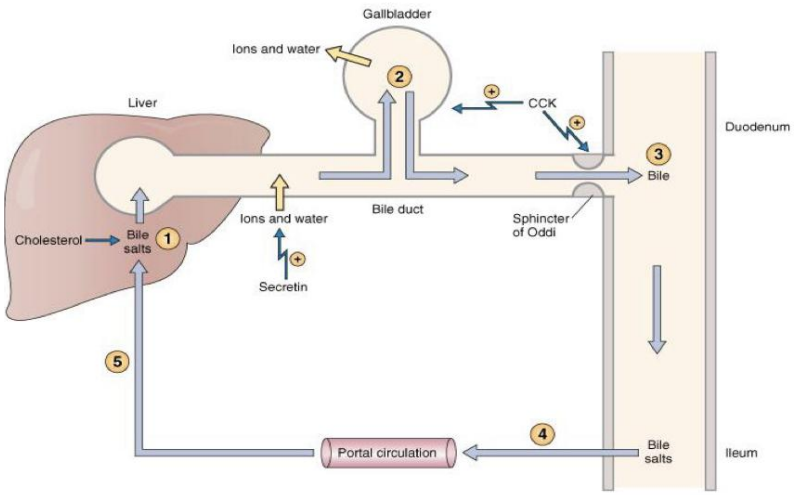
The most powerful regulatory mechanism is the feedback mechanism (enterohepatic circulation)

- Bile secretion is primarily regulated by a ***feedback*** mechanism, with secondary **hormonal** and **neural** controls.
- The major determinant of bile acid synthesis is its concentration in hepatic portal blood (feedback control) how much bile pool i have, if it's too much it will stop secreting, it it's little will stimulate hepatocyte.
- CCK, secretin and estrogen (hormonal control).
- Parasympathetic (vagal) stimulation results in contraction of the gallbladder and relaxation of the sphincter of Oddi, as well as increased bile formation.
- Bilateral vagotomy results in reduced bile secretion after a meal, suggesting that the parasympathetic nervous system plays a role in mediating bile secretion.
- By contrast, stimulation of the sympathetic nervous system results in reduced bile secretion and relaxation of the gallbladder.

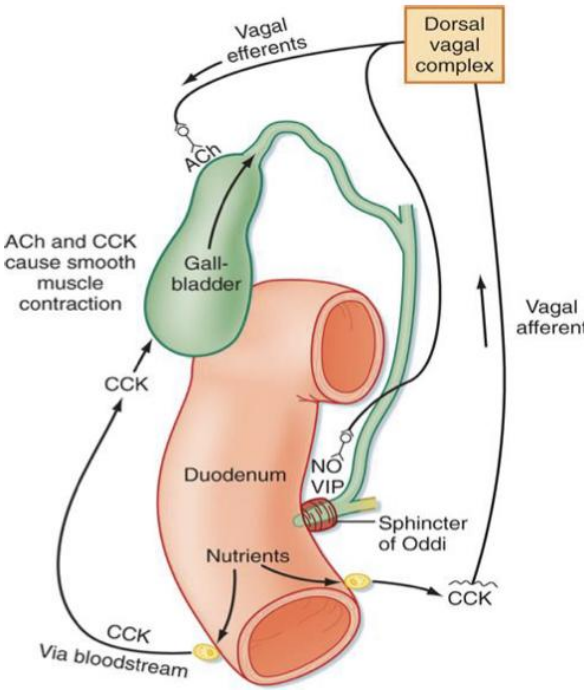
Feedback control of biliary secretion (enterohepatic circulation of bile salts)

