Lipids Chemistry
Lecture 3

Professor Sameeh Al-Sarayreh
Professor of Medical Biochemistry
Department of Biochemistry and Molecular Biology
Faculty of Medicine, Mutah University

- **Plasma lipoproteins**

- **Lipoproteins function in the body is to transport lipids (triacylglycerols and cholesterol) from the small intestine or the liver out to peripheral tissues and then back again to the liver.**

- **Lipoproteins differ in the ratio of proteins to lipids, and in the particular apoproteins and lipids that they contain.**

- **The lipoprotein particles include:**
- **Chylomicrons, very-low-density lipoproteins (VLDL), low-density lipoproteins (LDL), and high-density lipoproteins (HDL).**

Lipoproteins Structure

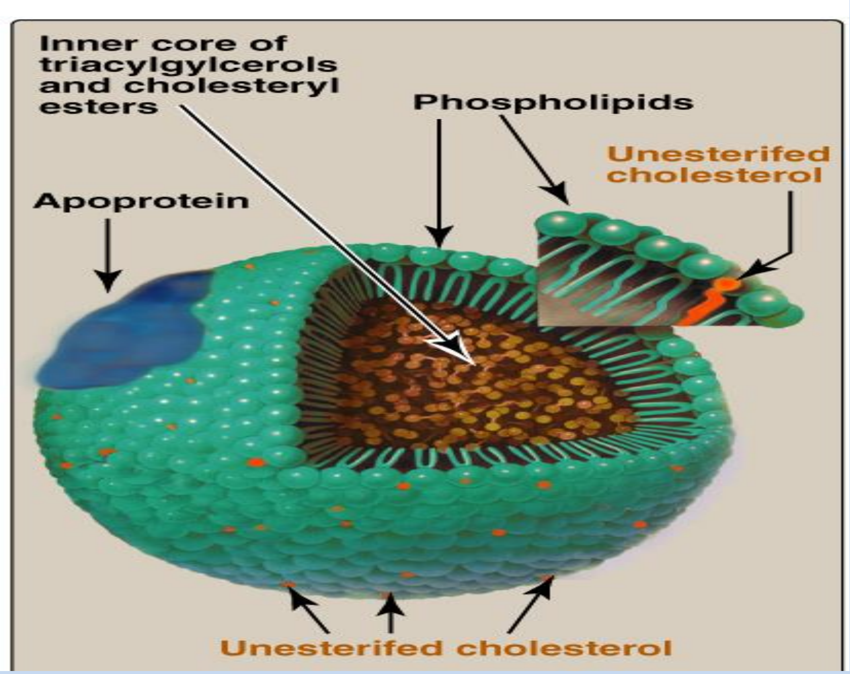
- The lipoproteins are spherical complexes of lipids and specific proteins (apoproteins).

1- A polar monolayer of phospholipids and free cholesterol located on the outer part of the lipoprotein with their charged groups pointing out towards the water molecules.

2-Hydrophobic lipids (esterified cholesterol and triacylglycerol), which are located in the core of the lipoprotein particle. These form the central droplet

3- Apoproteins, these can span the region between the central core and the outer envelope, and have part of their structure exposed at the surface.

4- Enzymes



Outer coat:

- Apoproteins.
- Phospholipids(PL)
- Cholesterol(Unesterified)

Inner core:

- Triacylglycerol (TAG).
- Cholesteryl ester (CE)

Size and density of lipoprotein

Depending on the size of the lipoprotein, and the ratio of protein to lipid, lipoproteins have different densities as determined by density gradient centrifugation:

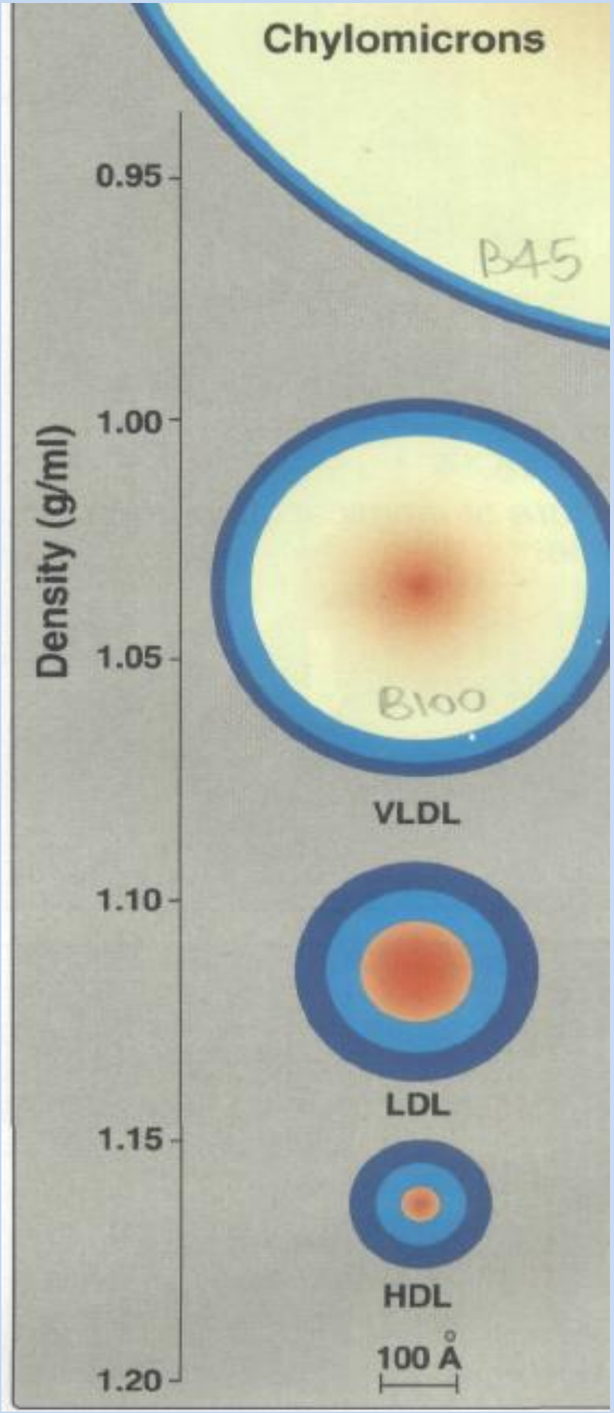
Chylomicrons (CM) are the lipoprotein particles lowest in density and largest in size, and contain the highest percentage of lipid and the smallest percentage of protein.

VLDLs and LDLs are successively denser, having higher ratios of protein to lipid.

HDL particles are the densest.

Triacylglycerol (TAG) is the predominant lipid in chylomicrons and VLDL,

whereas cholesterol and phospholipid (PL) are the predominant lipids in LDL and HDL.



Composition of lipoproteins

Lipoprotein classes	Total protein (%)	Total lipids (%)	Percent composition of lipid fractions			
			PL	ChE	Ch	TAG
CM	1.5-2.5	97-99	7-9	3-5	1-3	84-98
VLDL	5-10	90-95	15-20	10-15	5-10	50-65
LDL	20-25	75-80	15-20	35-40	7-10	7-10
HDL	40-45	55	35	12	4	5

apoproteins

The protein components of lipoproteins are known as apoproteins or apolipoproteins. There are nine major species identified by the letters A, B, C, D and E with Roman numerals used for sub-species. Apoproteins have characteristic amino acid sequences, chain lengths and possess different physiological and biochemical properties and are responsible for the structural integrity of the lipoproteins.

