Physiology of *Gastrointestinal System*

Bile Formation, Enterohepatic Circulation & Bile Salts (L8)

Dr. Hayam Gad
Associate Professor of Physiology
College of medicine, KSU

Learning Objectives

- Functions of the bile and stages of bile secretion.
- Characteristics of bile.
- The main constituents of bile.
- Functions of gall bladder.
- Differences between hepatic bile and gall bladder bile.
- Control of biliary system.
- Primary and secondary bile acids.
- Enterohepatic circulation of bile salts.
- Absorption and uptake of bile acids.
- Functions of bile acids.

Functions of Bile

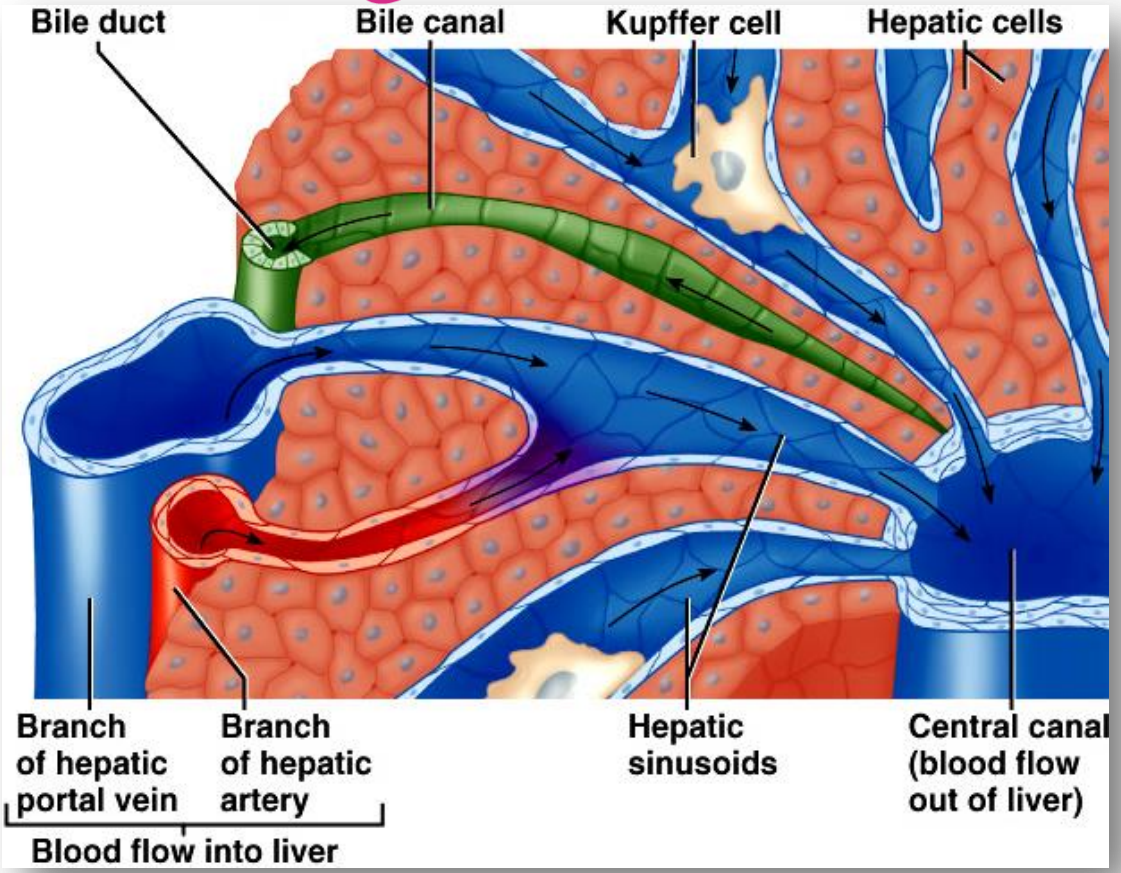
- The main digestive function of the liver is the secretion of bile.
- Bile serves two important functions:

  1- It plays an important role in fat digestion and absorption by its contents of bile salts.

  2- Bile serves as a means for excretion of waste products from the blood. These include especially bilirubin.

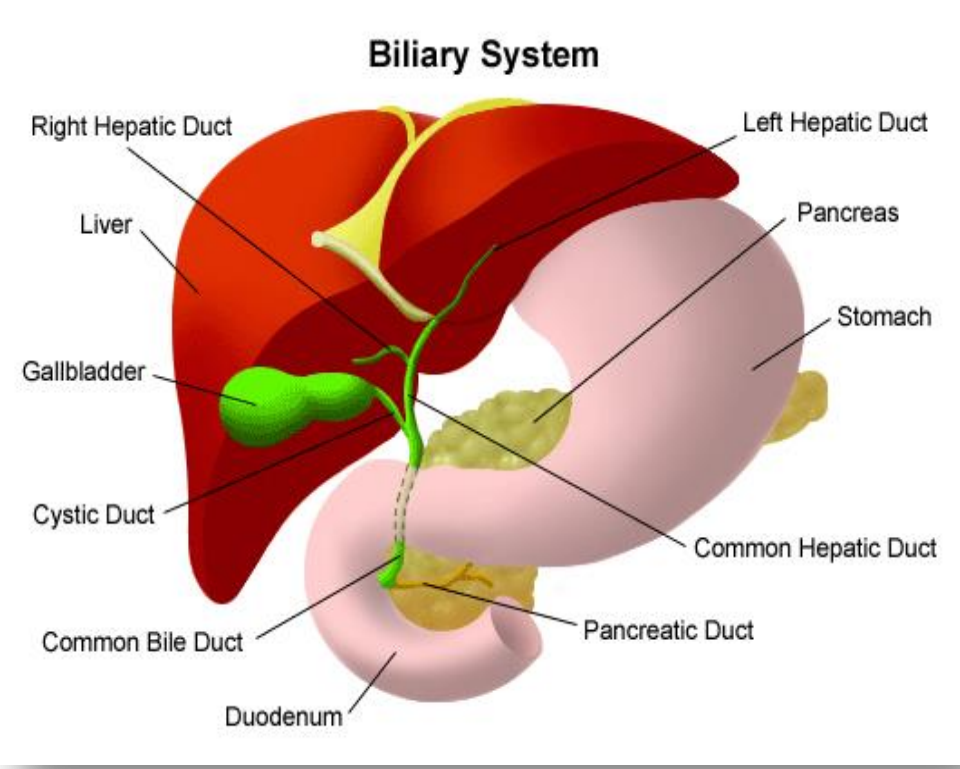
Bile is secreted in two stages:

