BILE FORMATION, ENTEROHEPATIC CIRCULATION & BILE SALTS

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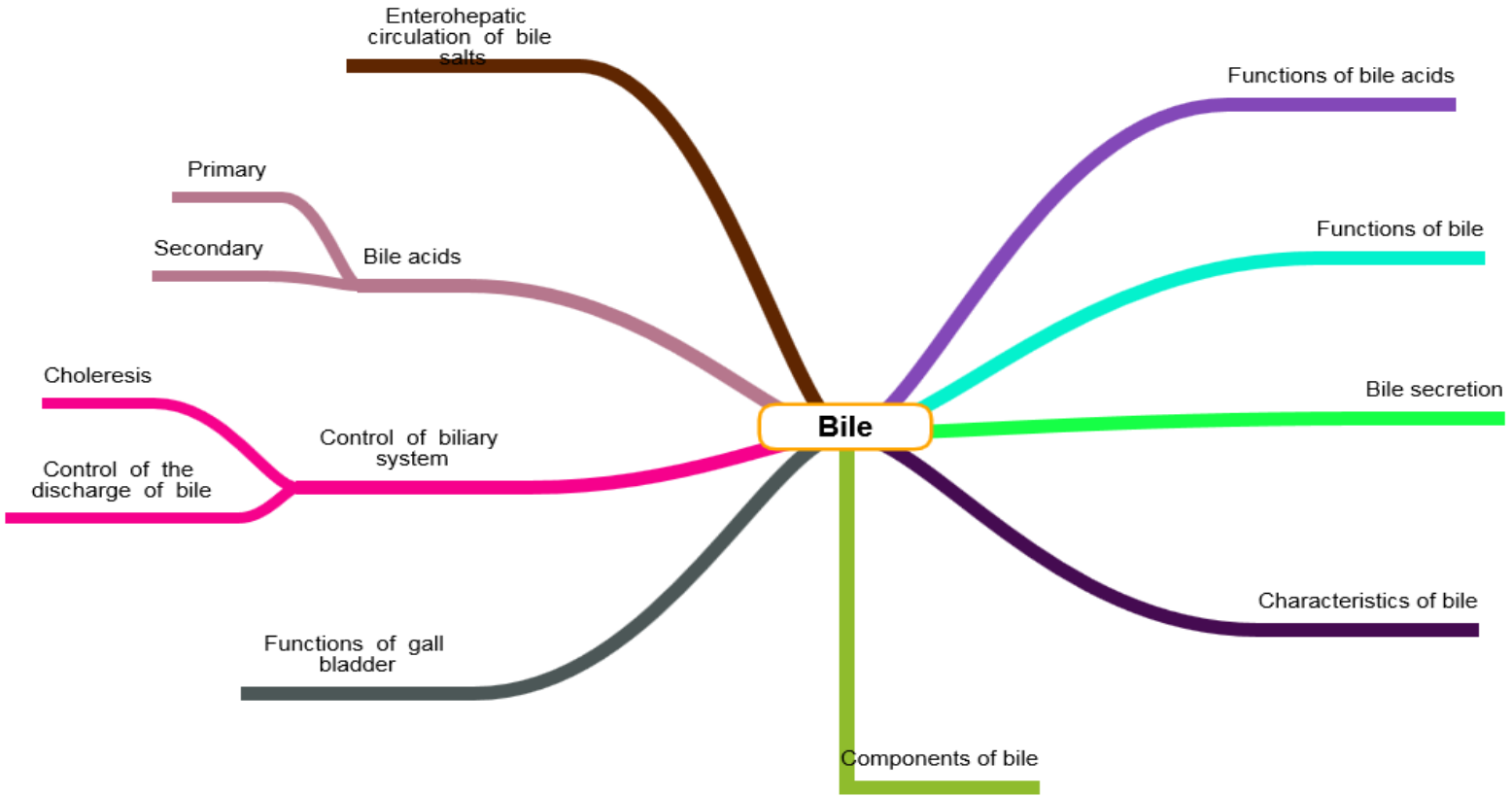
From min (6.35 -12.12) for the lecture
The rest will be helpful for the block