Apoproteins functions

(1) They form part of the structure of the lipoprotein
eg, apo B

(2) They are enzyme cofactors, eg, apo C-II for lipoprotein lipase
or enzyme inhibitors, eg, apo A-II and apo C-III for lipoprotein lipase

(3) They act as ligands for interaction with lipoprotein receptors in tissues (bind to cell surface receptors)
eg, apo B-100 and apo E for the LDL receptor

Chylomicrons

Function: **carry dietary lipids from intestine to the peripheral tissues.**

- **Fate of chylomicrons**
- **Chylomicrons are synthesized in intestinal mucosal cells, secreted by the process of exocytosis into the lymph, pass into the blood, and become mature chylomicrons.**

- **On capillary walls in adipose tissue and muscle particularly cardiac muscle, lipoprotein lipase (LPL) an extracellular enzyme digests the triacylglycerols of chylomicrons to fatty acids and glycerol.**

- **Fatty acids are delivered mainly to adipose tissue, heart, and muscle (80%), while about 20% goes to the liver.**

- **In this way, the circulating chylomicron becomes progressively smaller, its triacylglycerols content decreases and it becomes relatively richer in cholesterol and proteins.**

VLDL:

Are produced in the liver.

- **Function: is to carry lipid from the liver to the peripheral tissues.**

- **Fatty acids for VLDL synthesis in the liver may be obtained from the blood or they may be synthesized from glucose.**

- **In a healthy individual, the major source of the fatty acids of VLDL triacylglycerol is excess dietary glucose.**

Formation of LDL

- **As VLDL pass through the circulation, the triacylglycerol they contain is degraded by lipoprotein lipase, causing the release of fatty acids and glycerol from a portion of core triacylglycerols.**

- **When additional core triacylglycerols are removed then VLDL is transformed to Intermediate-Density Lipoprotein (IDL) .**
- **With the removal of additional triacylglycerols from IDL, LDL is generated.**

- **LDL (the bad cholesterol)**

- **The primary function** of LDL particles is to provide cholesterol to the peripheral tissues.

- LDL particles are rich in cholesterol and cholesterol esters.
- Approximately 60% of the LDL is transported back to the liver.

- The remaining 40% of LDL particles are carried to extrahepatic tissues (outside liver) such as adrenocortical and gonadal cells for the synthesis of steroid hormones.

- The elevated levels of LDL, leads to the formation of atherosclerotic plaques

(HDL) (the good cholesterol)

1. Synthesis of HDL

- **HDL particles can be created by a number of mechanisms.**

One mechanism is the synthesis of nascent HDL by the liver and intestine as a relatively small molecule whose shell, like that of other lipoproteins, contains phospholipids, free cholesterol, and a variety of apoproteins.

2. Maturation of nascent HDL

In the process of maturation, the nascent HDL particles accumulate phospholipids and cholesterol from cells lining the blood vessels. As the central hollow core of nascent HDL progressively fills with cholesterol esters, HDL takes on a more globular shape to eventually form the mature HDL particle.

- **HDL accepts free cholesterol from peripheral tissues, such as cells in the walls of blood vessels.**

- **This cholesterol is converted to cholesterol ester, part of which is transferred to VLDL, and returned to the liver by IDL and LDL.**

- **The remainder of the cholesterol is transferred directly as part of the HDL molecule to the liver.**

- **The liver reutilizes the cholesterol in the synthesis of VLDL, converts it to bile salts, or excretes it directly into the bile.**

- **HDL therefore tends to lower blood cholesterol levels.**

3. Reverse cholesterol transport

- **A major benefit of HDL particles derives from their ability to remove cholesterol from cholesterol loaded cells and to return the cholesterol to the liver, a process known as reverse cholesterol transport.**

- **This is particularly beneficial in vascular tissue; by reducing cellular cholesterol levels**

- **The esterification of cholesterol in the HDL particle prevent cholesterol from leaving the HDL**

- **High levels of HDL in the blood, therefore, are believed to be vasculoprotective, because these high levels increase the rate of reverse cholesterol transport "away" from the blood vessels and "toward" the liver.**

The desired values in most adults are (from NIH U.S.A):

- **LDL cholesterol: Optimal Less than 100 mg/dL and borderline high 130-159 mg/dL**
- **HDL cholesterol: Greater than 40-60 mg/dL (higher numbers are desired)**
- **Total cholesterol: Desirable Less than 200 mg/dL and borderline high is 200-239 mg/dL**
- **Triglycerides: 10-150 (lower numbers are desired)**
- **VLDL: 2-38**

Cholesterol synthesized in the liver has essentially three fates

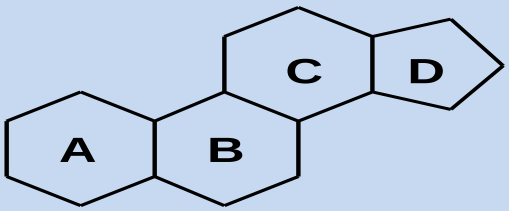
1) It can be esterified with a fatty acid by the enzyme acyl-CoA-cholesterol acyl transferase (ACAT) to make cholesterol esters that are stored in lipid droplets

2) It can be exported to the peripheral tissues through packaging into lipoprotein particles

3) It can be converted into bile acids which are transported to the bile duct and secreted into the small intestine to aid in fat absorption.

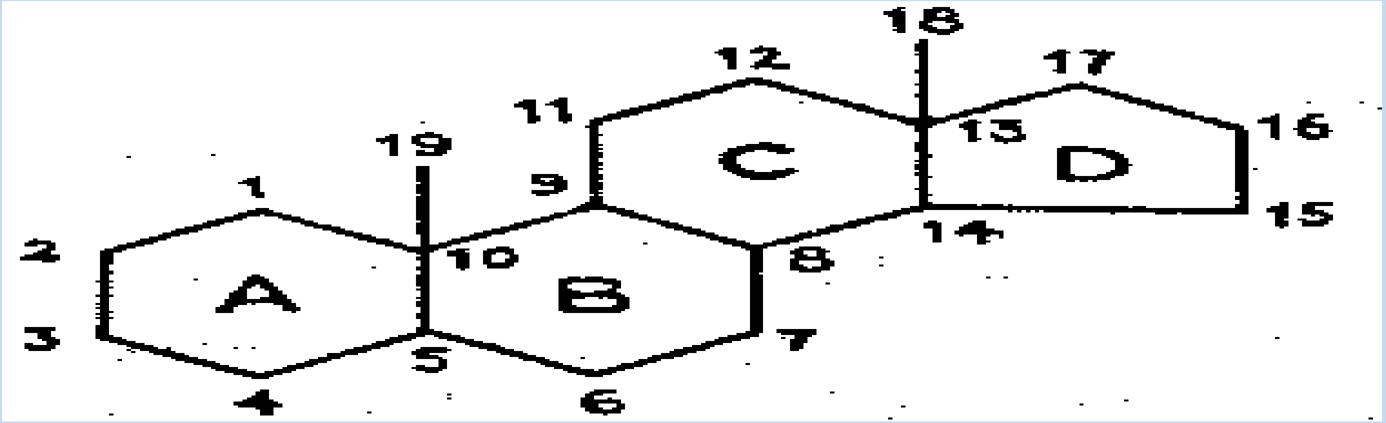
Steroids

- **Steroids are group of plant and animal lipids that have a similar tetracyclic nucleus.**



Steroid nucleus:

- **So this tetracyclic nucleus is composed of 17 carbon atoms besides two methyl groups (C_{18}, C_{19}).**
- **There is a methyl group at C_{10} (it makes C 19).**
- **And there is another methyl group at C_{13} (it makes C18).**



Steroids include:

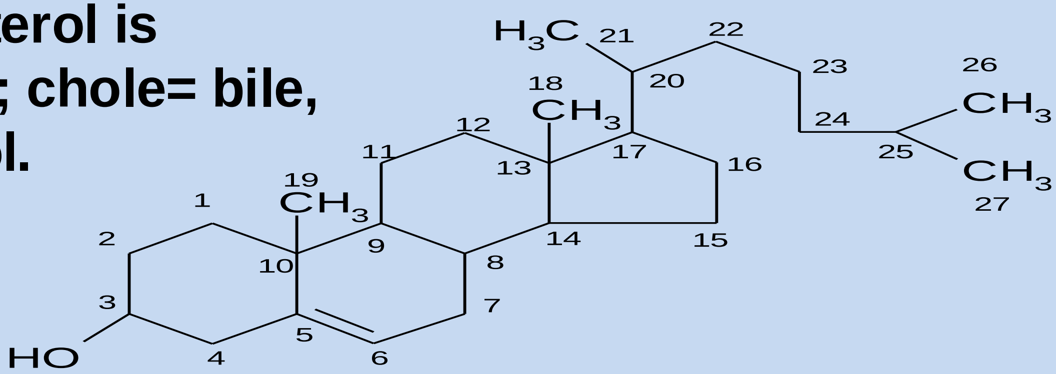
Sterols, Bile acids and salts, Steroid hormones, Vitamin D.