- ✓ The initial portion is continually secreted by the hepatocytes.
- ✓ It is secreted into bile canaliculi that originate between the hepatic cells.
- ✓ The bile flows in the canaliculi toward the hepatic duct and common bile duct.

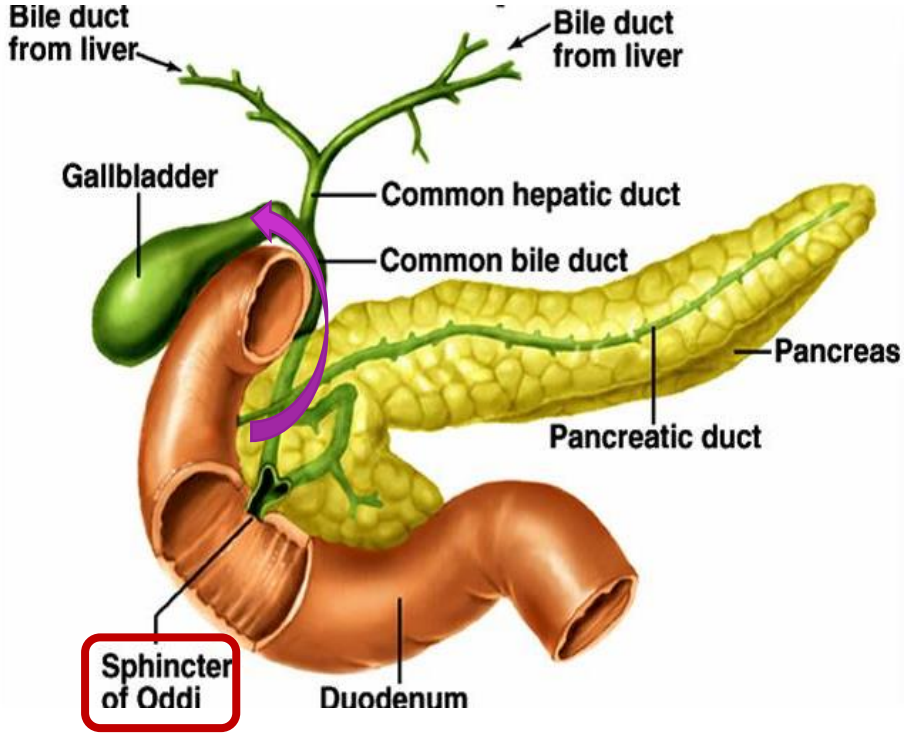


Bile is secreted in two stages: (Cont.)

- From the common bile duct, bile either empties directly into the duodenum or is diverted through the cystic duct into the gallbladder
- This is the second portion of liver secretion which is added to the initial bile.



- Between meals, bile is diverted into gall bladder.
- 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 (choledochoduodenal sphincter).



Characteristics of bile

- Bile is a viscous golden yellow or greenish fluid with bitter taste.
- It is isotonic with plasma and slightly alkaline.
- $NaHCO_3$ 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 700-1200 ml/day are poured into the duodenum.

What are the components of bile?

The main constituents of bile are:

- 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%).

All of these constituents are secreted by **hepatocytes** into bile canaliculi, along with an isotonic fluid that resembles plasma in its electrolyte conc.

- Electrolytes mainly HCO_3^- , these in addition to H_2O are secreted by epithelial cells that line **bile ducts**, and contribute to the volume of hepatic bile.
- HCO_3^- aids in neutralization of acid chyme.

Composition of bile

From ducts

Aqueous alkaline Solution ($NaHCO_3$)

From hepatocytes

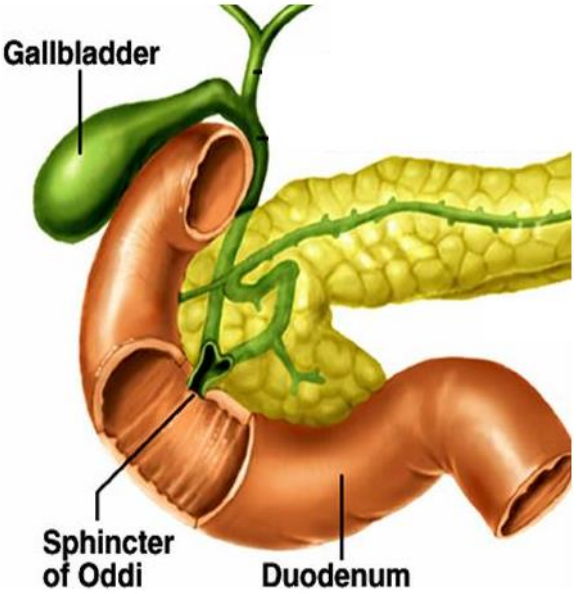
Organic constituents

- Bile salts(65%)
- Lecithin (20%).
- Bilirubin (0.3%)
- Proteins (5%)
- Cholesterol (4%)

Functions of gall bladder

I. Gall bladder not only stores bile but it concentrates bile.

The total secretion of bile each day is about 700-1200 ml per day. The maximum volume of the gall bladder is only 30-60 ml. As much as 12 hours bile secretion can be stored & concentrated in the gall bladder 5 - 20 folds.