Enterohepatic circulation of bile salts

Please check out this link before viewing the file to know if there are any additions/changes or corrections. The same link will be used for all of our work Physiology Edit

Mind map


Bile
Enterohepatic circulation of bile salts
Primary
Secondary
Bile acids
Choleresis
Control of the discharge of bile
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Functions of bile
Functions of bile acids

The main digestive function of the liver is the secretion of bile

(600-1000 ml/day)

Functions of Bile

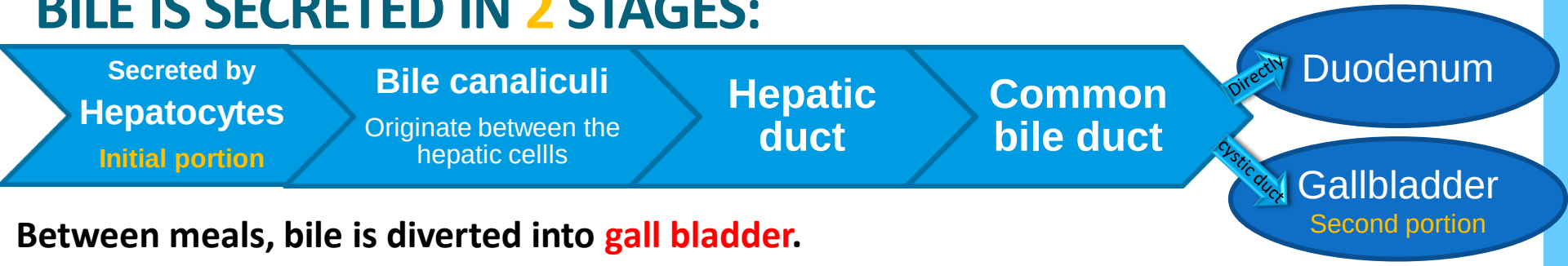
Fat digestion and absorption by its contents of bile salts by:

- Emulsifying large fat particles of the food into minute particles.
- Aid in absorption of the digested fat end products through the intestinal mucosal membrane.

Excretion of waste products from the blood.

especially bilirubin

BILE IS SECRETED IN 2 STAGES:



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.

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 700-1200 ml/day are poured into the duodenum. The rest are stored in gallbladder

COMPONENTS OF BILE

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%)

→ secreted by **hepatocytes** into bile canaliculi, along with an isotonic fluid that resembles plasma in its electrolyte conc.

Electrolytes mainly HCO3-

H2O

HCO3- aids in neutralization of acid chyme.

→ secreted by epithelial cells that line **bile ducts**, and contribute to the volume of hepatic bile.

FUNCTIONS OF GALL BLADDER

Gall bladder stores & concentrates bile.

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.

Gall bladder epithelium secretes mucus which has protective function.

Buffer of biliary pressure by storing of bile → it prevents increase in biliary pressure & enables the liver to secret bile

because hepatic cells can not secret against high pressure.

Concentration of bile in the gall bladder occur by:

- Active absorption of Na+, Cl-, and HCO3- by the lining epithelium.
- Associated passive water movement out of the lumen.

This result in drop of pH of gall bladder bile due to decreased NaHCO3 concentration.