STEROLS:

- **This group of steroids has a hydroxyl group (OH) at C_3 i.e. it is an alcohol, and an aliphatic side chain at C_{17}.**

e.g: Cholesterol

- **Naming: The word cholesterol is derived from Greek words; chole= bile, steros= solid, ol= alcohol.**



Chemistry of cholesterol:

It is a solid alcohol of 27 carbon atoms and contains steroid nucleus.
it has a double bond between C_5 and C_6.
One hydroxyl group at C3 which is characteristic to all sterols.
The OH group is beta oriented, projecting above the plane of ring.

Properties of cholesterol:

- **It has amphipathic properties which allow it to play structural role in membrane and in the outer layer of lipoprotein.**

Biomedical importance:

1- **It is the main sterol in human body (Nervous tissue, brain, suprarenal gland, and in bile, ,,).**

2- **It is present in blood (normal level 150-200 mg / dl).**

3- **It is often found as cholesterol ester (in combination with fatty acids). The fatty acid is attached to the hydroxyl group e.g. Cholesteryl oleate or linoleate.**

4- It is a major constituent of the plasma membrane.

The fused ring system makes cholesterol less flexible than most other lipids.

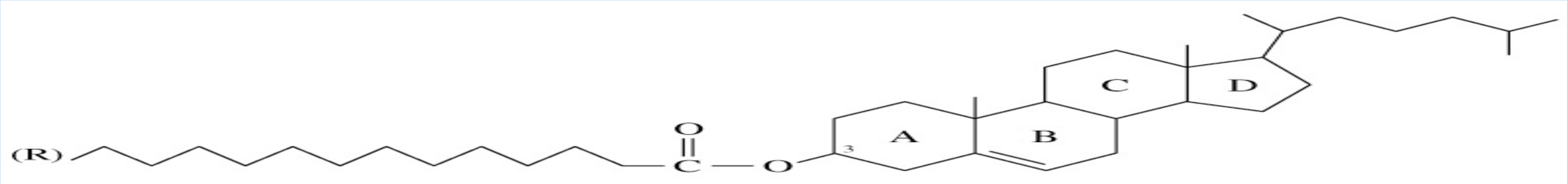
5- **It is the precursor of:**

- **Sex hormones, Cortical hormones, Vitamin D, Bile acids.**

6- **High level of cholesterol in blood will lead to its precipitation in the wall of blood vessels "atherosclerosis". Also high levels of blood cholesterol may lead to stones in gall bladder (gall stone).**

Cholesterol esters (CE)

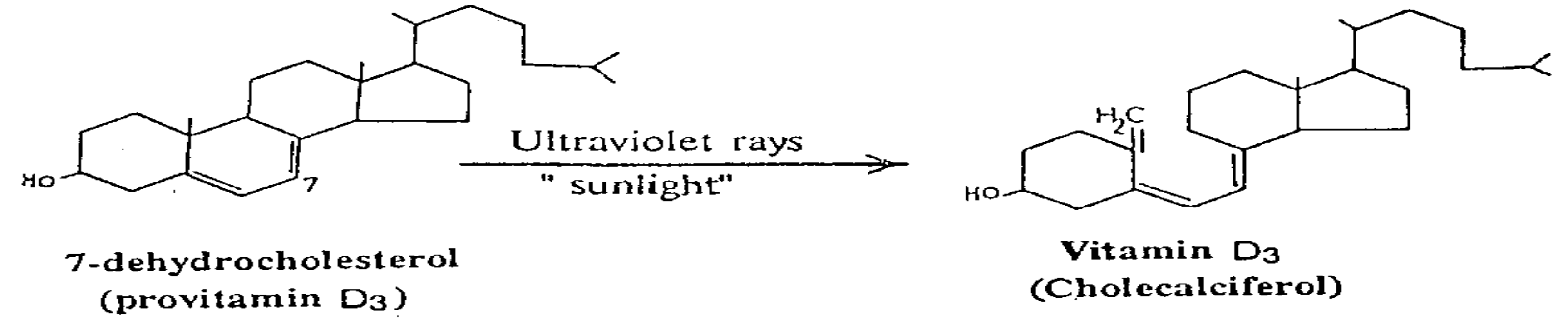
Cholesterol is converted to cholesteryl esters for cell <u>storage</u> or <u>transport</u> in blood. Fatty acid is esterified to C-3 OH of cholesterol



7-dehydrocholesterol (pro-vitamin D3)

7-dehydrocholesterol is stored under the skin, and by the effect of ultraviolet rays(in sunlight) it is transformed to cholecalciferol (vit. D_3 .)

Insufficient sunlight can lead to a deficiency of vitamin D_3, interfering with Ca^{2+} transport and bone development. Rickets can result.



Clinical correlation

- **Low density lipoproteins (LDL) transports cholesterol from liver through blood to the tissues (Bad cholesterol)**

- **High density lipoprotein (HDL) transports cholesterol from blood to the liver where it is metabolised (Good cholesterol)**

- **↑LDL, ↑ Cholesterol High risk of heart attack**

- **↑HDL, ↓ Cholesterol Low risk of heart attack**

Bile acids

Bile acids are hydroxylated steroids, synthesized in the liver from cholesterol. Peroxisomal enzymes assist in the hepatic biosynthesis of bile acids.

Bile acids are found predominantly in the bile of mammals and other vertebrates. Diverse bile acids are synthesized in the liver.

Bile acids are conjugated with taurine or glycine residues to give anions called bile salts

Approximately 600 mg of bile salts are synthesized daily to replace bile acids lost in the feces

Classification of bile acids/salts

- **Bile acids: primary & secondary.**
- **Bile acids: conjugated & non-conjugated.**
- **Bile salts: sodium & potassium salts of bile acids.**

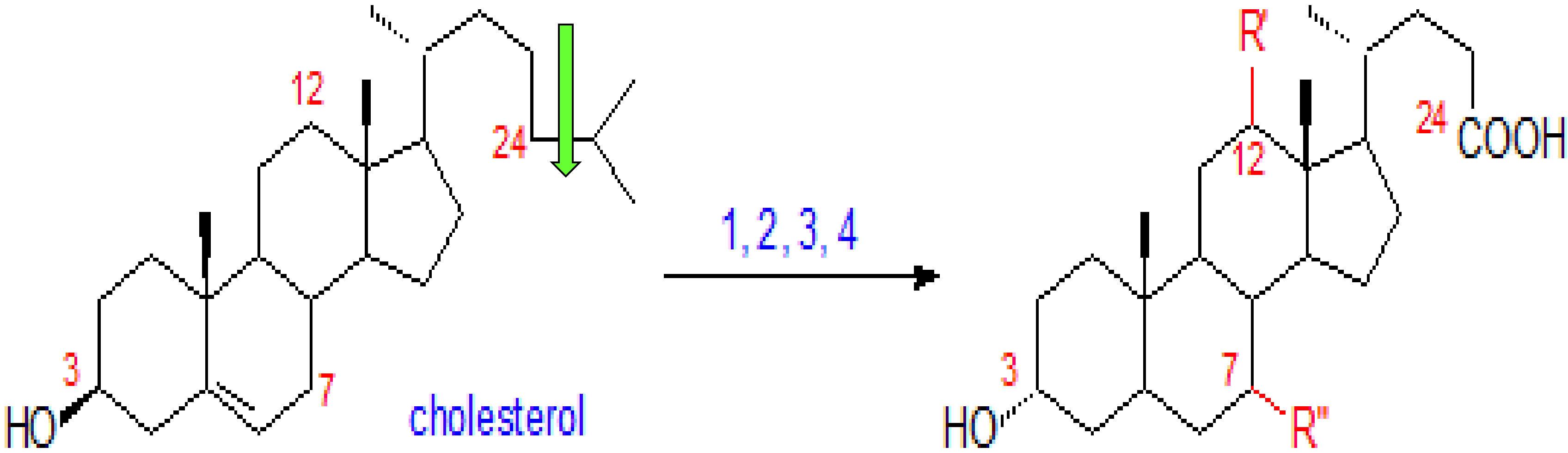
Bile acids: structure

- **Bile salts constitute a large family of molecules, composed of a steroid structure with four rings, a side-chain terminating in a carboxylic acid, and the presence of different numbers of hydroxyl groups.**