Concentration of bile in the gall bladder occur by:

a. Active absorption of Na^+, Cl^-, and HCO_3^- by the lining epithelium.

b. Associated passive water movement out of the lumen.

This result in drop of pH of gall bladder bile due to decreased $NaHCO_3$ concentration.

II. Gall bladder epithelium secretes mucus which has protective function.

III. Buffer of biliary pressure by storing of bile, so it prevents increase in biliary pressure & enables the liver to secret bile, because hepatic cells can not secret against high pressure.

	Hepatic bile	Gall bladder 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
HCO_3^-	28	10
Ca^{++}	5	23
Cl^-	100	25
K^+	5	12
pH	8.3	7.5

Control of biliary system

- The human liver secretes bile at a pressure of about 25 cm H_2O.
- Between the meals, the choledochoduodenal sphincter is closed offering a resistance of about 30 cm H_2O.
- Bile secreted by liver is thus diverted to the gall bladder during the interdigestive peroids.
- Pressure in the lumen of the gall bladder varies between 0-16 cm H_2O.

There are 2 aspects for control

1) Secretion of bile by liver cells (choleresis).
2) Control of the discharge of bile into intestine.

1. Control of choleresis

Substances that stimulate hepatic secretion of bile (choleresis) are ***choleretics***.

- The deriving force for bile secretion is active transport of ***bile acids*** into canaliculi with passive H_2O flow along osmotic gradient.
- In the biliary ducts HCO_3^- is secreted independently of bile acid secretion & is followed passively by water.
- Total bile flow is thus due to 2 components:
  - *Bile acid dependent component*
  - *Bile acid independent component*

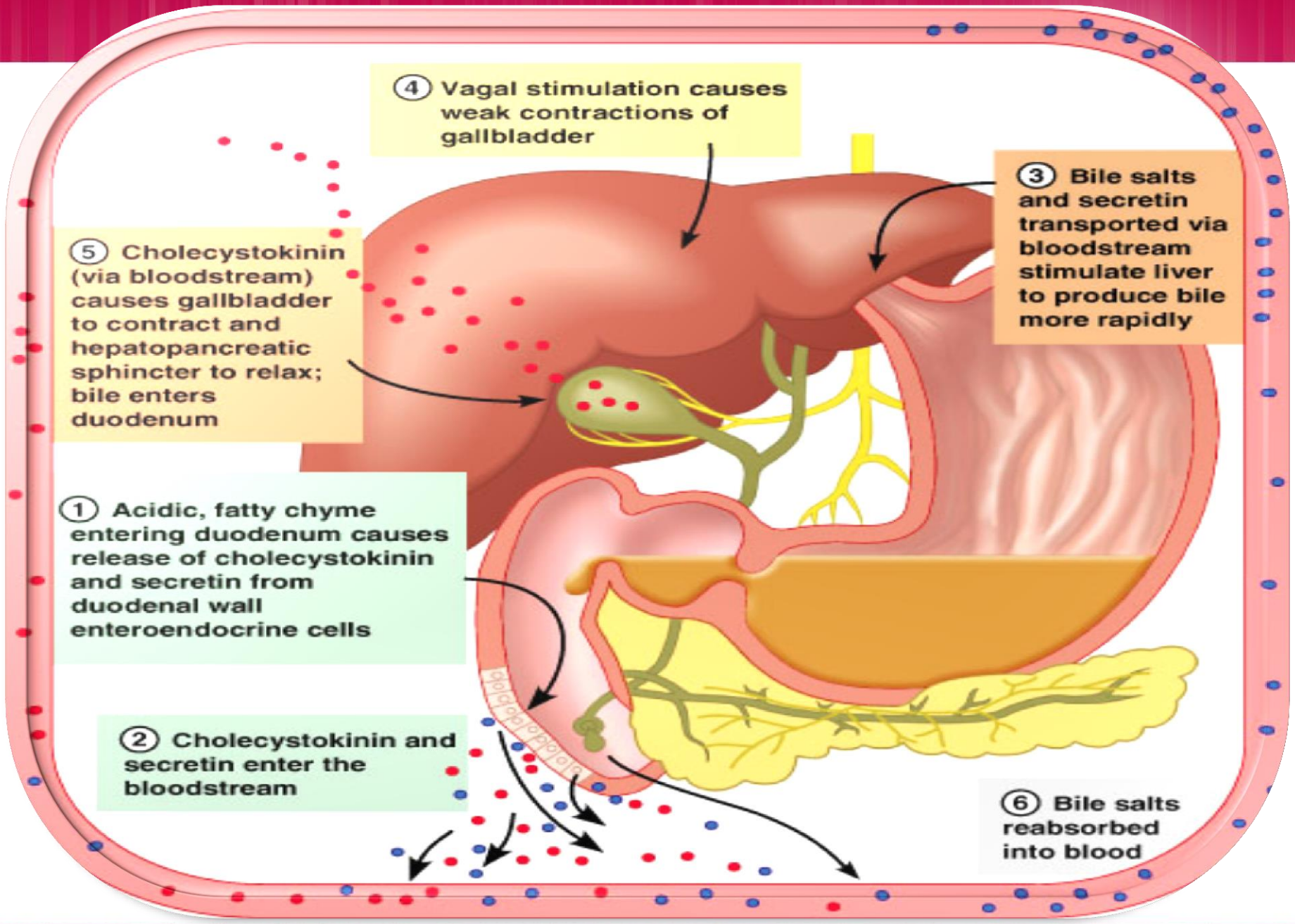
Bile acid dependent component

- It depends mainly on the integrity of the enterohepatic circulation.
- At least 90% of the rate of secretion of bile acids is determined by the rate of clearance of reabsorbed bile acids from the portal vein.
- The remaining 10% is due to synthesis of new bile acids by hepatocytes.
- Interruption of the enterohepatic circulation results in markedly reduced choleresis.

