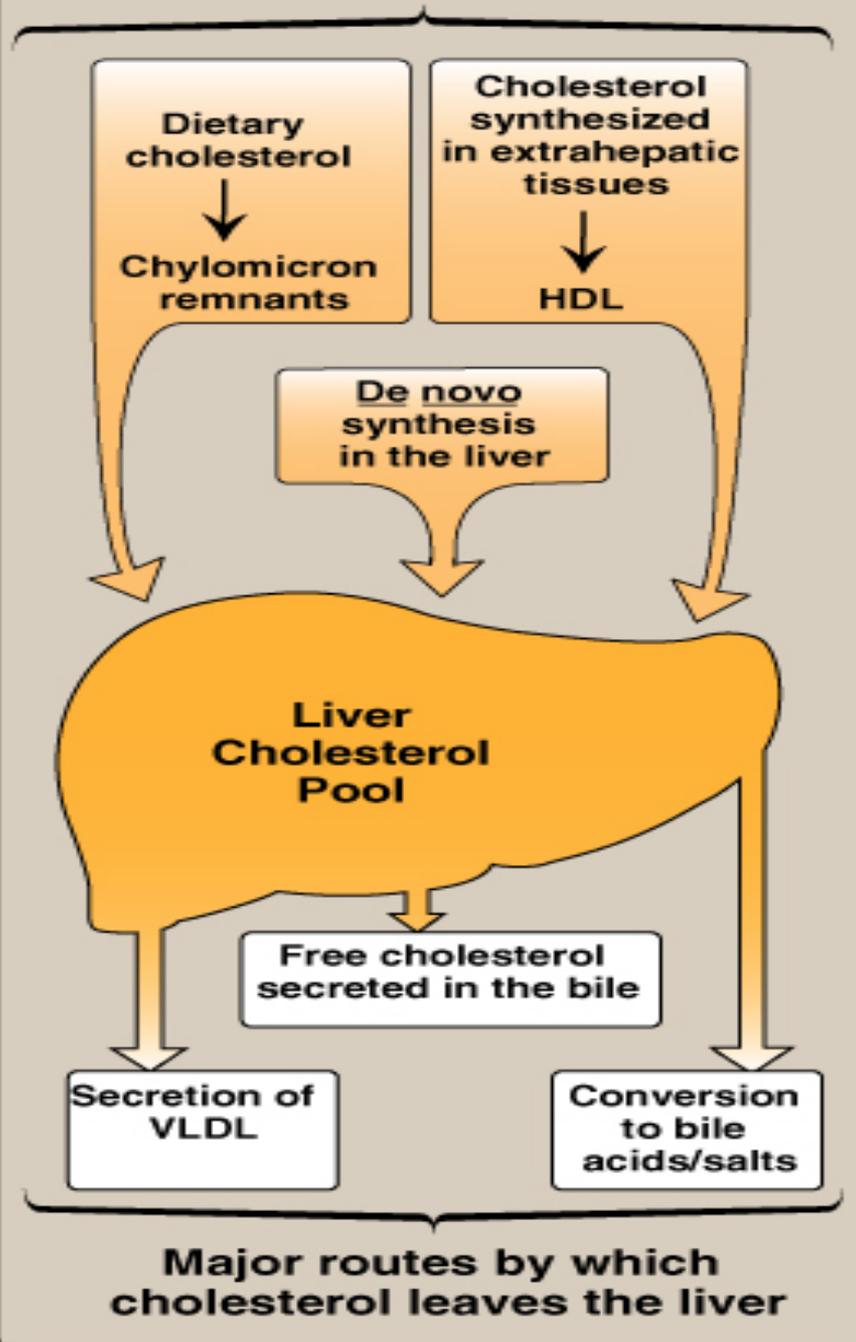
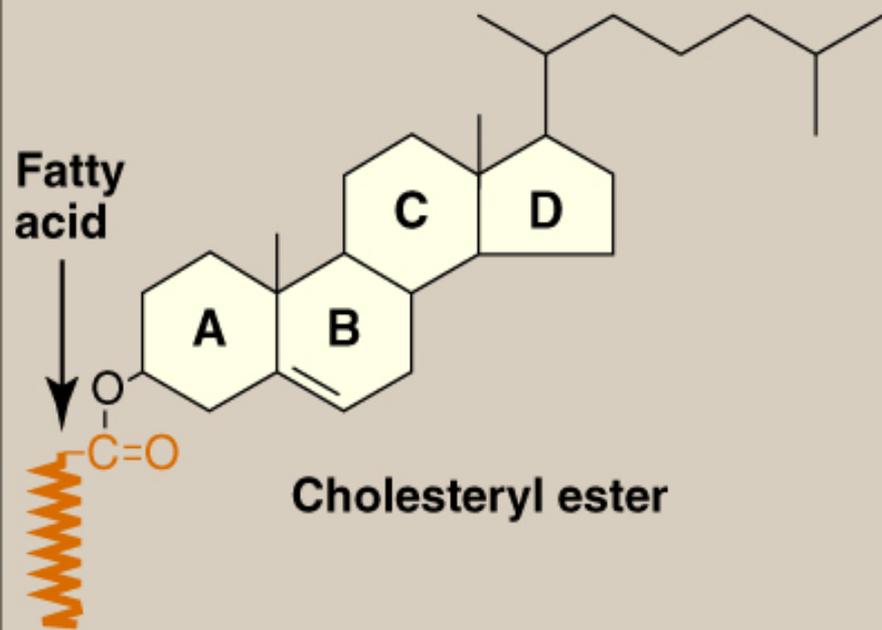