- **All bile acids have a 3-hydroxyl group (OH at carbon number 3), derived from the parent molecule, cholesterol.**

- **Bile acids/salts are polar derivatives of cholesterol.**
- **Bile acids are amphipathic.**

Biosynthesis of bile acids



1, hydroxylation reactions

2, epimerization of the 3β-hydroxyl group

3, saturation of the double bond

4, side-chain cleavage/oxidation

R' = H, R'' = OH, chenodeoxycholic acid

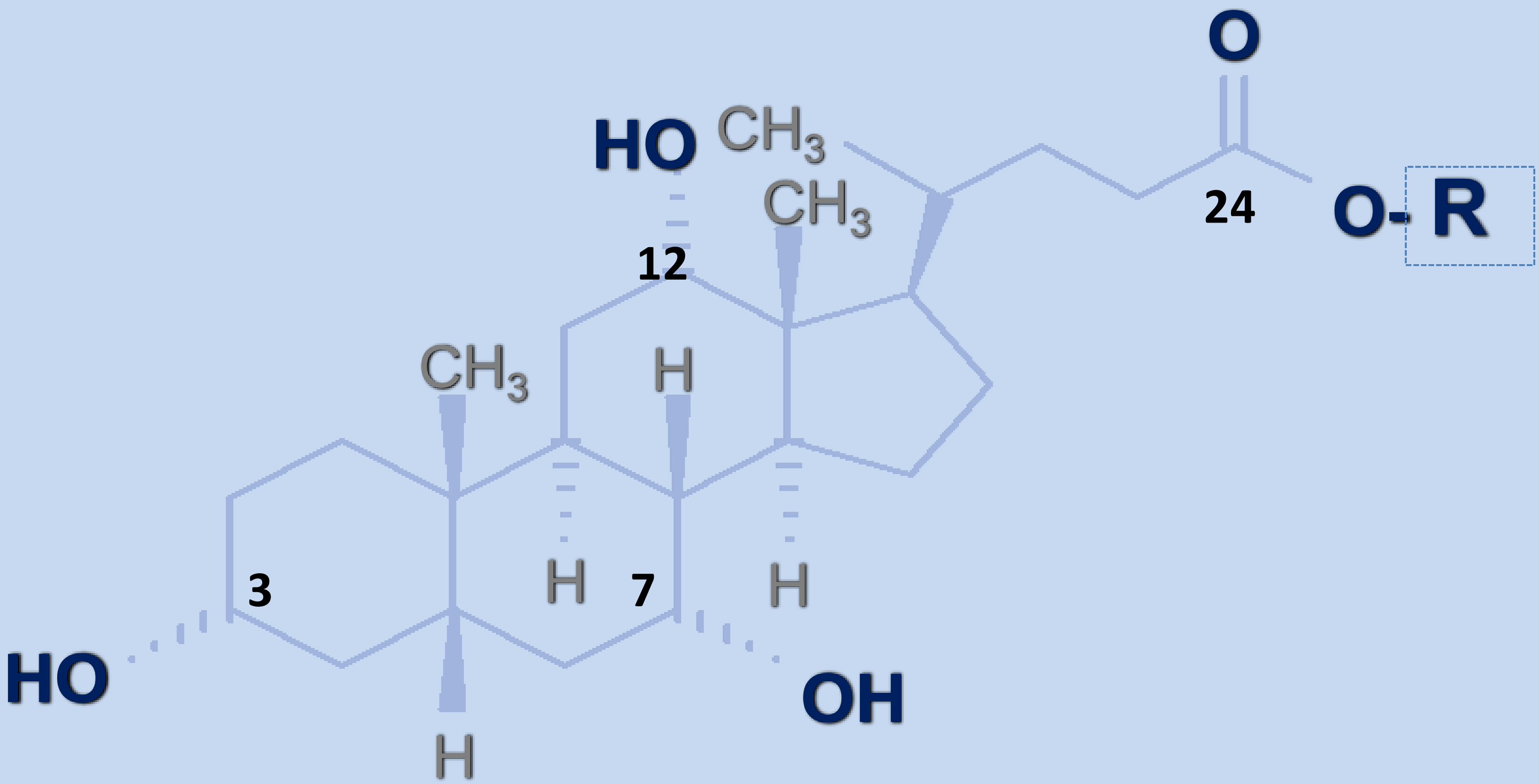
R = OH, R'' = OH, cholic acid

R' = OH, R'' = H, deoxycholic acid

↓

glycine and taurine conjugates

Bile acids/salts



R= H in non-conjugated bile acids.

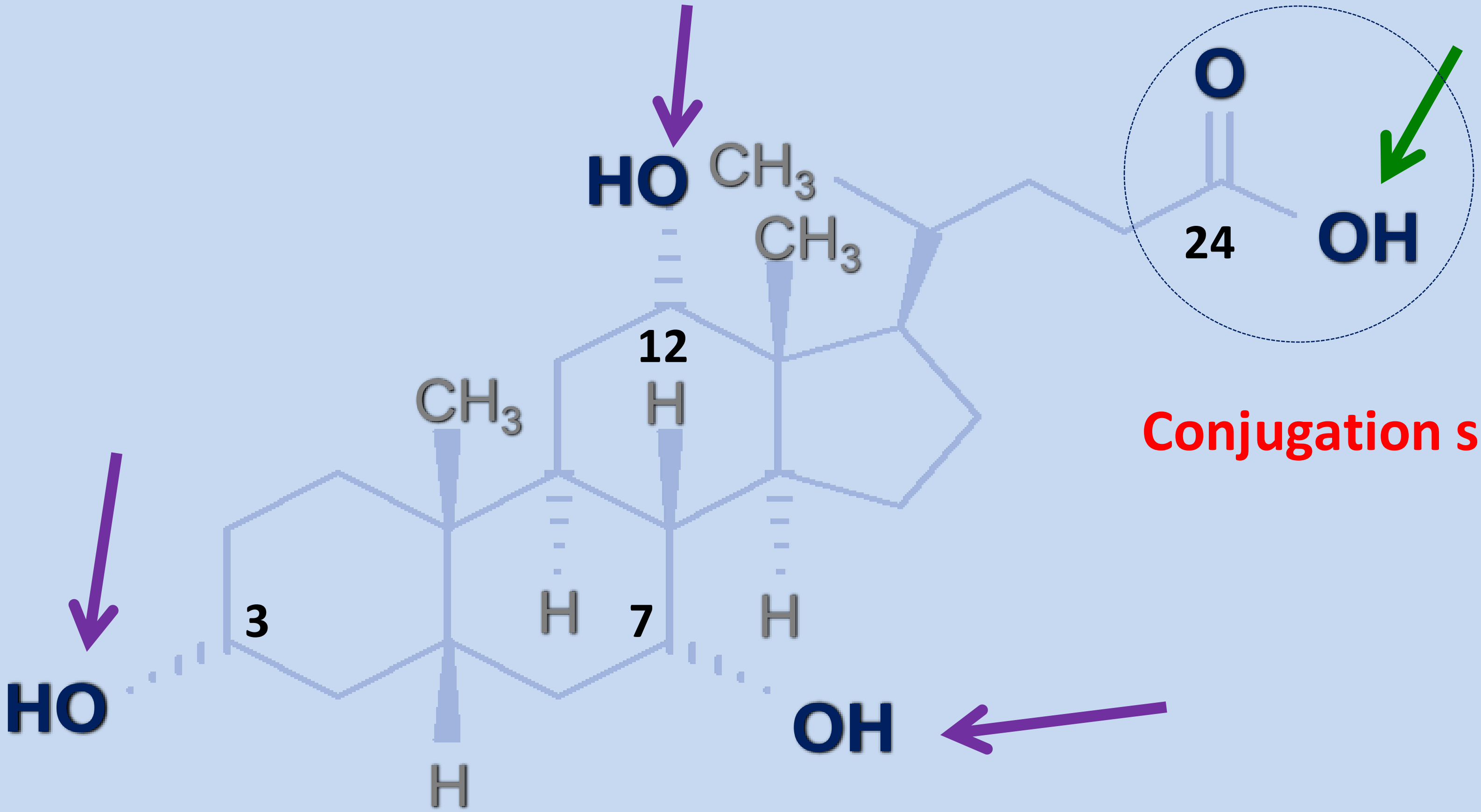
R= Na+/K+ in non-conjugated bile salts.