summary

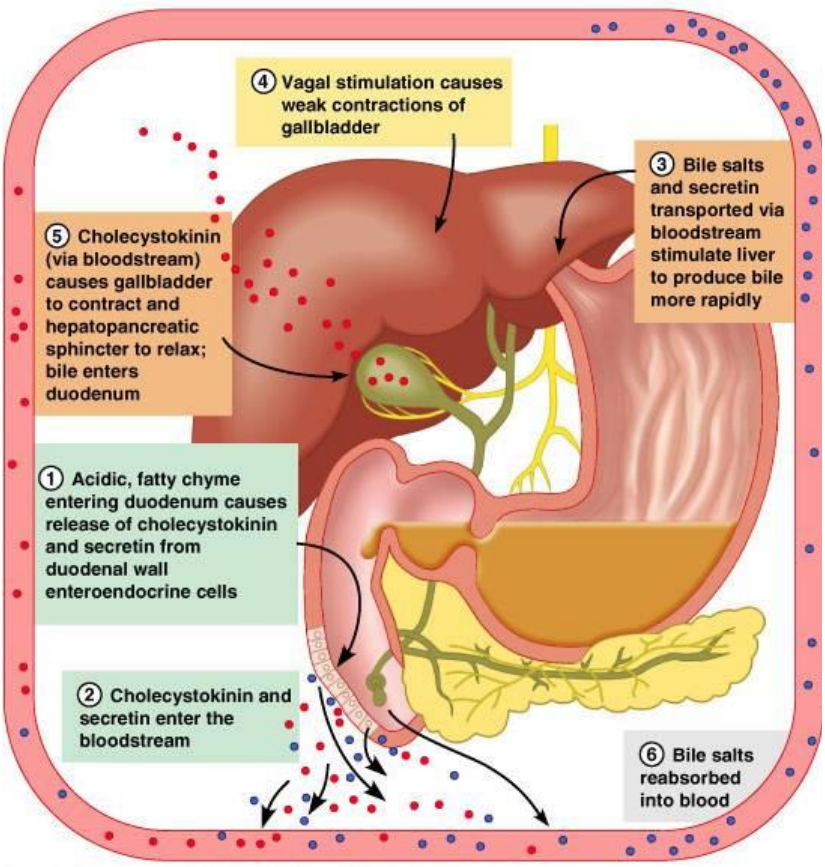
bile acid/salt is synthesized from cholesterol then actively secreted to lumen, secretin hormone activate cholangiocyte to release ions and water. If the bile goes to the gallbladder these ions and water will be absorbed.
In presence of fat CCK will stimulate gallbladder to release bile salt and will relax sphincter of oddi
Reabsorption of bile salt take place in the ilium in order to give time to bile salt to emulsify the lipid then the bile salt return to the liver