	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

organic

inorganic

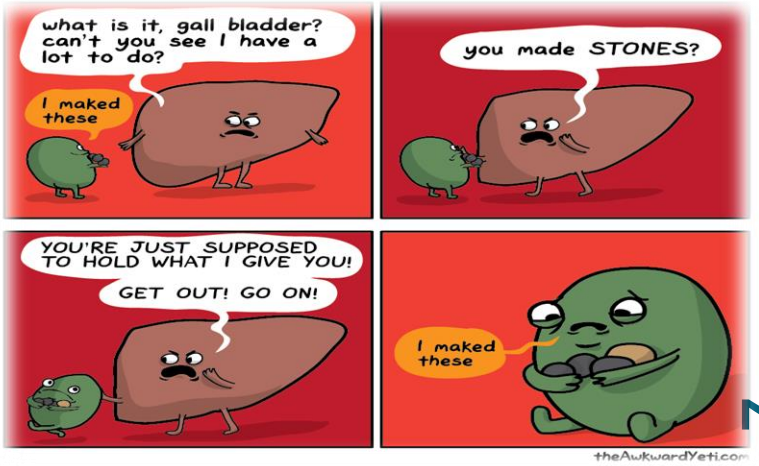
You don't have to memorize the values

This is just to show that concentration of Na+, HCO_3^-, Cl^- & water are less in gall bladder bile than in hepatic bile because they are reabsorbed.

Also low pH in gall bladder bile to protect against stone formation

Ca++ more soluble in acidic medium

↓pH → ↑solubility of Ca++



CONTROL OF BILIARY SYSTEM

The human liver secretes bile at a pressure of about 25 cm H2O.

Between the meals, the choledochoduodenal sphincter is closed offering a resistance of about 30 cm H2O.

Bile secreted by liver is thus diverted to the gall bladder during the interdigestive peroids (in between meals).

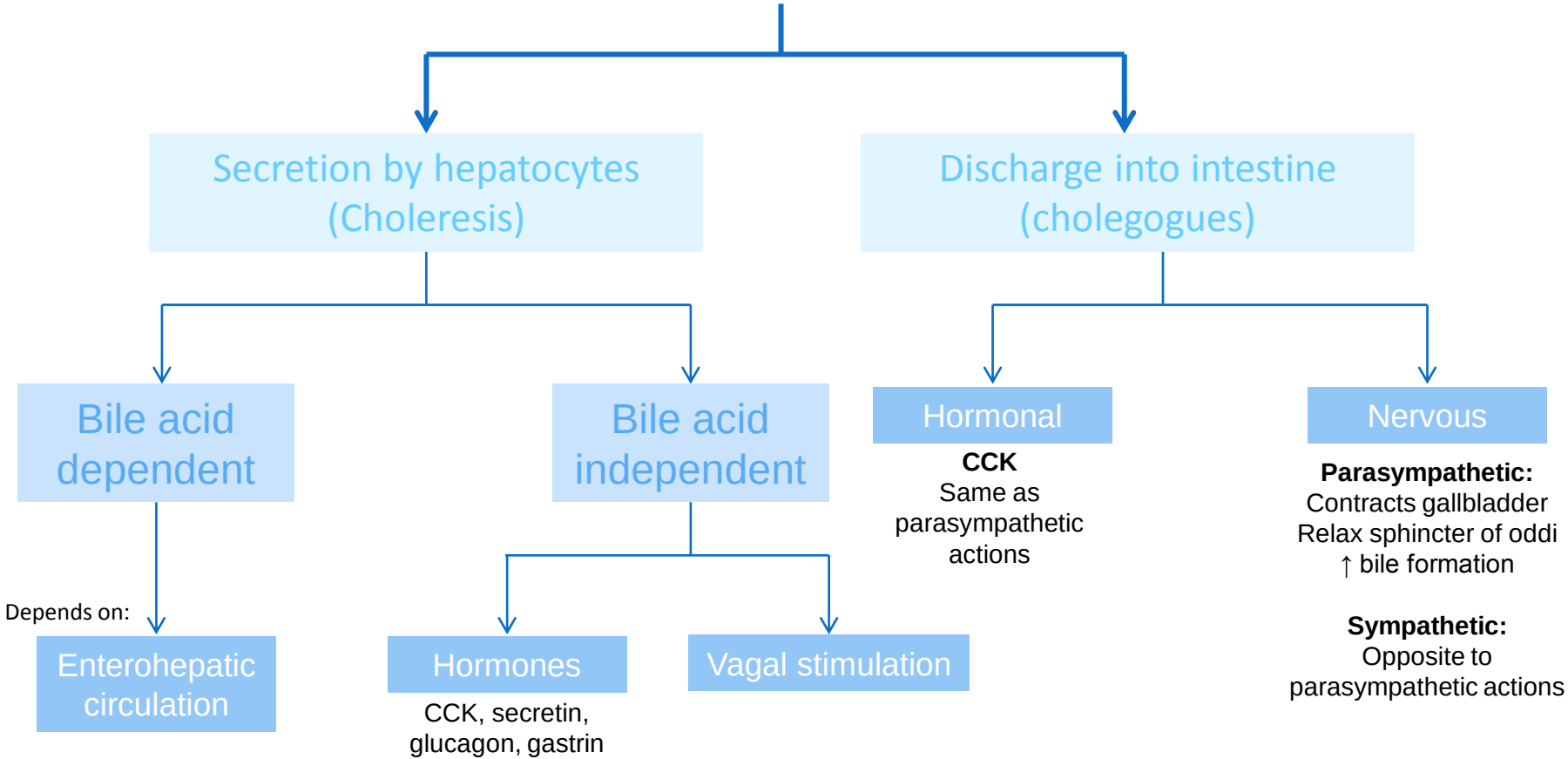
Pressure in the lumen of the gall bladder varies between 0-16 cm H2O.