R= glycine/taurine in conjugated bile acids.

R= Na+/K+ salts of glycine/taurine in conjugated bile salts.

Bile acids: Cholic acid

non-conjugated bile acid



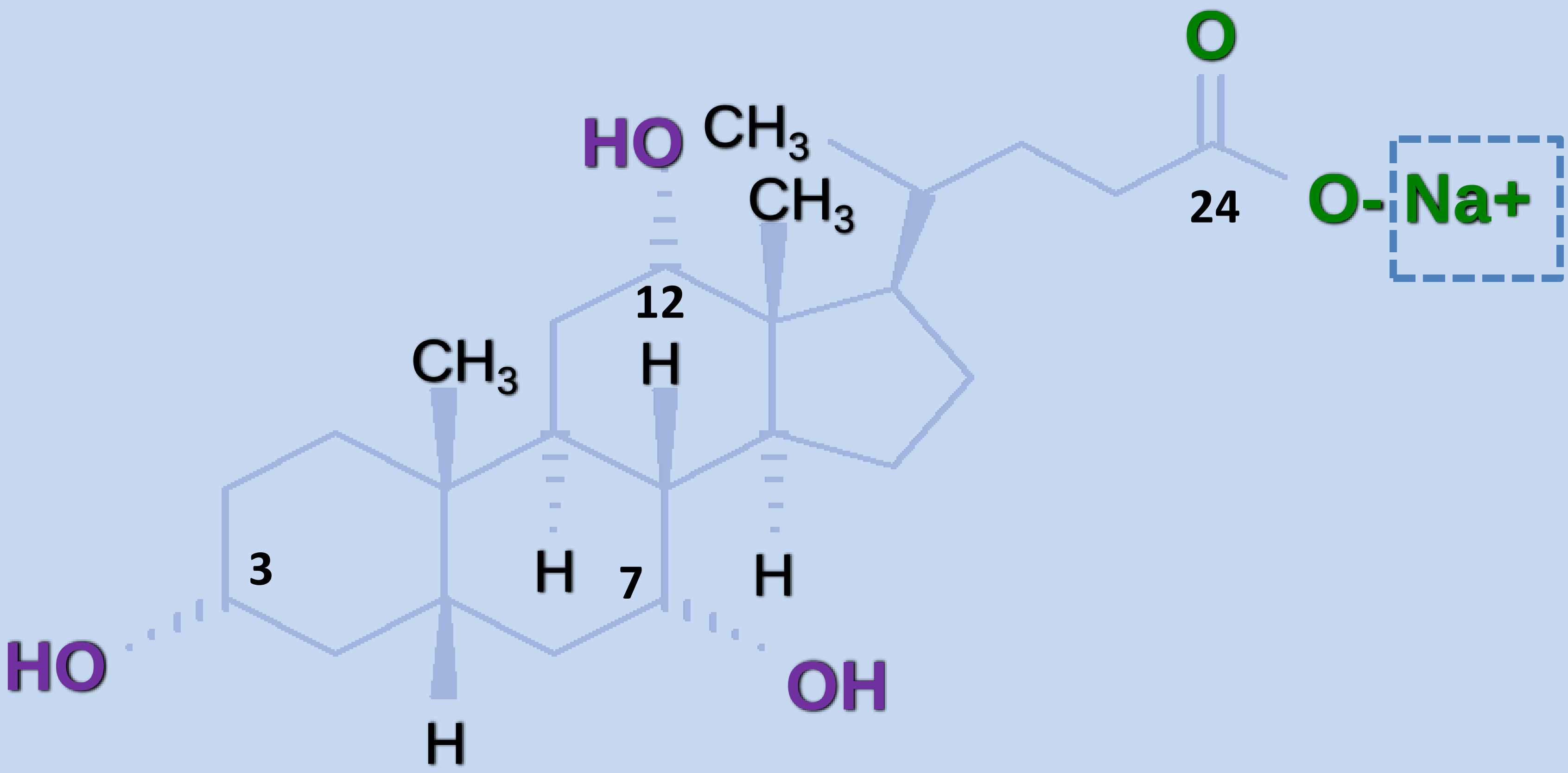
Polar groups are:

- OH groups
- COOH group

Cholic acid is the most common bile acid. It contains 3 OH groups at 3, 7, 12.

Bile salts: Sodium Cholate

(non-conjugated bile salt)



Conjugation

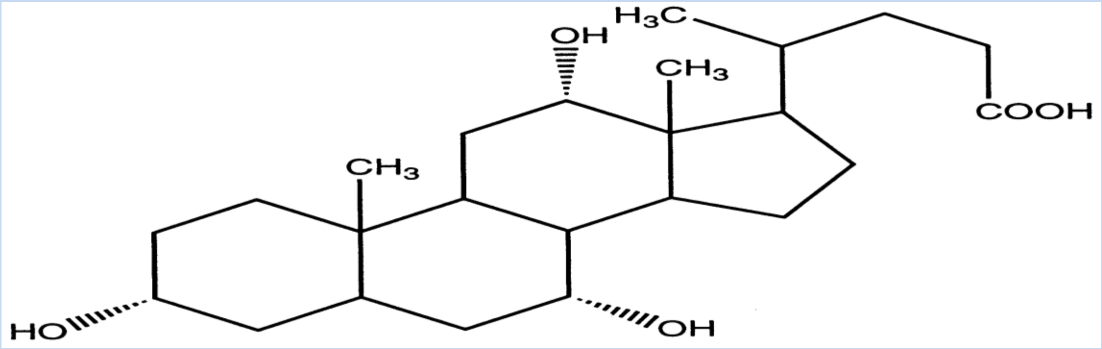
- **Prior to secreting any of the four bile acids (primary and secondary), liver cells conjugate them with one of two amino acids, glycine or taurine, to form a total of 8 possible conjugated bile acids.**

➢ **Glycine= NH2-CH2-COO-**

➢ **Taurine = NH2-CH2-CH2-SO3-**

- **Conjugated bile acids are almost always in their deprotonated (A-) form in the duodenum, which makes them much more water soluble thus, able to emulsify fats.**