Neurohumoral control of gallbladder contraction & biliary secretion



Regulation of bile secretion

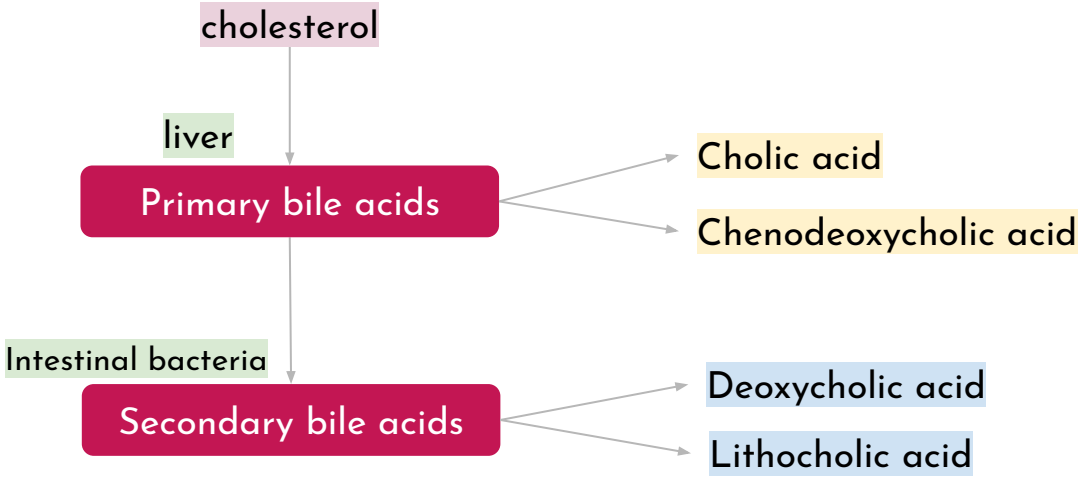


Bile acids & salts

- Bile acids are steroid acids, synthesized in the liver from cholesterol by the enzyme ***cholesterol 7α- hydroxylase.***
- Bile acids include:
  - Primary: cholic, chenodeoxycholic acids.
  - Secondary: deoxycholic, lithocholic acids.
- The principal primary bile acids conjugated with glycine or taurine to form glyco and taurocholic bile acids.

Primary bile acids + Glycine / Taurine = Conjugated bile acids
e.g. cholic + Glycine = Glycocholic acid

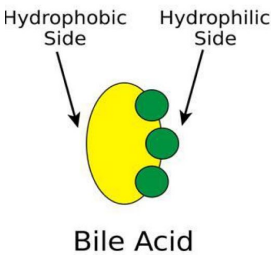
Primary and secondary bile acids



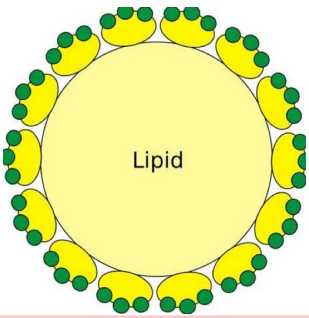
- At a neutral pH, conjugated bile acids are mostly ionized by hepatocytes lowering pka of bile acid , more water soluble and are present almost entirely as salts of various cations (mostly Na+) e.g., sodium glycocholate and are called bile salts.
- Bile salts are much more polar than bile acids and have greater difficulty penetrating cell membranes. Consequently, the small intestine absorbs bile salts much more poorly than bile acids.
- This property of bile salts is important because they play an integral role in the intestinal absorption of lipid. Therefore, it is important that the small intestine absorb bile salts only after all of the lipid has been absorbed. The bile salts remain in the intestine until all the fat is absorbed.

- Bile acids are amphipathic that is having both hydrophilic & hydrophobic domains and tend to form molecular arrangement called micelles.
- In bile acid micelle, the hydrophobic side of bile acid faces inside & away from water. The hydrophilic surface faces outward towards the water.
- Bile acid micelles form when the conc. of bile acids exceed a certain limit (**critical micelle conc.**). Above this conc., any additional bile acid will join the micelle.
- Normally bile acid conc. in bile is much greater than critical micelle conc.

*So the bile acids are always present as micelles.
* this is important for keeping the cholesterol in soluble form.

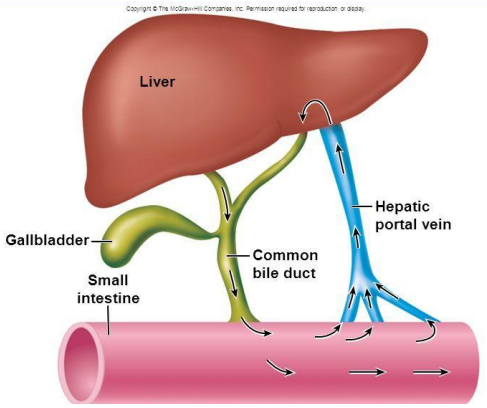


The hydrophilic side has many negative charges come from carboxyl hydroxyl and **sulfonic acid** (powerful charged)