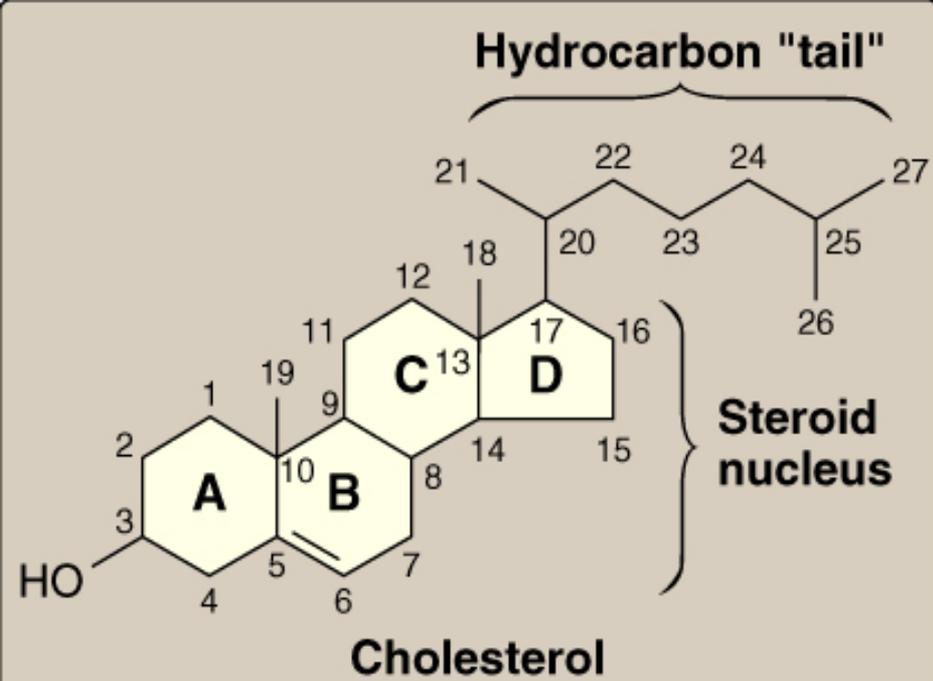