Bile Acid Conjugation

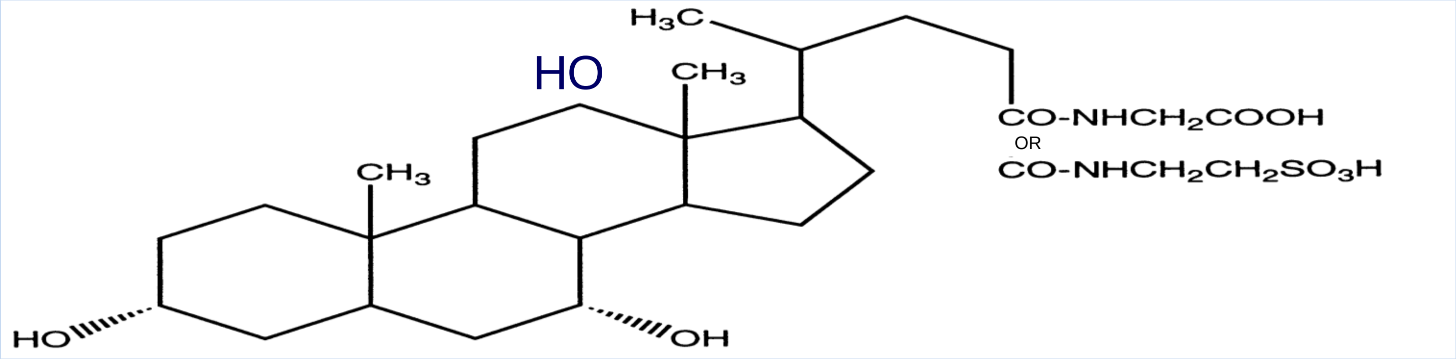


Cholic acid

\+ **Glycine**

OR

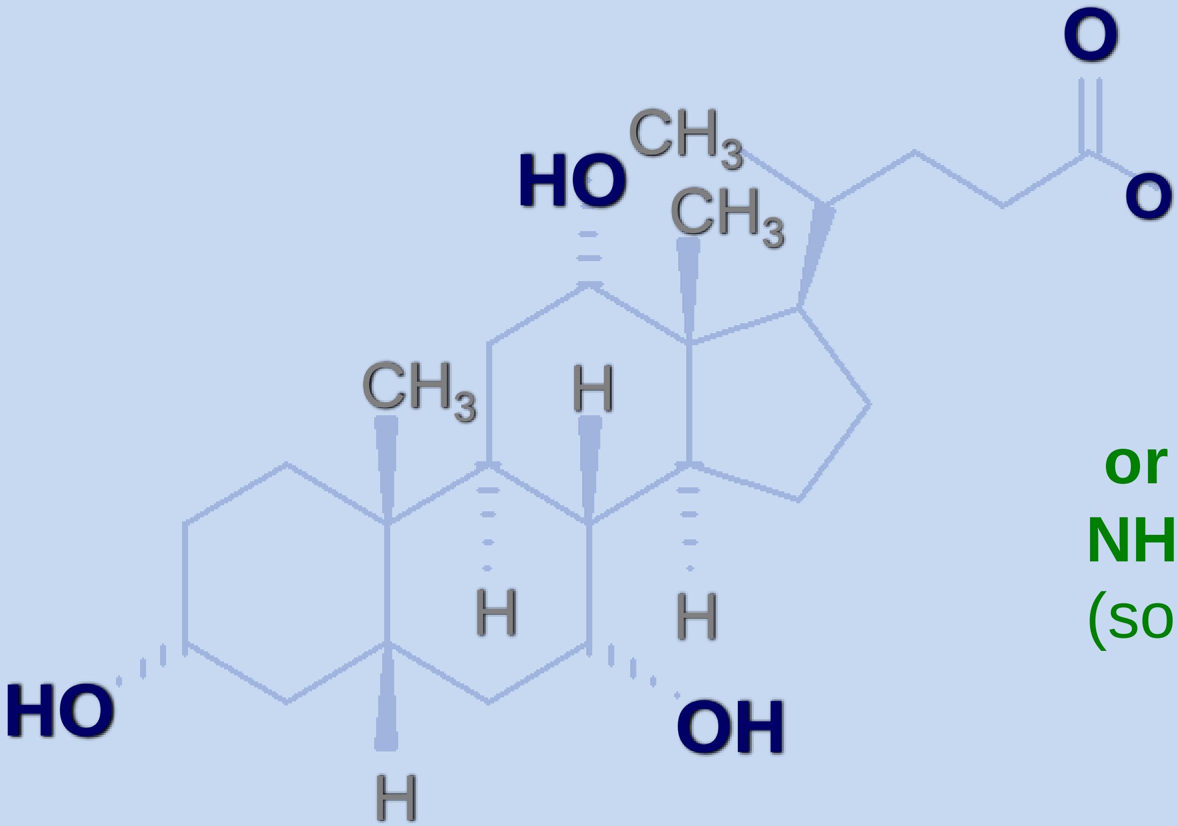
Taurine



Glycocholic acid Or Taurocholic acid

Bile salts: Sodium taurocholate

(conjugated bile salt)



$NHCH_2CH_2SO_3Na$

or

NH-CH2-COO-Na

(sodium glycocholate)

Biosynthesis of bile acids & Enterohepatic circulation

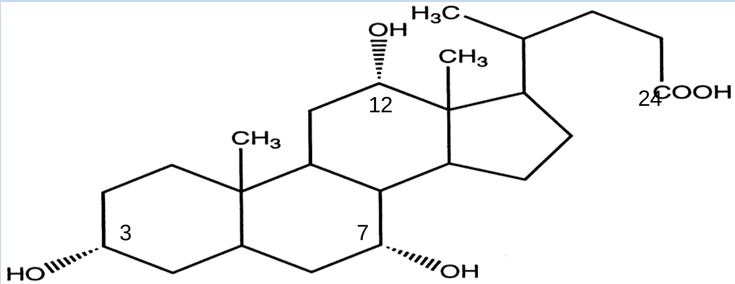
- Bile acid synthesis occurs in liver cells which synthesize primary bile acids in humans from cholesterol.
- Bile acids are stored in the gallbladder and are cycled between the intestines and liver via the enterohepatic circulation.

- When these bile acids are secreted into the lumen of the intestine, bacterial partial dehydroxylation (OH at carbon 7) forms the secondary bile acids.
- Cholic acid is converted into deoxycholic acid and chenodeoxycholic acid is converted into lithocholic acid.

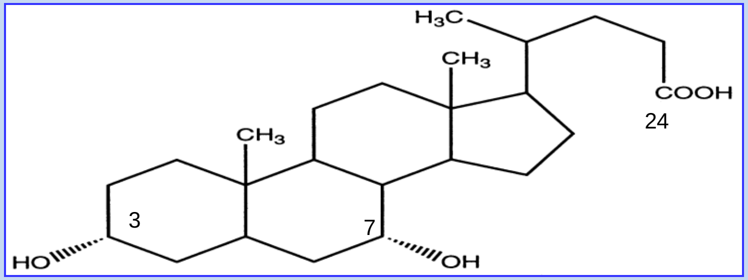
- All these bile acids can be taken back up into the blood stream (~ 95%), return to the liver, and be re-secreted in a process known as enterohepatic circulation. ~5% are excreted in faeces.