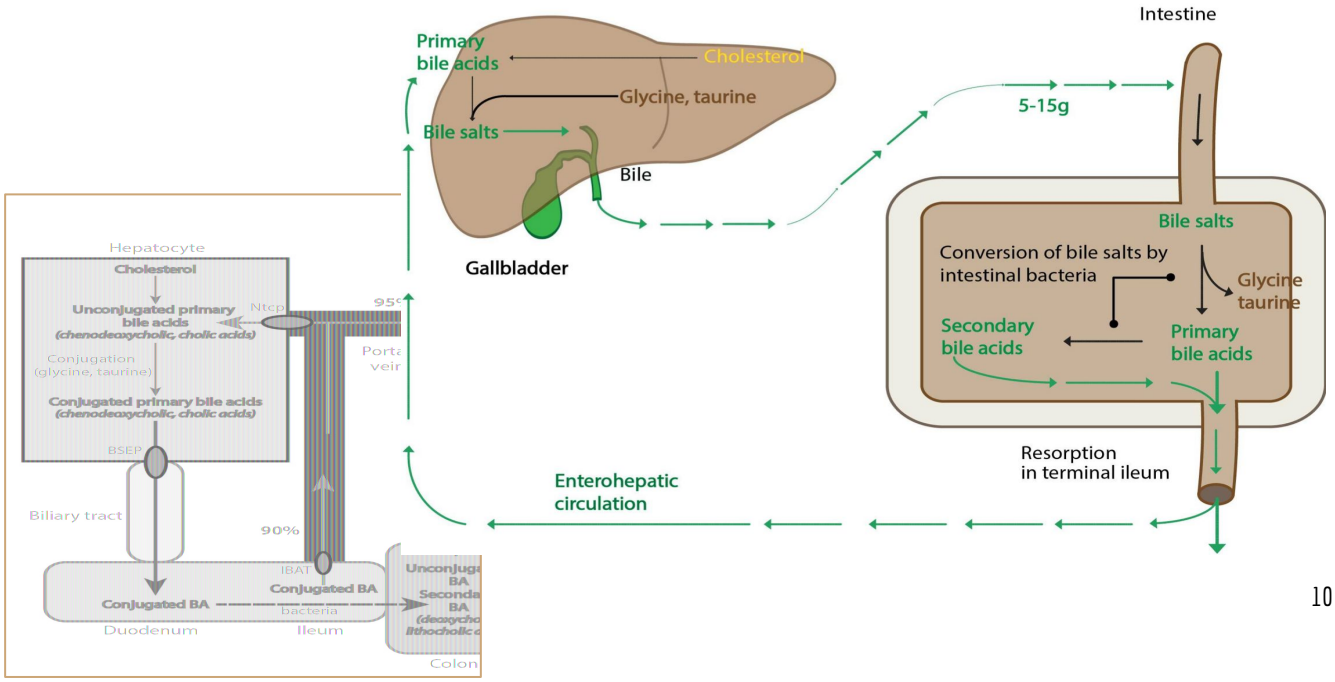
Enterohepatic circulation of bile salt

- It is the recycling of bile salts between the small intestine and the liver.
- The total amount of bile acids in the body, primary or secondary, conjugated or free, at any time is defined as ***the total bile acid pool***.
- In healthy people, the bile acid pool ranges from 2 to 4 g.

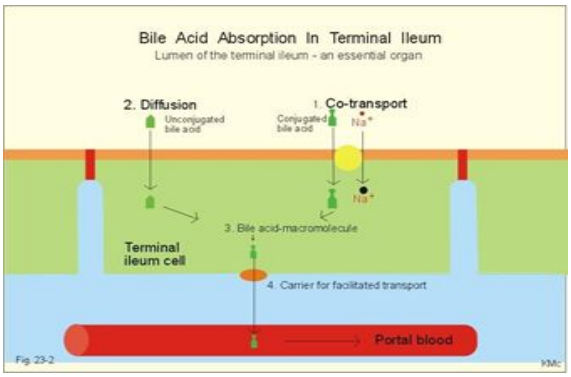


Some patient who has IBD undergoes resection of terminal ileum (the place where the bile salt absorbed) which affect bile salt reabsorption which then will have more demand of bile salt synthesis, the patient may end up having satehorria.