There are 2 aspects for control:

1)Secretion of bile by liver cells (choleresis).

2)Control of the discharge of bile into intestine.

CONTROL OF BILIARY SYSTEM



More details in the following slides..

1- Control of choleresis

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

Bile acid dependent component

The deriving force for bile secretion is **active transport** of **bile acids** into canaliculi with **passive H_2O flow** *along osmotic gradient*

It depends mainly on the integrity of the enterohepatic circulation.

- 90% of the rate of secretion of bile acids is determined by the rate of clearance of reabsorbed bile acids from the portal vein.
- 10% is due to synthesis of new bile acids by hepatocytes.
- Interruption of the enterohepatic circulation (e.g. surgical removal) results in markedly reduced choleresis.

Bile acid independent component

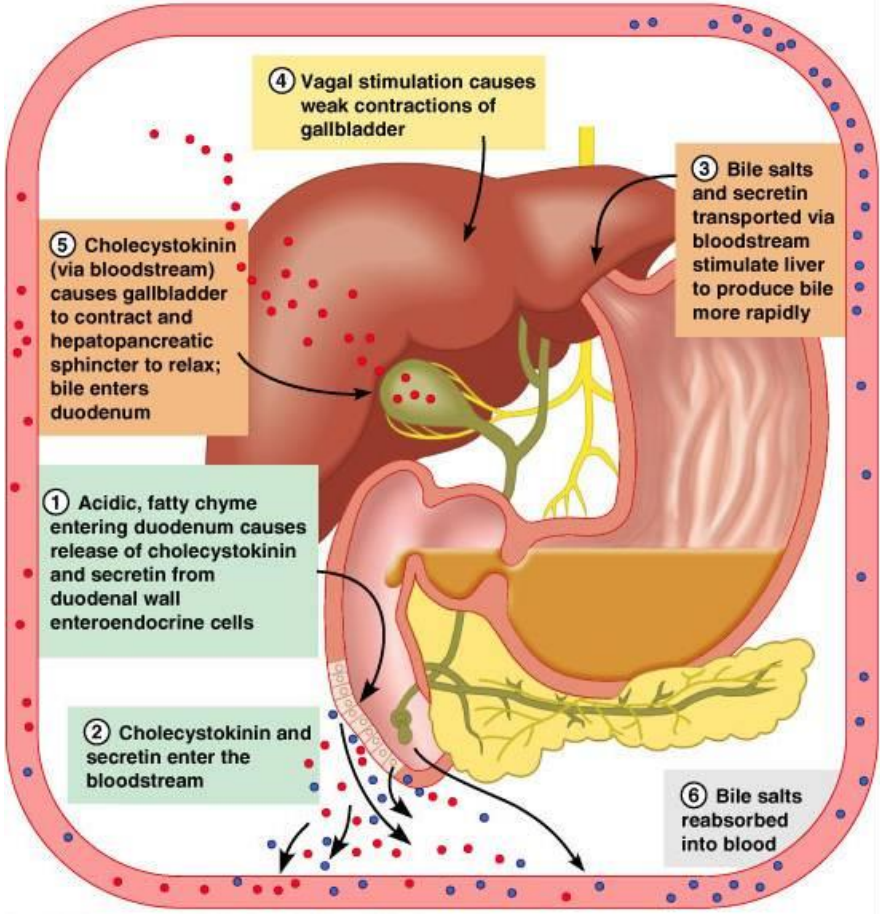
In the biliary ducts HCO_3^- is secreted independently of bile acid secretion & is followed passively by water