Primary and secondary bile acids

Primary Bile Acids



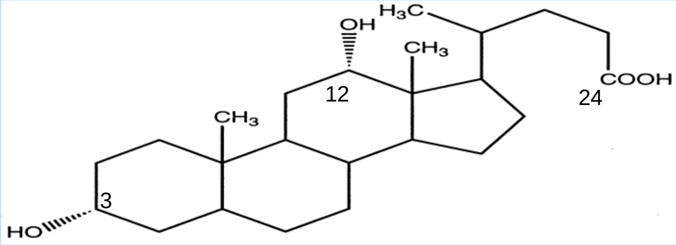
Cholic acid
(3 OH groups)



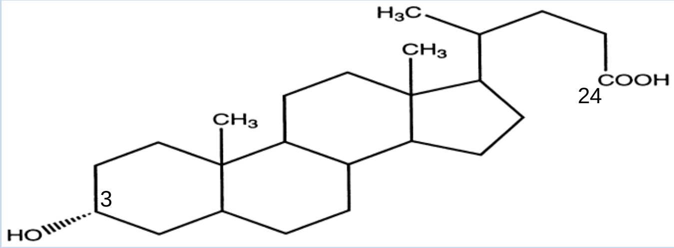
Chenodeoxycholic acid
(2 OH groups)

7-dehydroxylation by gut bacteria

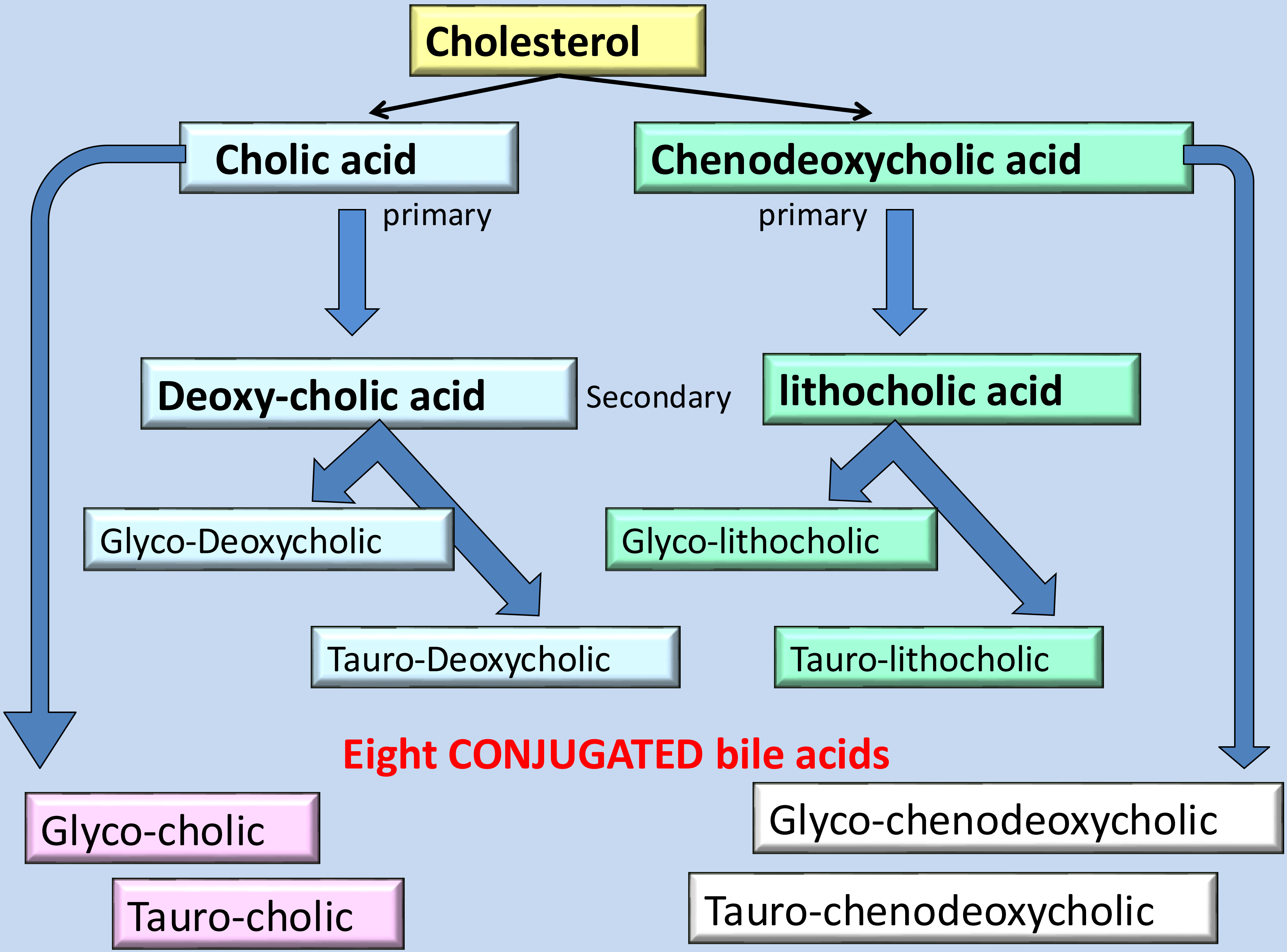
Secondary Bile Acids



Deoxycholic acid
(2 OH groups)



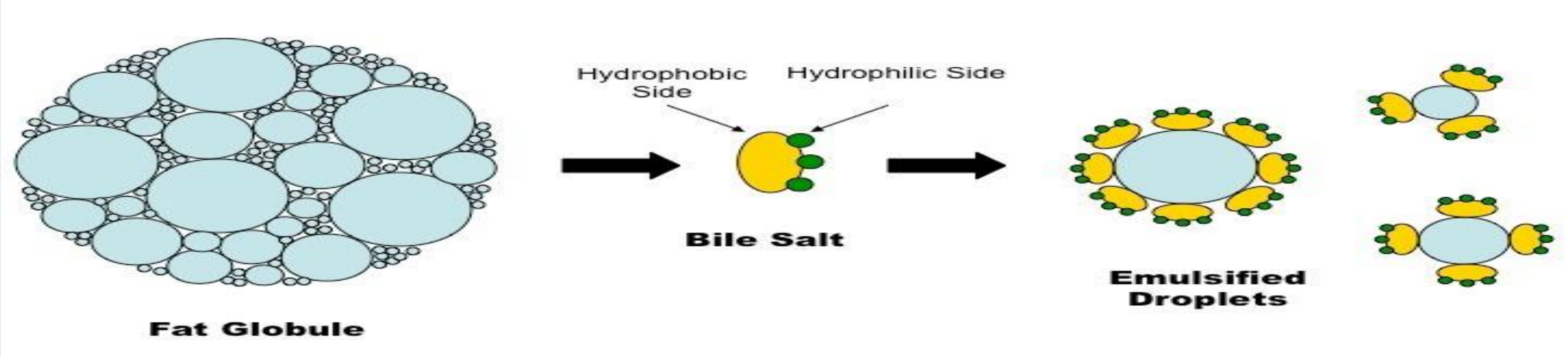
Lithocholic acid
(1 OH group)


Cholesterol
Cholic acid
Chenodeoxycholic acid
primary
primary
Deoxy-cholic acid
Secondary
lithocholic acid
Glyco-Deoxycholic
Glyco-lithocholic
Tauro-Deoxycholic
Tauro-lithocholic
Eight CONJUGATED bile acids
Glyco-cholic
Glyco-chenodeoxycholic
Tauro-cholic
Tauro-chenodeoxycholic

Functions of bile acids/salts

1. The main function of bile acids is to act as **powerful detergents** or **emulsifying agents** in the intestines to aid the **digestion and absorption** of ***fatty acids***, ***monoacylglycerols***, ***fat-soluble vitamins*** and other fatty products.

- As amphipathic molecules, conjugated bile salts sit at the lipid/water interface to form **micelles** and can **solubilize lipids**.
- Bile acid-containing micelles aid **lipases** to digest lipids.