Bile acid independent component

- This fraction of bile secretion is due to secretion of HCO_3^- followed by water by the biliary duct cells. It depends on active sodium transport.
- It is stimulated by:

1. ***Hormones*** as secretin, glucagon, CCK and gastrin. They all stimulate HCO_3^- & passive water transfer by the biliary duct cells.
2. ***Vagal stimulation*** also stimulates bile flow. The effect is mediated mainly indirectly, through stimulation of gastric acid secretion, which leads to release of secretin & CCK.


4 Vagal stimulation causes weak contractions of gallbladder
3 Bile salts and secretin transported via bloodstream stimulate liver to produce bile more rapidly
5 Cholecystokinin (via bloodstream) causes gallbladder to contract and hepatopancreatic sphincter to relax; bile enters duodenum
1 Acidic, fatty chyme entering duodenum causes release of cholecystokinin and secretin from duodenal wall enteroendocrine cells
2 Cholecystokinin and secretin enter the bloodstream
6 Bile salts reabsorbed into blood

N.B:

- Increase portal blood flow during digestion increases bile secretion.

- But when the liver is markedly congested bile secretion stops due to increase intrahepatic vascular pressure.

2. Control of the discharge of bile into the intestine

- Discharge of bile into the duodenum occurs by contraction of gall bladder wall and relaxation of Oddi sphincter.
- The highest rate of gall bladder emptying occurs during the intestinal phase.
- Gall bladder evacuants are called ***cholagogues***.
- Discharge of bile into the duodenum is regulated by nervous & hormonal mechanisms

a) The nervous component

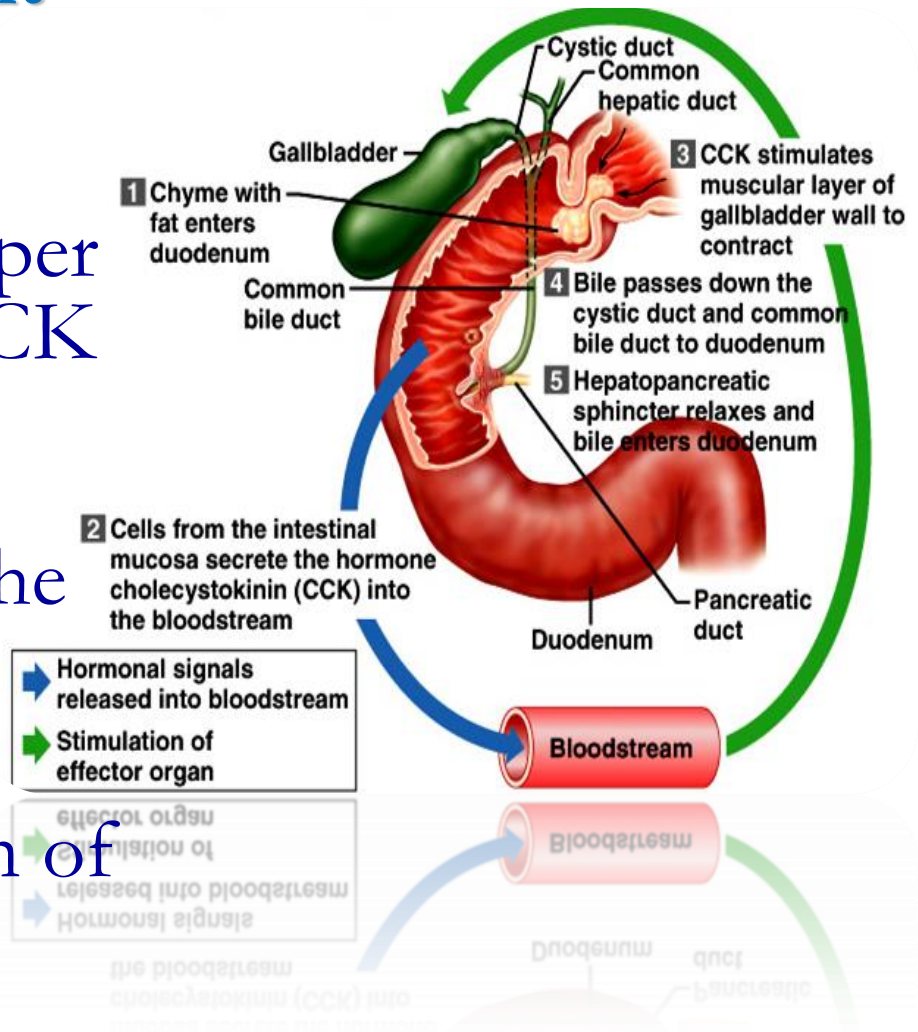
- Parasympathetic (vagal) stimulation results in:
  - Contraction of the gallbladder.
  - Relaxation of the sphincter of Oddi.
  - Increased bile formation.

N.B: Bilateral vagotomy results in reduced bile secretion after a meal.

- Stimulation of the sympathetic nervous system results in relaxation of the gallbladder and reduced bile secretion.