This fraction of bile secretion is due to secretion of HCO3- 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 HCO3- & 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.



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

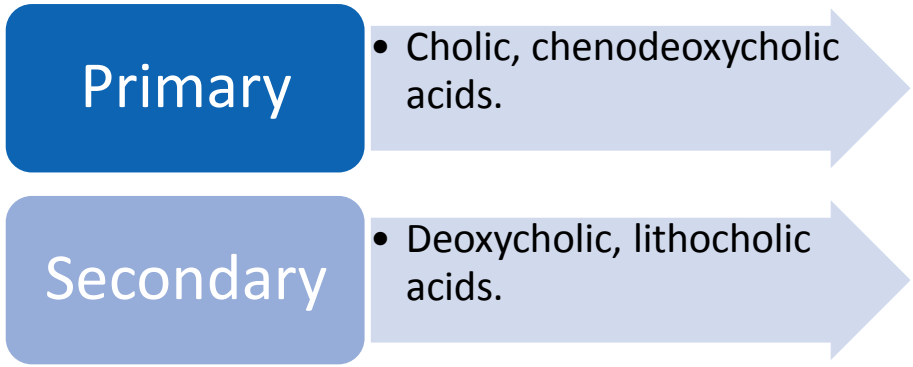
The nervous component	The hormonal component
Parasympathetic (vagal) stimulation results in: - Contraction of the gallbladder. - Relaxation of the sphincter of Oddi. - Increased bile formation. N.B: Bilateral vagotomy results in reduced bile secretion after a meal. Stimulation of the sympathetic nervous system results in relaxation of the gallbladder and reduced bile secretion & contraction of sphincter.	- 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 - Discharging bile into the duodenum. - Both vagal excitation & secretin augment* the action of CCK on the gall bladder. CCK → most potent cholagogues Cholecystokinin: "cholcysto" = gall bladder, "kinin" = movement

*augment: increase

BILE ACIDS

Bile acids are steroid acids, synthesized in the liver from cholesterol by the enzyme cholesterol 7α-hydroxylase.

Bile acids include:



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.

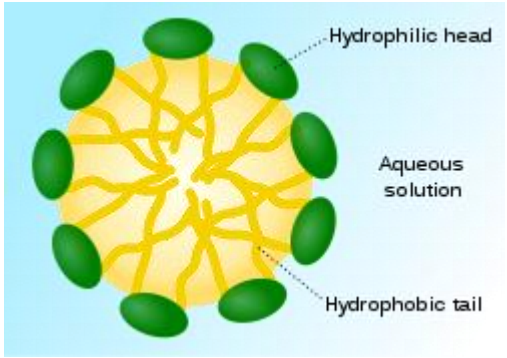
The bile salts are sodium and potassium salts of bile acids conjugated to glycine or taurine.