Functions of bile acids/salts

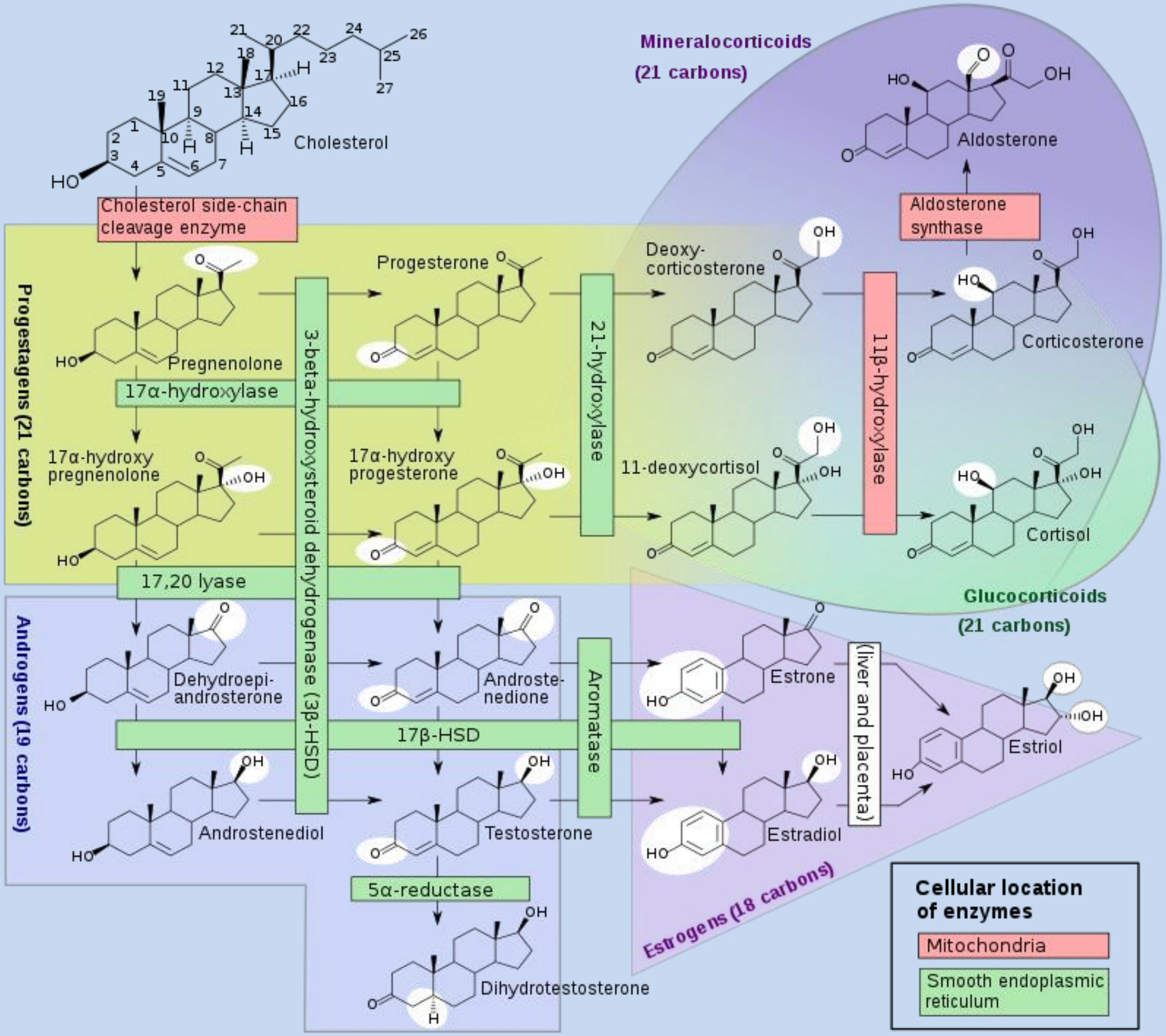
2. Prevent the precipitation of cholesterol in bile.

3. This is the major pathway for the removal of cholesterol from the body as ~ 5% of bile acids is lost into the faeces.

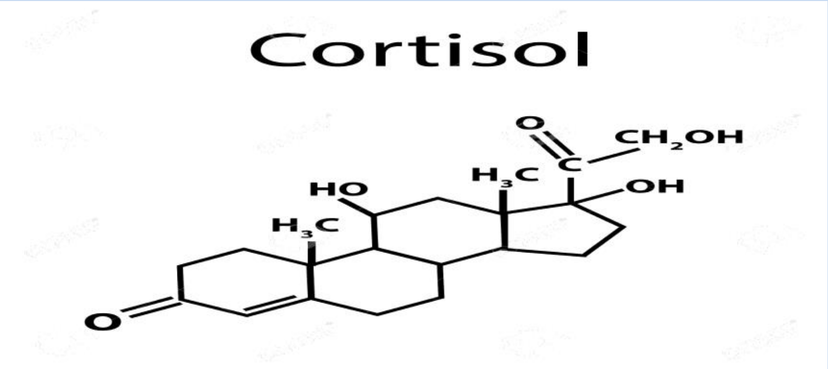
4. bile acids act as signaling molecules.

- **They have an influence on the metabolism of lipids and of glucose.**

Steroid Hormones



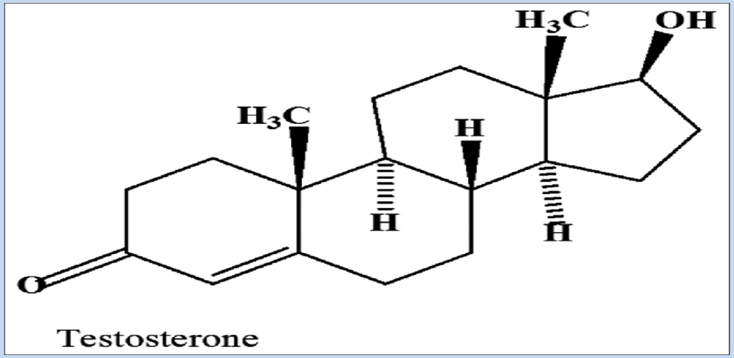
Corticosteroids:



Corticosteroids are a class of steroid hormones that are produced in the adrenal cortex of vertebrates.

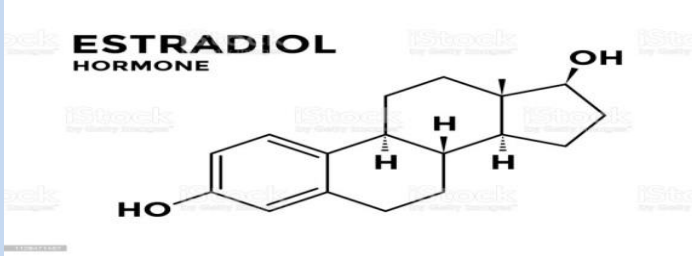
Male sex hormones:

Testosterone



Testosterone is a hormone found in humans, as well as in animals. The testicles primarily make testosterone in men. Women's ovaries also make testosterone, though in much smaller amounts.

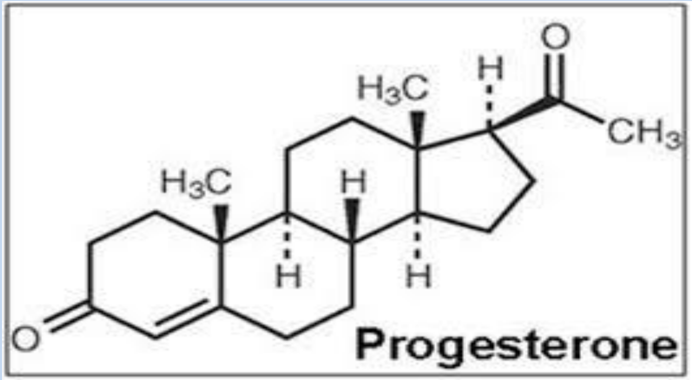
Female sex hormones:
Estradiol



Estradiol , also spelled oestradiol, is an estrogen steroid hormone and the major female sex hormone.

Estradiol is responsible for the development of female secondary sexual characteristics such as the breasts, widening of the hips, and a female-associated pattern of fat distribution

Female sex hormones:
Progesterone



Progesterone is an endogenous steroid and progestogen sex hormone involved in the menstrual cycle, pregnancy, and embryogenesis of humans and other species.

Progesterone has a variety of important functions in the body.