b)The hormonal component

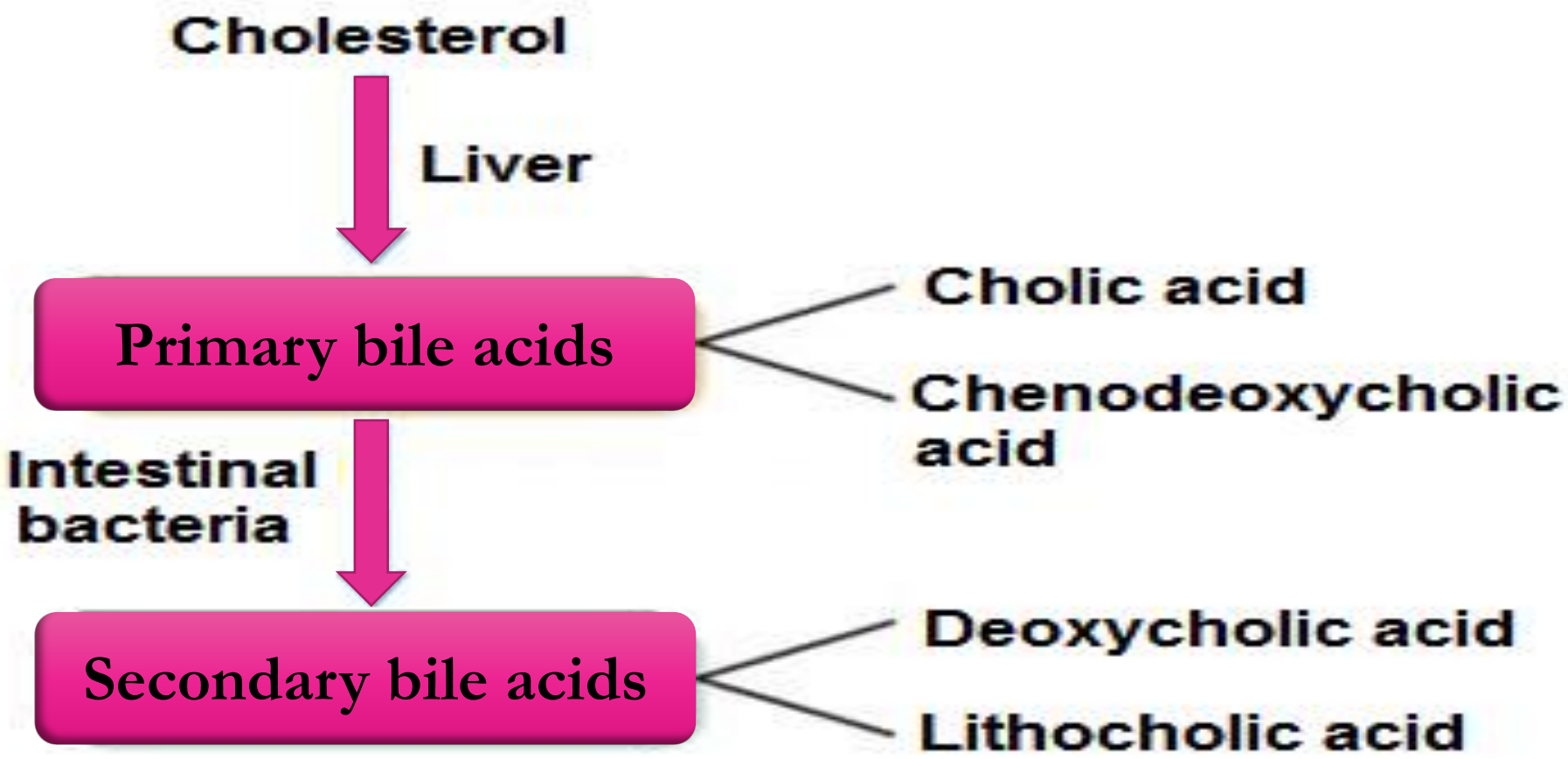
- The presence of digestive products of fat & proteins releases ***CCK*** from the upper intestine into the blood. CCK contracts gall bladder and relaxes sphincter of Oddi, thus discharging bile into the duodenum.
- Both vagal excitation & secretin augment the action of CCK on the gall bladder.



Bile acids & salts

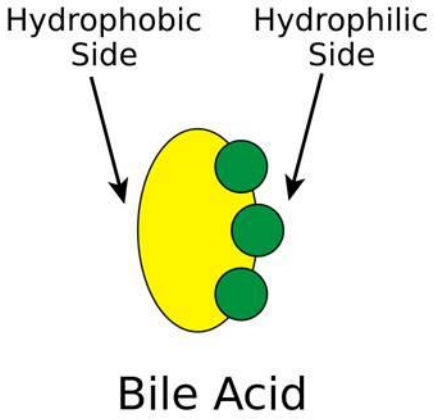
- Bile acids are steroid acids, synthesized in the liver from cholesterol by the enzyme cholesterol 7α-hydroxylase. Bile acids include:
  - Primary: cholic, chenodeoxycholic acids.
  - Secondary: deoxycholic, lithocholic acids.
- The principle primary bile acids conjugate with glycin or taurine to form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

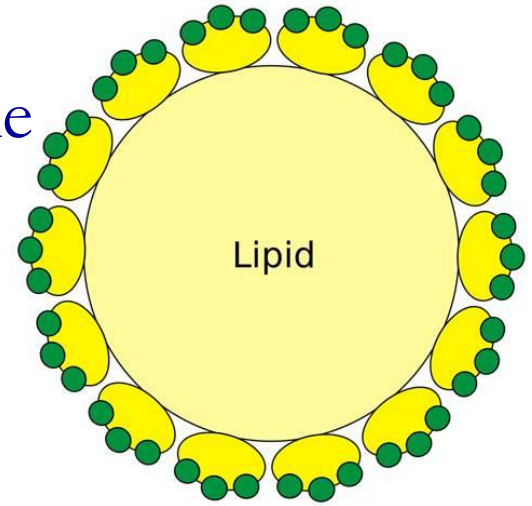
Primary and secondary bile acids



- ✓ At a neutral pH, conjugated bile acids are mostly ionized, 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.