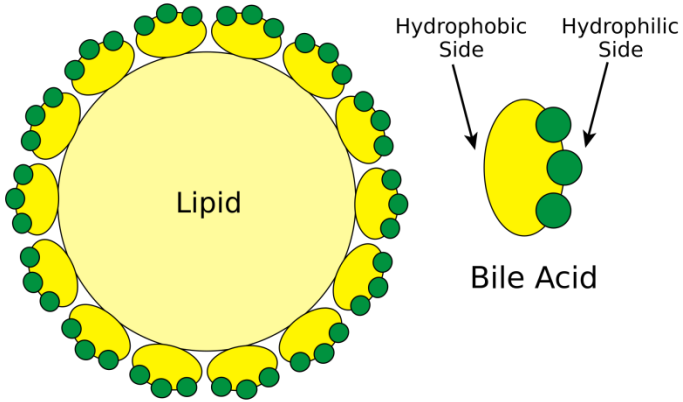
• Bile salts are much more polar than bile acids and have greater difficulty penetrating cell membranes. Consequently, the small intestine absorbs bile salts much more poorly than bile acids.

• 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.

PRIMARY AND SECONDARY BILE ACIDS

- 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 concentration of bile acids exceed a certain limit (critical micelle conc).
- Above this concentration, any additional bile acid will join the micelle.
- Normally bile acid concentration in bile is much greater than critical micelle conc.





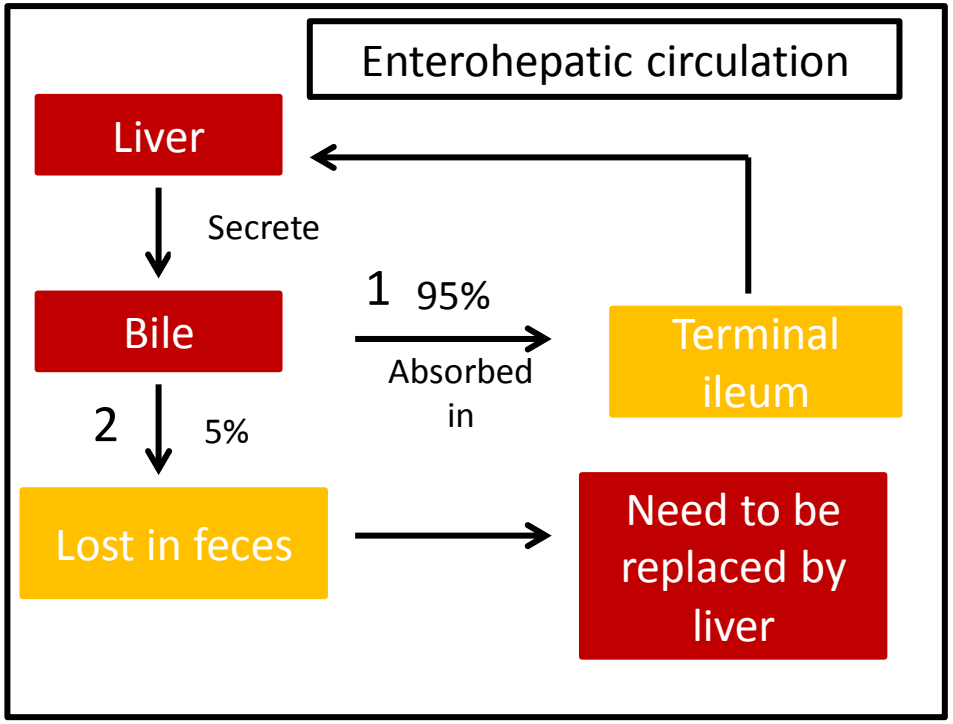
ENTEROHEPATIC CIRCULATION OF BILE SALTS

It is the recycling of bile salts between the small intestine and the liver.