- About 5-15 g of bile acids are poured into the duodenum /day.
- In the intestine, some of bile acids are deconjugated and dehydroxylated in the 7 α position by intestinal bacteria that normally colonize in the digestive tract.
- Dehydroxylation results in the production of secondary bile acids. Cholic acid is converted to deoxycholic acid and chenodeoxycholic acid to lithocholic acid.
- On reaching the terminal ileum, about 95% of bile acids are absorbed and reach the liver through the portal vein.
- About 0.3-0.5 g of bile acids are lost in feces daily (15-35% of total bile acid pool). These are replaced by new synthesis in liver.



Absorption of bile acids in the intestinal lumen



Bile acids are absorbed largely in the ***terminal part of the ileum***.

They cross the brush border plasma membrane by two routes:

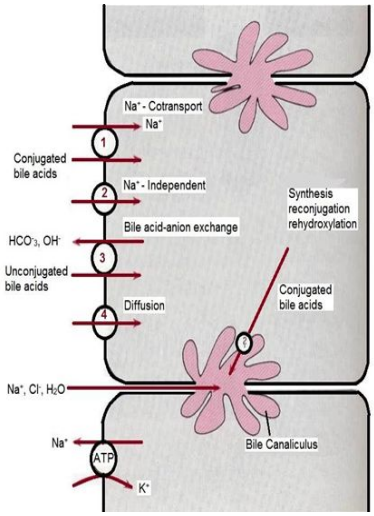
Conjugated bile acids are 2ry active transported powered by the Na^+ gradient across the brush border membrane.

Unconjugated bile acids are less polar and are better absorbed by **simple diffusion.**

Absorption of bile acids/salt back into hepatocyte

Multiple transport mechanisms are located in the hepatocyte plasma membrane for uptake of bile acids from sinusoidal blood include:

- An active carrier-mediated process.
- Facilitated diffusion.
- Bile acid HCO_3^- or OH^- Exchange
- Passive diffusion (very little).

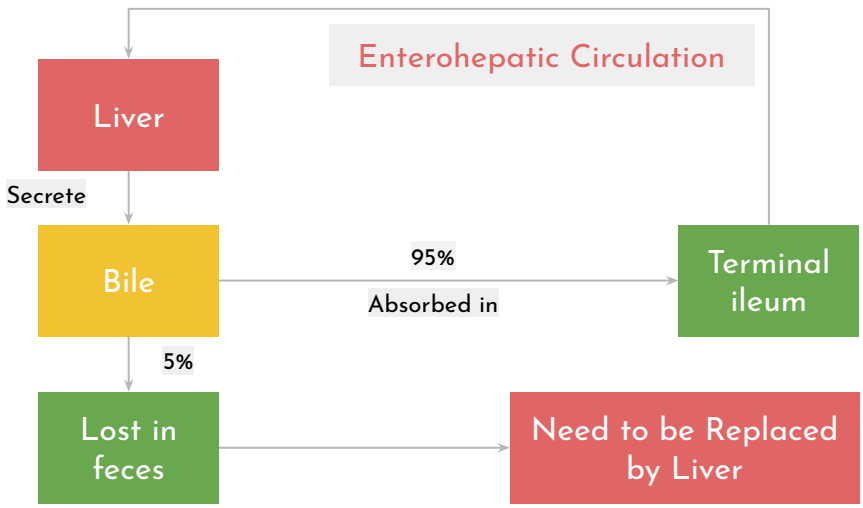


- Hepatocytes extract bile acids, essentially clearing the bile acids from the blood in a single pass through the liver.
- In the hepatocytes, most deconjugated bile acids are reconjugated & some 2ry bile acids are rehydroxylated. Converted to primary bile acids.
- The reprocessed bile acids, together with newly synthesized bile acids, are secreted into bile.

Importance of enterohepatic circulation of bile salts

1. It is essential for stimulating and maintaining the secretion of bile by hepatocytes.
2. The greater the quantity of bile salts in the enterohepatic circulation, the greater the rate of bile secretion. (Positive feedback mechanism)
3. By cycling several times during a meal, a relatively small bile acid pool can provide the body with sufficient amounts of bile salts to promote lipid absorption.
4. In a light eater, the bile acid pool may circulate 3-5 times a day; in a heavy eater, it may circulate 14 to 16 times a day.
5. If enterohepatic circulation is interrupted (e.g. due to obstruction by disease or surgical removal or inflammation of the terminal ileum), bile flow is markedly reduced and large quantities of bile salts are lost in the feces.
6. Depending on the severity of illness, malabsorption of fat may result (steatorrhea).