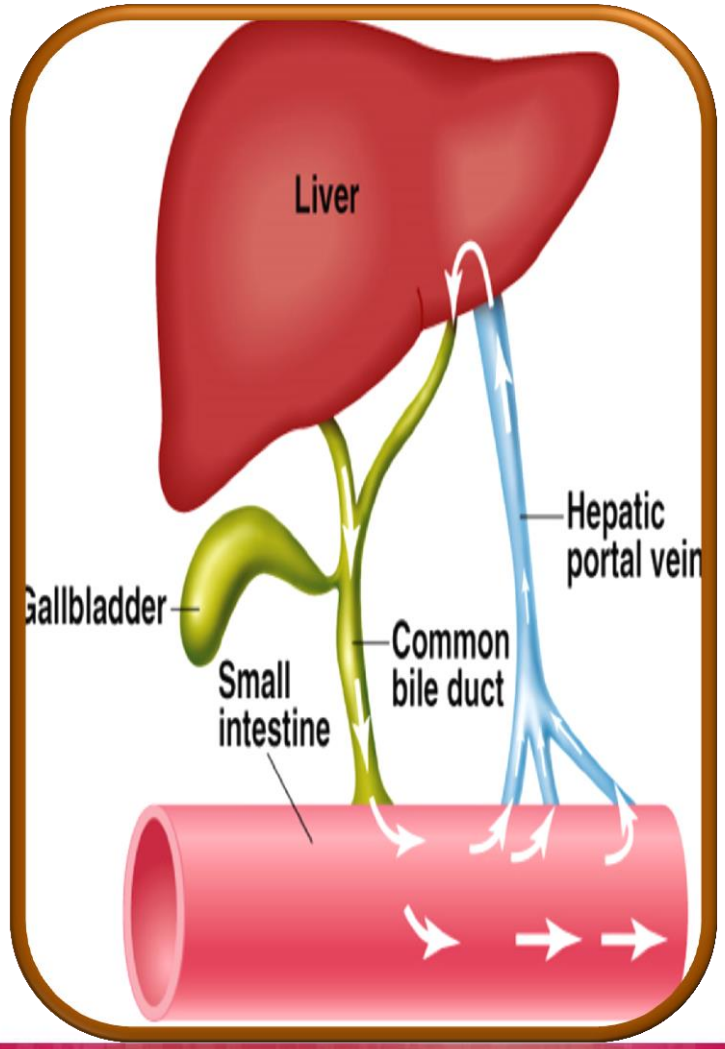
- Bile acids are amphipathic that is having both hydrophilic & hydrophobic domains and tend to form molecular arrangement called micelles.
- In bile acid micelle, the hydrophobic side of bile acid faces inside & away from water. The hydrophilic surface faces outward towards the water.
- Bile acid micelles 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.

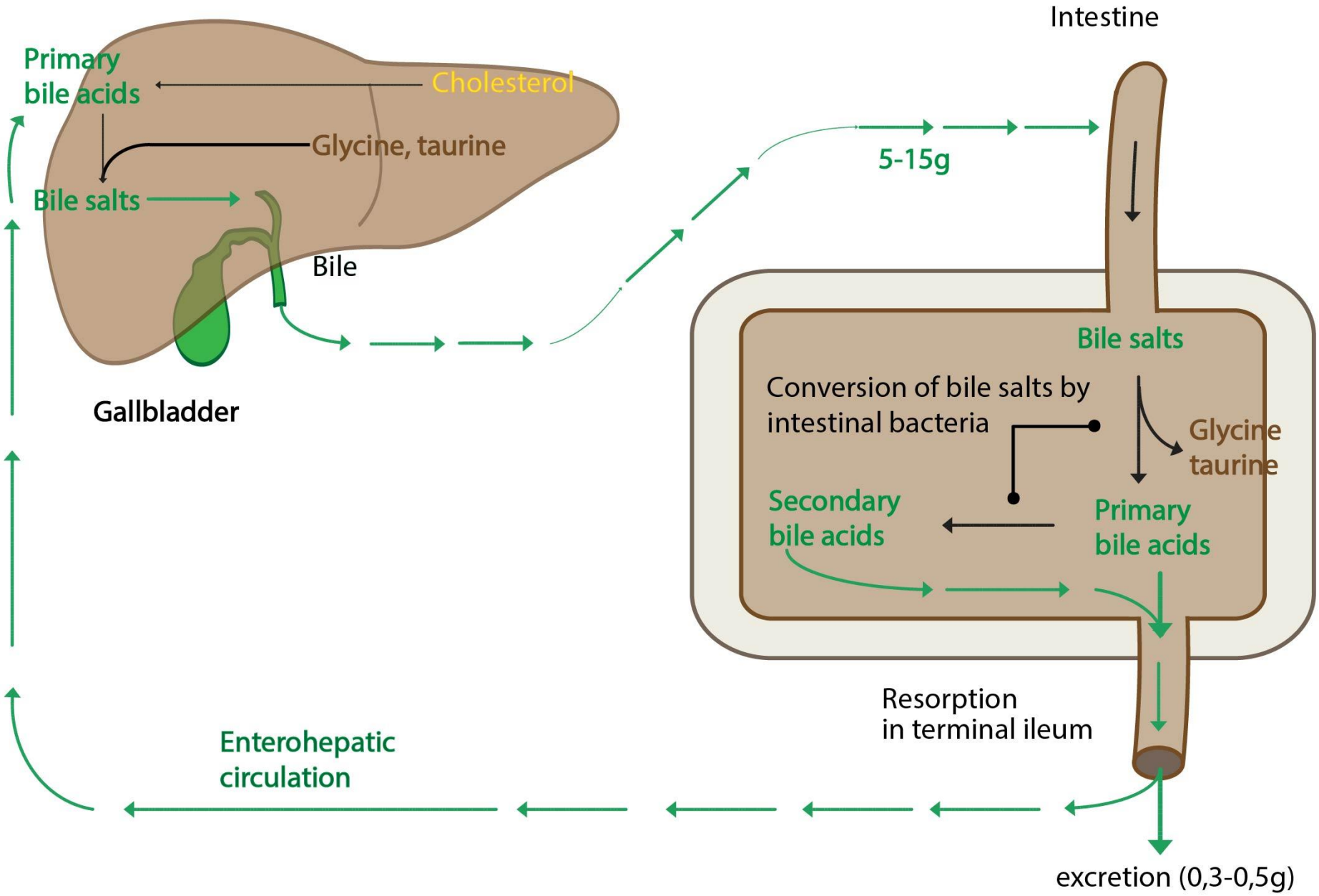




Enterohepatic Circulation of Bile Salts.

