BIOCHEMISTRY

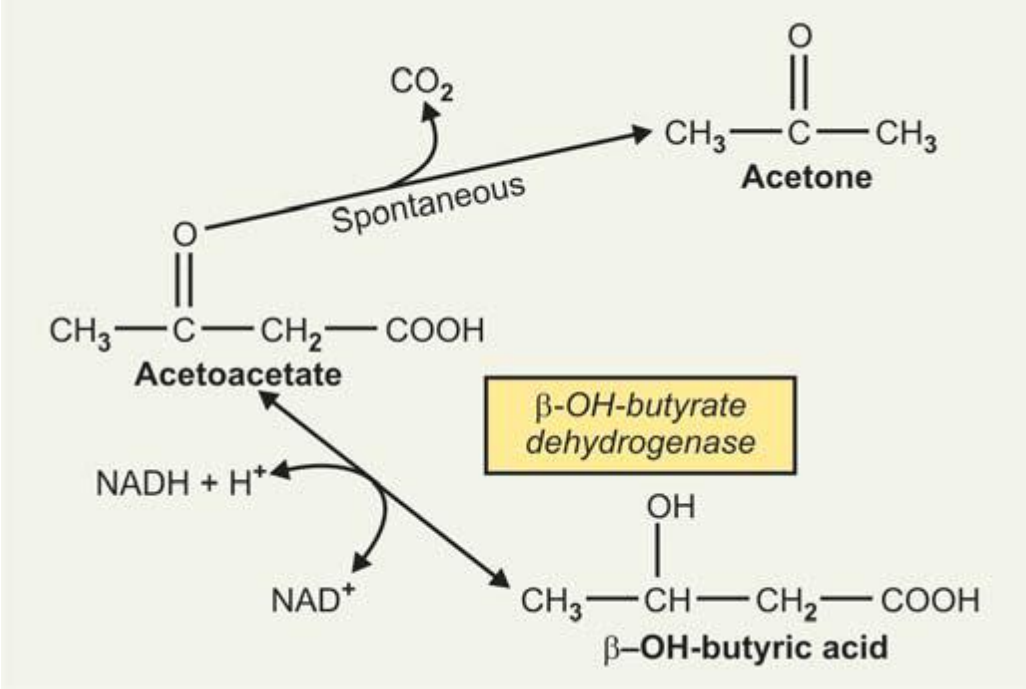
Lec:7 : 2nd stage **Dr. Shaimaa S.Mutlak**

METABOLISM OF LIPIDS

KETOSIS

Under certain metabolic conditions associated with a high rate of fatty acid oxidation, liver produces considerable quantities of compounds like **acetoacetate** and β-**OH butyric acid**, which pass by diffusion into the blood.

Acetoacetate continually undergoes spontaneous decarboxylation to produce **acetone**. ***These three substances are collectively known as "ketone bodies" (or "acetone bodies").*** Sometimes also called as "ketones". **Inter-relationship of these three substances are shown below:**



Concentration of Ketone Bodies

Concentration of total ketone bodies in the blood of wellfed individuals does not normally exceed 1 mg/100 ml (as acetone equivalents).

Urine: Loss via urine is usually less than 1 mg/ 24 hrs in humans.

Ketoacidosis: Acetoacetic acid and β-OH-butyric acid are moderately strong acids. They are buffered when present in blood and tissues, entailing some loss of buffer cations (Na^+,K^+,$HCO3^-$,H^+) which progressively depletes the **alkali reserve**↓ causing ketoacidosis.

Note: This may be fatal in uncontrolled diabetes mellitus.

Ketonaemia: Rise of ketone bodies in blood above normal level is known as ketonaemia**.**

Ketonuria: When the blood level of ketone bodies rises above the renal threshold, they are excreted in urine and is called as **ketonuria.**

Ketosis: Accumulation of abnormal amount of ketone bodies in tissues and body fluids is termed as ketosis, where the urinary excretion of β-OH butyric acid exceeds 200 mg daily (normal 5 to 10 mg).