- N.B: Excess amount of bile acids entering the colon may result in diarrhea.



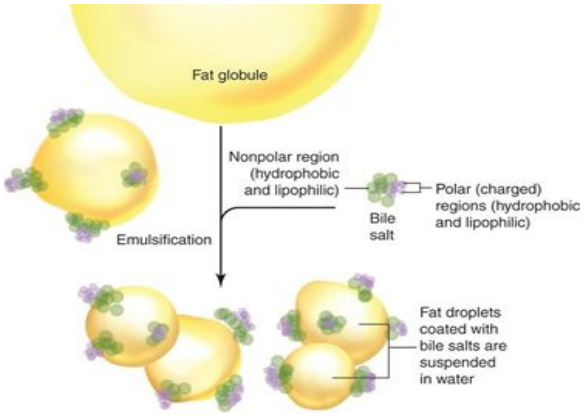
Enterohepatic Circulation Needed for recycling of Bile Salts

Why Recycling of Bile Salts is needed?
Single meal Requires Up to 5 times the available Bile Salts

Function of bile acids

1. Digestion of fats

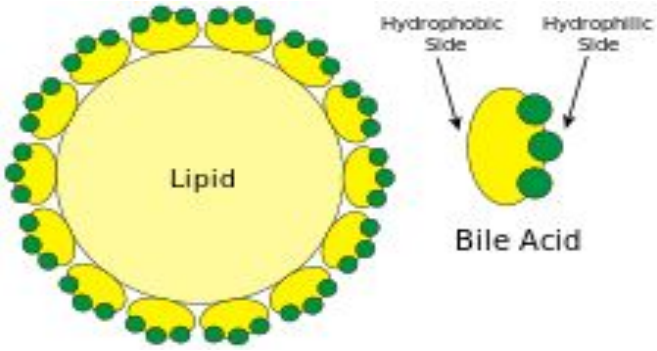
Bile salts have a detergent action that help fat digestion by decreasing fat surface tension resulting in emulsification of fats into small particles. This increase the surface area upon which the digestive enzymes will act.



2. Absorption of fats

- Bile salts combine with fats to form micelles (water soluble compounds) from which fatty acids, monoglycerides, cholesterol, and other lipids can be absorbed from the intestinal tract.
- Without the presence of bile salts in intestinal tract up to 40% of lipids are lost into the stools (steatorrhea).

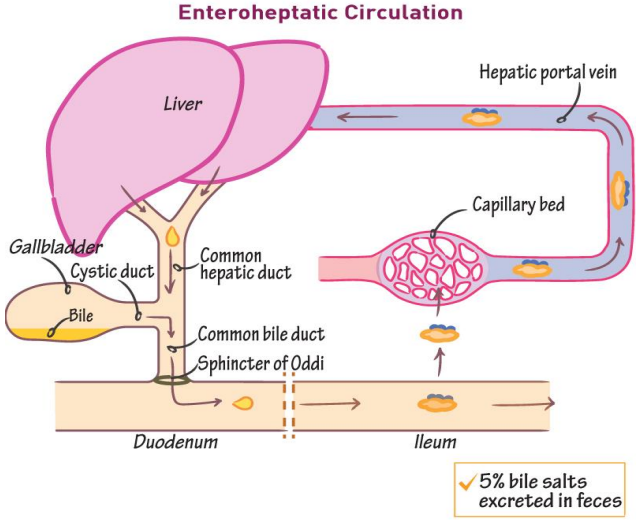
Act as a transporter of fat from the lumen to the brush border.



3.**Bile salts** are essential for absorption of **fat soluble vitamins** (A, D, E and K).