- 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.




Intestine
Primary bile acids
Cholesterol
Glycine, taurine
Bile salts
Bile
5-15g
Gallbladder
Bile salts
Conversion of bile salts by intestinal bacteria
Glycine taurine
Secondary bile acids
Primary bile acids
Resorption in terminal ileum
Enterohepatic circulation
excretion (0,3-0,5g)

- About 20-30 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, 90 % 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 so that the total bile acid pool is maintained constant at 2 - 4 g.
- Since the amount of bile acids poured into the duodenum each day is 20-30 g, the daily turnover of total bile acid pool through the enterohepatic circulation must be 6-10 times.

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:
  - Active transport process. It is 2^{ry} active transport powered by the Na^+ gradient across the brush border membrane.
  - Simple diffusion.

- The Conjugated bile acids are the principal substrates for active absorption.
- Unconjugated bile acids have poor affinity for the transporter. They are less polar than conjugated bile acids, they are better absorbed by simple diffusion.

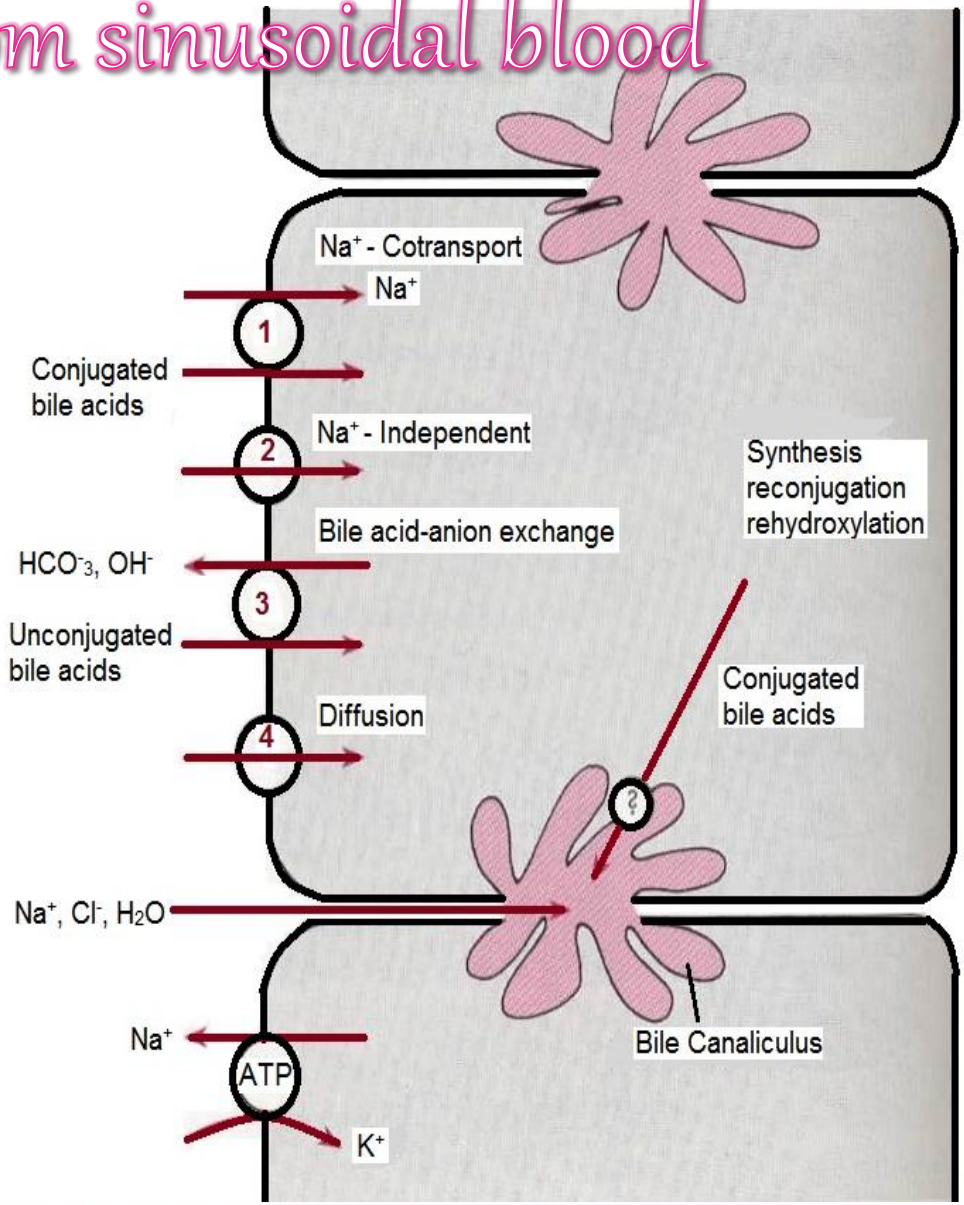
- Bile acids may be bound to proteins, (which remain to be identified), in intestinal epithelial cells.
- Absorbed bile acids are carried away from the intestine in the portal blood, mostly bound to albumins.

N.B:

- In the small intestine, cholic acid is absorbed faster than chenodeoxycholic acid, and primary bile acids are absorbed better than secondary bile acids.
- Some unconjugated bile acids are absorbed passively in the colon and reach the liver through portal vein.

Uptake of bile acids from sinusoidal blood

- Multiple transport mechanisms are located in the hepatocyte plasma membrane for uptake of bile acids from sinusoidal blood.
- An active carrier-mediated process.
- Facilitated diffusion.
- Bile acid-HCO_3^- or OH^- exchange.
- Passive diffusion (very little).