Causes of ketosis:-

1. Starvation: Simplest form of ketosis occurs in starvation.

Mechanism: Involves depletion of available carbohydrate reserve, coupled with mobilization of FFA and oxidation to produce energy.

2. In Pathologic States

• In **Diabetes mellitus:** Clinical and experimental.

• In some types of **alkalosis:** Ketosis may develop.

• Pregnancy toxaemia.

3. In prolonged **ether anaesthesia.**

4. Other non-pathologic forms of ketosis are found under conditions of:

• **High fat feeding.**

• **After severe exercise** in the post-absorptive state.

5. Injection of anterior pituitary extracts.

BILE ACID

Bile acids: are formed from cholesterol.

Types of bile acid:

(a) Primary bile acids: They are synthesized in the liver from cholesterol. They are mainly two:

• **Cholic acid:** Quantitatively the largest in amount in bile.

• **Chenodeoxy cholic acid.**

(b) Secondary bile acids: They are produced in intestine from the primary bile acids by the action of intestinal bacteria, they are produced by deconjugation and 7-α-dehydroxylation. **They are mainly two:**

• **Deoxycholic acid:** Formed from cholic acid

• **Lithocholic acid:** Formed from chenodeoxycholic acid.

BIOSYNTHESIS OF BILE ACIDS

1. First step is the 7-α-hydroxylation of the cholesterol to form 7-α-OH cholesterol, the reaction is catalysed by the enzyme **7-α-hydroxylase**, a microsomal enzyme. The reaction requires:

• Molecular O2

• NADPH, and

• Cytochrome P-450.

The enzyme is a typical mono-oxygenase. The enzyme also requires vit. C as a coenzyme.

Note

• It is the **rate-limiting** reaction and controls the synthesis of bile acids.

• Vitamin C deficiency interferes with bile acid formation and leads to cholesterol accumulation and atherosclerosis in scorbutic animals.

2. Pathway of bile acid biosynthesis from 7-α-OH-cholesterol to two directions:

- Cholic acid formation, and
- Chenodeoxy cholic acid formation.

The conversion of 7-α-OH-cholesterol to formation of cholic acid/or chenodeoxycholic acid is catalyzed by 12-α-hydroxylase and involves several steps. The enzyme requires:

• Molecular O2

• NADPH and

• CoA-SH.

• Propionyl-CoA is split off the side chain leaving 'cholyl CoA'/"chenodeoxy cholyl-CoA" respectively.

3. A second enzyme catalyses the conjugation of the CoA-derivatives with glycine or taurine, to form the Primary bile acids:

• **Glycocholic acid** and/or **glycochenodeoxycholic acid**, and

• **Taurocholic and/or taurochenodeoxycholic acid.**

In humans, the ratio of the glycine to taurine conjugates is usually 3:1.

Since bile has alkaline pH and it has sodium and K, it is assumed that the bile acids exist in bile as corresponding sodium salts usually as **sodium glycocholate** and **sodium taurocholate**. Hence they are called as **bile salts**.

REGULATION OF BILE ACID SYNTHESIS

Each day, an amount of bile acid equivalent to that lost in the faeces is resynthesized in the liver from cholesterol, so that a constant pool of bile acids is maintained.

• The principal rate-limiting step in the biosynthesis of bile acids is the 7-α-hydroxylase step.

7-α-hydroxylase activity is also enhanced by cholesterol of endogenous and dietary origin and regulated by insulins, glucagon, glucocorticoids and thyroid hormones.

• The controlling enzyme for cholesterol biosynthesis is HMG-CoA reductase.

• Activities of both these probably change in parallel and undergo similar 'diurnal' variation. Both the enzymes may exist in 'active' and 'inactive' form which may be regulated by phosphorylation/dephosphorylation mechanisms.