4.In the liver, bile salts are important for **stimulating bile secretion and flow** (choleretic action)

Choleretic action: stimulate bile secretion by enterohepatic circulation.



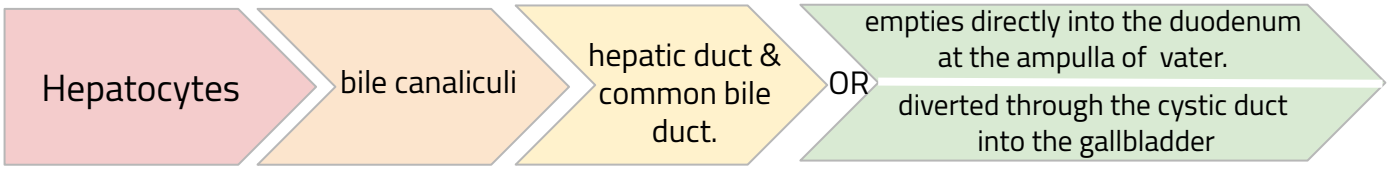
5.**Bile salts** also take part in the formation of micelles which render cholesterol soluble in bile.

Summary

Bile Function

1. Fat digestion and adsorption
2. Excretion of waste products **Especially** bilirubin

Bile secretion



-Hepatic Bile: **Isotonic** secretion, with **high** Na+, Cl- and HCO3 and **low** K+ and Ca2+.

-Gallbladder bile: **high** Bile acid anion and Ca2+ ; but **low** Na+ , Cl- , HCO3,H2O

Characteristic of Bile

- viscous golden or greenish fluid.
- isotonic
- NaHCO3 (alkaline reaction)
- liver produces 5 L /day,BUT 600- 1000 ml/day are poured into the duodenum.

Components of Bile

From hepatocytes	From bile ducts epithelial cells
• **Organic constituents** -Bile acids (bile salts) (65 %) of dry weight of bile . -Phospholipids , (90 %) as Lecithin (20 %) -Proteins (5 %) -cholesterol (4 %) , the major route for cholesterol excretion -Bilirubin and related bile pigments (0.3 %)	• **Aqueous alkaline Solution (NaHCO3)** -Electrolytes mainly HCO3- , in addition to H2O -These contribute to the volume of hepatic bile. -HCO3- aids in neutralization of acid chyme.

Function of gallbladder

- Storage (hold 30 to 60 mL)
- Secretion of mucous by contraction (5-fold to 20-fold)

MCQs

1)The liver regulates the circulating blood lipids by amount of:
A)VLDL
B)HDL
C)Cholesterol
D)TAG

2)Hepatic bile isotonic secretion has high..... and low.....:
A)Ca,K
B)Na,Cl
C)HCO,Na
D)Cl,Ca

3)Liver bile is:
A)Isotonic
B)Isotonic and slightly alkaline
C)Isotonic and slightly acidic
D)alkaline

4)Which one of the following is not a component of bile:
A)Bile pigments
B)LDL
C)lecithin
D)Phospholipids

5)Hormonal control of bile secretion by:
A)CCK
B)5-HT
C)gastrin
D)progesterone

6)Removal of the terminal ileum will most likely result in which of the following?
A)Decreased water content of the feces
B)Decreased bile acid concentration in the enterohepatic circulation
C)Increased absorption of fatty acids
D)Increased iron absorption

7)Which of the following would be expected with contraction of the gallbladder following a meal?
A)It is inhibited by the presence of amino acids in the duodenum.
B)It is stimulated by atropine.
C)It occurs in response to cholecystokinin.
D)It occurs simultaneously with the contraction of the sphincter of Oddi.

8)Which one of the following best describes bile acid function?
A)They are essentially water insoluble.
B)The majority of bile acids are absorbed by passive diffusion.
C)Glycine conjugates are more soluble than taurine conjugates.
D)The amount lost in the stool each day represents the daily loss of cholesterol.

1)A
2)D
3)B
4)B
5)A
6)B
7)C
8)D