Importance of enterohepatic circulation of bile acids

- It is essential for stimulating and maintaining the secretion of bile by hepatocytes.
- The greater the quantity of bile salts in the enterohepatic circulation, the greater the rate of bile secretion.
- 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.

- 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.
- 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.
- Depending on the severity of illness, malabsorption of fat may result (steatorrhea).

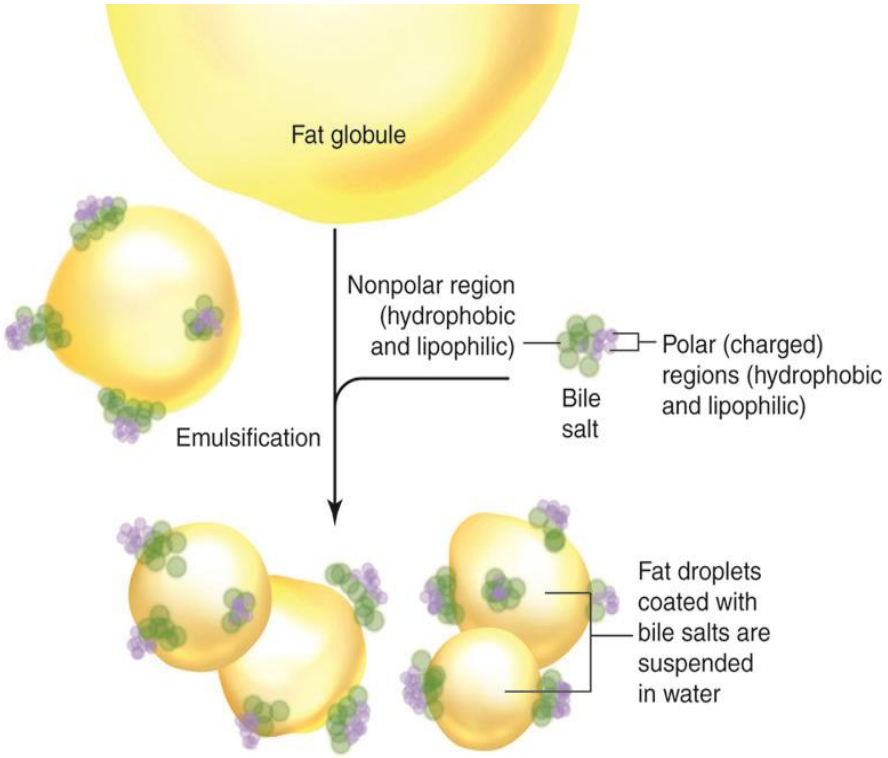
N.B: Excess amount of bile acids entering the colon may result in diarrhea.

- 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 2^{ry} bile acids are rehydroxylated.
- The reprocessed bile acids, together with newly synthesized bile acids, are secreted into bile.

Functions of bile acids

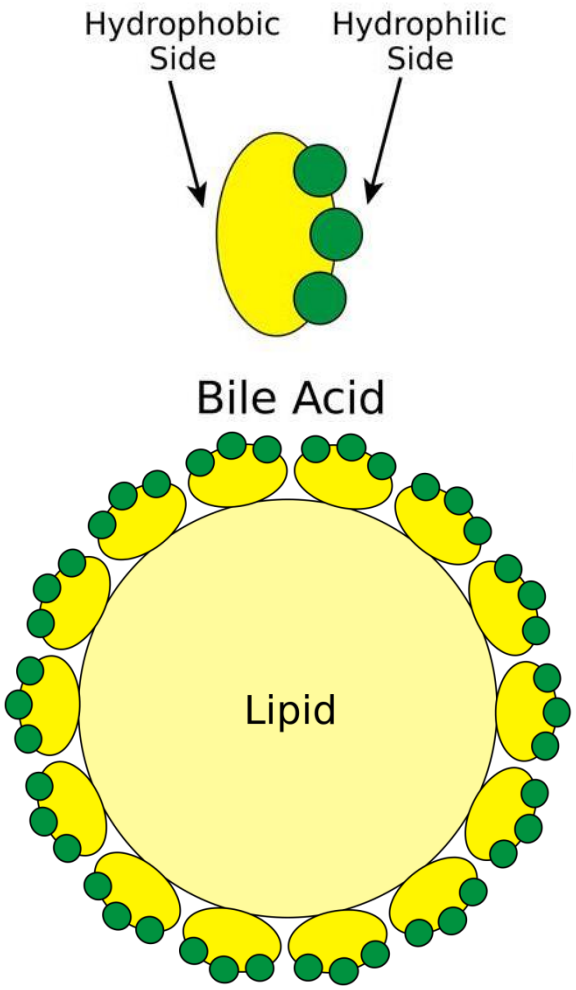
1. Digestion of fats:-

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).



3. bile acids are essential for absorption of **fat soluble vitamins** (A, D, E and K).
4. In the colon bile acids inhibit reabsorption of water & electrolytes, stimulate intestinal motility, prevent constipation & may cause diarrhea.
5. In the liver, bile salts are important for stimulating bile secretion and flow (choleretic action). They also take part in the formation of micells which render cholesterol soluble in bile.

6. Bile acids have a –ve feedback effect on the release of CCK from its cells in the upper intestine & thus contribute to the regulation of pancreatic secretion & the discharge of bile into intestine.
7. They have a –ve feedback effect on the synthesis of cholesterol by the intestinal mucosal cells.
8. Anti putrifactive: Bile acids have no direct anti septic effect but they prevent putrifaction by absorption of fat. In their absence undigested fats cover the protein particles & hinder their digestion.

Cholesterol secretion in bile

- About 1-2g of cholesterol appears in bile per day.
- No specific function is known for cholesterol in the bile & it is presumed that it is simply a byproduct of bile salt formation & secretion.
- Cholesterol is water insoluble; it is solubilized by incorporation in micelles along with the bile acids & phospholipid.


Thanks!
spicecomments.com