• Cholesterol feeding exerts a stimulatory effect on 7-α−hydroxylase. Bile acids, on the other hand, exert a "feedback" inhibition on the enzyme 7-α-hydroxylase.

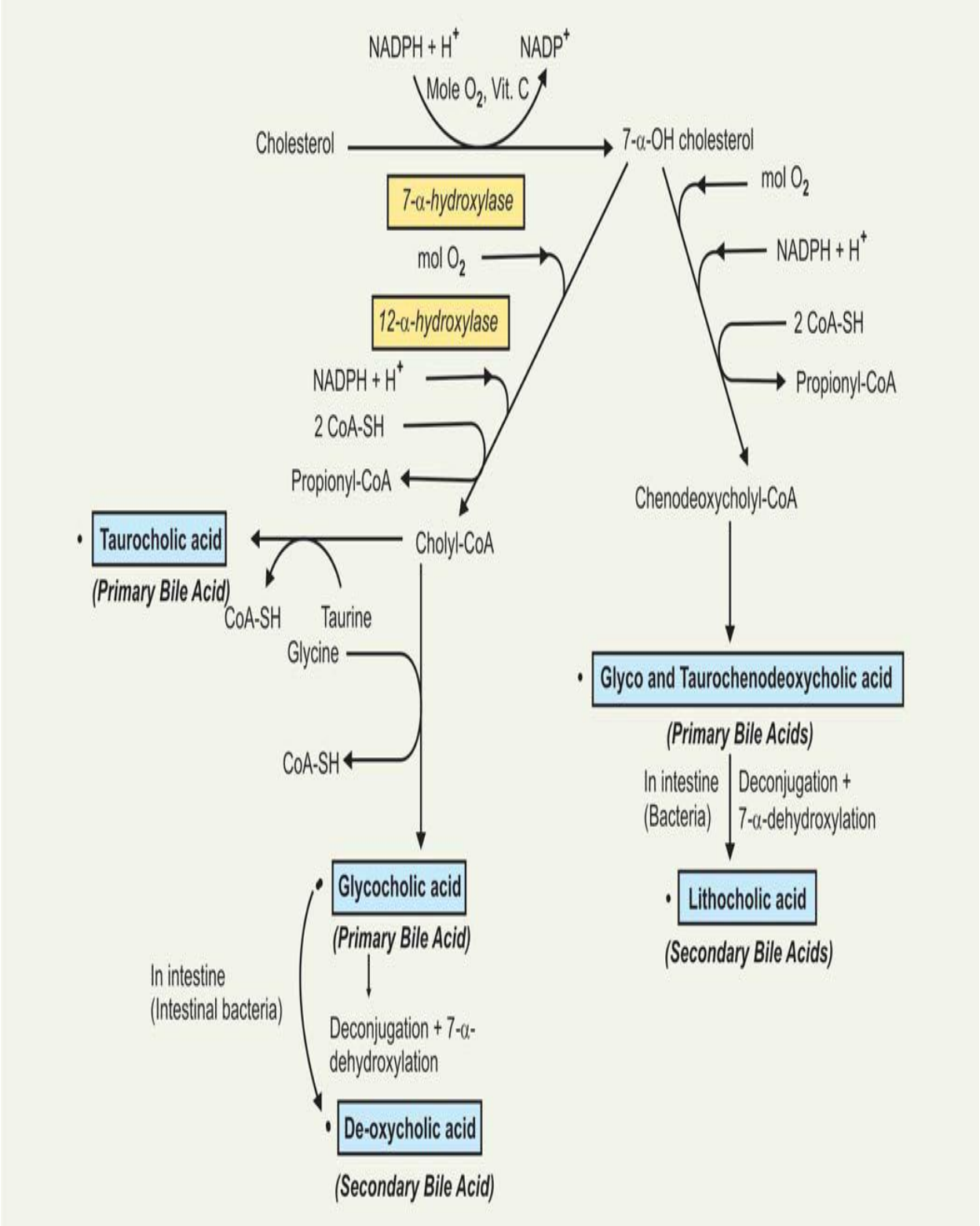


Fig: formation of bile acid

BILE

Bile is a viscous fluid produced by the liver cells. Strictly speaking it is not a digestive secretion as it does not contain any digestive enzymes but it helps in digestion and absorption of lipids. It is secreted continuously by the liver and through bile canaliculi and bile duct it accumulates in the gallbladder, where it is stored.