1- On reaching the terminal ileum, 90-95 % of bile salts are absorbed and reach the liver through the portal vein.

2- about 0.2-0.6 g of bile salts are lost in feces daily (15- 35% of total bile acid pool)

*These are replaced by new synthesis in liver.



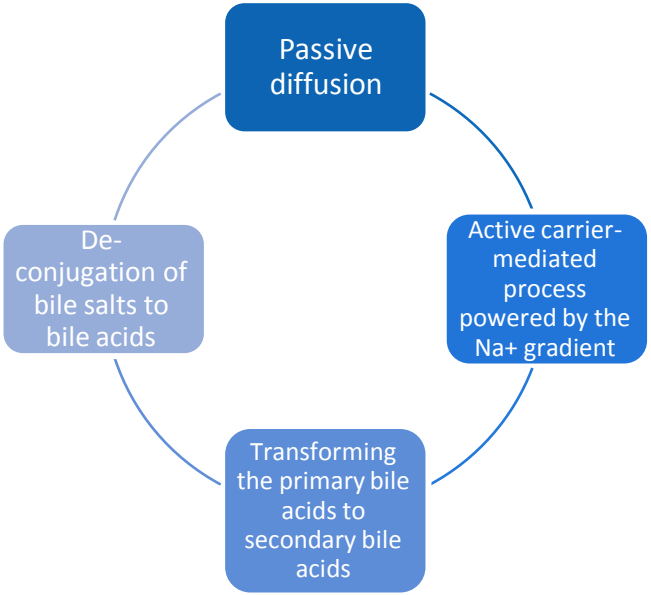
Total bile acid pool:

Is The total amount of bile acids in the body, primary or secondary, conjugated or free, at any time. It should be ranges from 2-4 g. (that's why the lost in faces is replaced).

About 20-30 g of bile acids are poured into the duodenum /day. (the daily turnover of total bile acid pool through the enterohepatic circulation must be 6-10 times). And twice per meal. 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.

- 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 0.2-0.6 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.

Absorption of bile acids in intestinal lumen



Absorbed bile acids are carried away from the intestine in the portal blood, mostly bound to albumins.

Notes:

1- Primary bile salts are absorbed better than secondary .

2- Cholic acid is absorbed faster than chenodeoxycholic acid.

3- Unconjugated bile acids are absorbed passively in the colon.

Uptake of bile acids from sinusoidal blood:

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

1. An active carrier-mediated process .
2. Facilitated diffusion.
3. Bile acid-HCO_3-or OH-exchange.
4. Passive diffusion (very little).

IMPORTANCE OF ENTEROHEPATIC CIRCULATION OF BILE ACIDS

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.
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 enterohepaticcirculation 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, malabsorptionof fat may result (steatorrhea).

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

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.