In gallbladder, certain changes take place by reabsorption of large amount of water leading to concentration of bile. Water is absorbed along with inorganic components as isotonic solution. Mucin is added and bicarbonate and chlorides are reabsorbed.

Hence organic constituents like cholesterol, bile pigments—bilirubin get concentrated in gallbladder bile. During digestion, gallbladder contracts by the stimulation of the GI hormone cholecystokinin which is produced by small intestine and release bile rapidly to the intestine by the way of common bile duct. Approximately 500 to 1000 ml of bile is secreted by liver in a day.

Functions of Bile Salts

1. Lowering of surface tension: Because of their power of lowering surface tension, they aid in the emulsification of fats and tend to stabilize such emulsions. The emulsification is a prerequisite for action of pancreatic lipase on fats.
2. Bile salts accelerate the action of pancreatic lipase:

In the presence of bile salts, a co-lipase (molecular wt = 10,000) binds to lipase and shifts the optimal pH of the enzyme from 9.0 to 6.0.

3. Micelles formation: Bile salts form ‘micelles’ with fatty acids, mono and diacyl glycerols and also TG which are made water soluble and helps absorption.
4. Absorption of vitamins: They aid in the absorption of fat soluble vitamins (A, D, E and K) and also carotene by forming complexes more soluble in water (“hydrotropic” action).
5. Intestinal motility: They stimulate intestinal motility.
6. Choleretic action: They have great “choleretic” action.

Thus the liver is stimulated to secrete bile as long as bile salts are absorbed.

7. Solubility of cholesterol: Bile salts keep cholesterol in solution. Cholesterol remains soluble in gallbladder by bile salts.

CLINICAL ASPECT

• Estimation of Bile Acids and Bile Salts in Blood: This has been recently used for as liver function test. Bile salts in blood are increased greatly in clinical obstructive jaundice. After prolonged obstruction, the concentration of bile salts in blood may decrease due to diminished synthesis as a result of progressive parenchymal damage.

• **Cholelithiasis (Gallstones):** Bile salts keep cholesterol in solution in gallbladder. In the absence of bile salts, cholesterol may get precipitated producing gallstones. In the gallbladder, the cholesterol is soluble and held in ‘micelles’ with the help of conjugated bile salts and phospholipids. Solubility depends on ratio of cholesterol with the conjugated bile salts + phospholipid. Secretion of phospholipid into the bile depends on availability of the conjugated bile salts. If bile salts content is decreased due to any cause, the phospholipid also decreases leading to an imbalance of the ratio. The solubility of cholesterol is hampered as a result it crystallises out. The crystals grow to form the stones.

A. Conditions of Stone Formation

1. Infection causes:

• Deconjugation of bile acids leading to decrease in solubility.

• Production of phospholipase, which converts Lecithin to Lysolecithin.

Thus, the ratio is disturbed leading to precipitation of cholesterol.

2. Decreased availability of bile salts (Reduction in bile salt pool):

• Defect in enterohepatic circulation.

• Disease of terminal ileum.

• In patients with cirrhosis liver.

B. Types of Gallstones:

Gallstones can be of mainly three types:

1. **Cholesterol stones:** They are single or multiple, mainly formed of cholesterol, mulberry-shaped and are not radiopaque.
2. **Pigment stones:** Consist of bile pigments and calcium with other organic substances. Small multiple stones, dark green or black, not radiopaque.
3. **Mixed stones:** Consist of mixture of cholesterol + pigments + calcium and organic material. Most common form, may be radiopaque. Stones: Faceted and dark brown.