Functions of bile acids

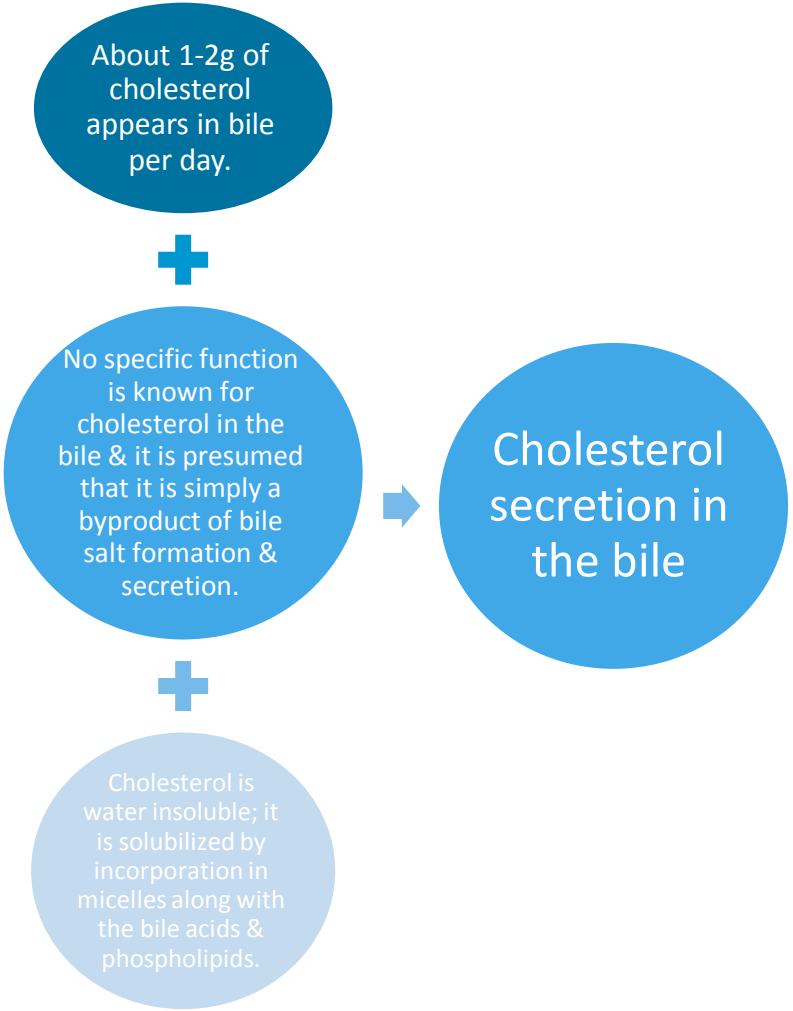
5.In the liver, bile salts are important for stimulating bile secretion and flow (choleretic action).

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.


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 secretion in the bile
Cholesterol is water insoluble; it is solubilized by incorporation in micelles along with the bile acids & phospholipids.

MCQs

Answer key: 1-B , 2-D , 3-C , 4-A , 5-B , 6-A , 7-C , 8-B

1- Which of the following aids in neutralization of acid chyme?
A. NaHCO3
B. HCO3-
C. Proteins
D. Cholesterol

2- Which of the following is due to increase intrahepatic vascular pressure?
A. Increase portal blood flow
B. Increase bile secretion
C. Decrease bile secretion
D. Stoppage of bile secretion

3- Maximum volume of gallbladder:
A. 5-20 ml
B. 7.5 ml
C. 30-60 ml
D. 700-1200 ml

4- Stimulation of sympathetic nervous system result in:
A. Relaxation of gallbladder & contraction of sphincter
B. Contraction of gallbladder & relaxation of sphincter
C. Relaxation of gallbladder & increase secretion
D. Contraction of gallbladder & decrease secretion

5- Which one of the following is primary bile acid:
A. Deoxycholic
B. chenodeoxycholic
C. lithocholic

6- Bile salts polarity comparing with bile acids:
A. more polar
B. less polar
C. Same polarity

7- Bile acids are:
A. Hydrophobic
B. Hydrophilic
C. Amphipathic

8-The total bile acid pool is:
A. 7-9 g
B. 2-4 g
C. 10-20 g

SAQs

Q1: Briefly mention the stages of bile secretion.

Ans: Hepatocytes → Bile canaliculi → Hepatic duct → Common bile duct → Duodenum or through cystic duct → gallbladder

Q2: What are cholretics?

Ans: Substance stimulate bile acid secretion by liver (hepatocytes)

HCO3- , hormones: secretin, glucagon, CCK and gastrin & vagal stimulation

Q3: The highest rate of gall bladder emptying occurs during?

Ans: The intestinal phase

Q4: The pathway for absorption of bile acid into hepatocyte is:

Ans: Na+/K+-ATPase

Thanks for checking our work

Good Luck

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