Major sources of liver cholesterol



Cholesterol and Steroid Metabolism

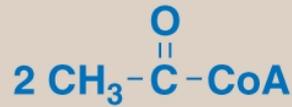
Cholesterol is synthesized by virtually all tissues with the greatest contributions made by liver, intestine, adrenal cortex, and reproductive tissues. It is a component of all cell membranes and functions as a precursor of bile acids, steroid hormones, and vitamin D. The liver plays a central role in the regulation of body's cholesterol balance. Cholesterol enters the liver by numerous routes, diet, de novo synthesis in liver and from extrahepatic tissues. It is eliminated as unmodified cholesterol in bile, bile acids and as components of plasma lipoproteins (see figure).



Cholesterol consists of four fused rings identified as A-D. It has 27 carbons, 8 of which constitute the hydrocarbon tail or branched from the D ring. **Sterols** are classified as having 8-10 carbon attached to carbon 17 and a OH group at C-3. A plant sterol β -sitosterol is poorly absorbed by humans. They can block the uptake of cholesterol in the intestine. Much of plasma cholesterol is as cholesteryl ester which has a fatty acid on C-3 (see figure).

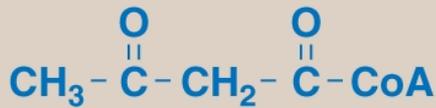
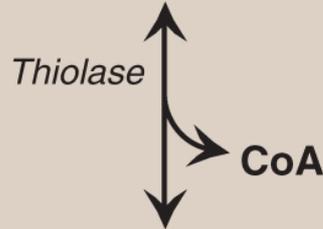
Synthesis of Cholesterol

All carbons in cholesterol synthesis are provided by acetate and NADPH provides the reducing equivalents. The formation of HMG CoA was previously studied in the section on the formation of Ketone bodies. Synthesis occurs in the cytoplasm with enzymes in both the cytoplasm and ER. Excessive secretion of Cholesterol into the bile could result in precipitation of cholesterol in the gall bladder and bile duct. The first two rxs are shown in this figure. The result is the formation of 3-hydroxy-3-methylglutaryl Co A. Liver parenchymal cells contain two isoforms of HMG Co A synthase. The cytosolic participates in cholesterol synthesis while the mitochondria form participates in the ketone body synthesis. The next step is the formation of Mevalonic acid (mevalonate).



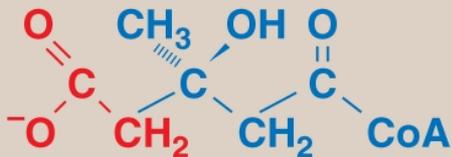
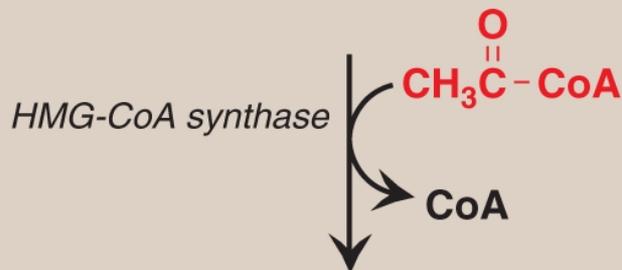
2 Acetyl CoA

(2C)



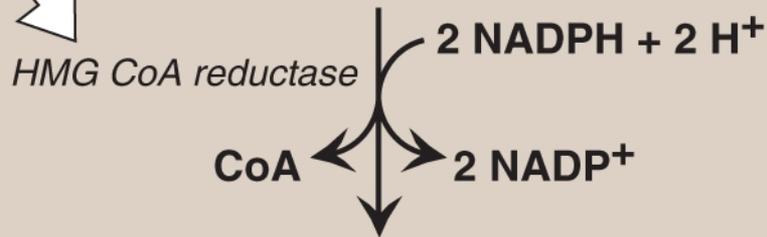
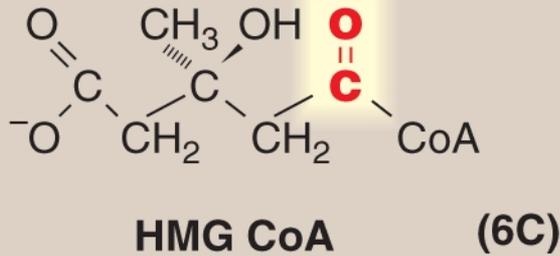
Acetoacetyl CoA

(4C)

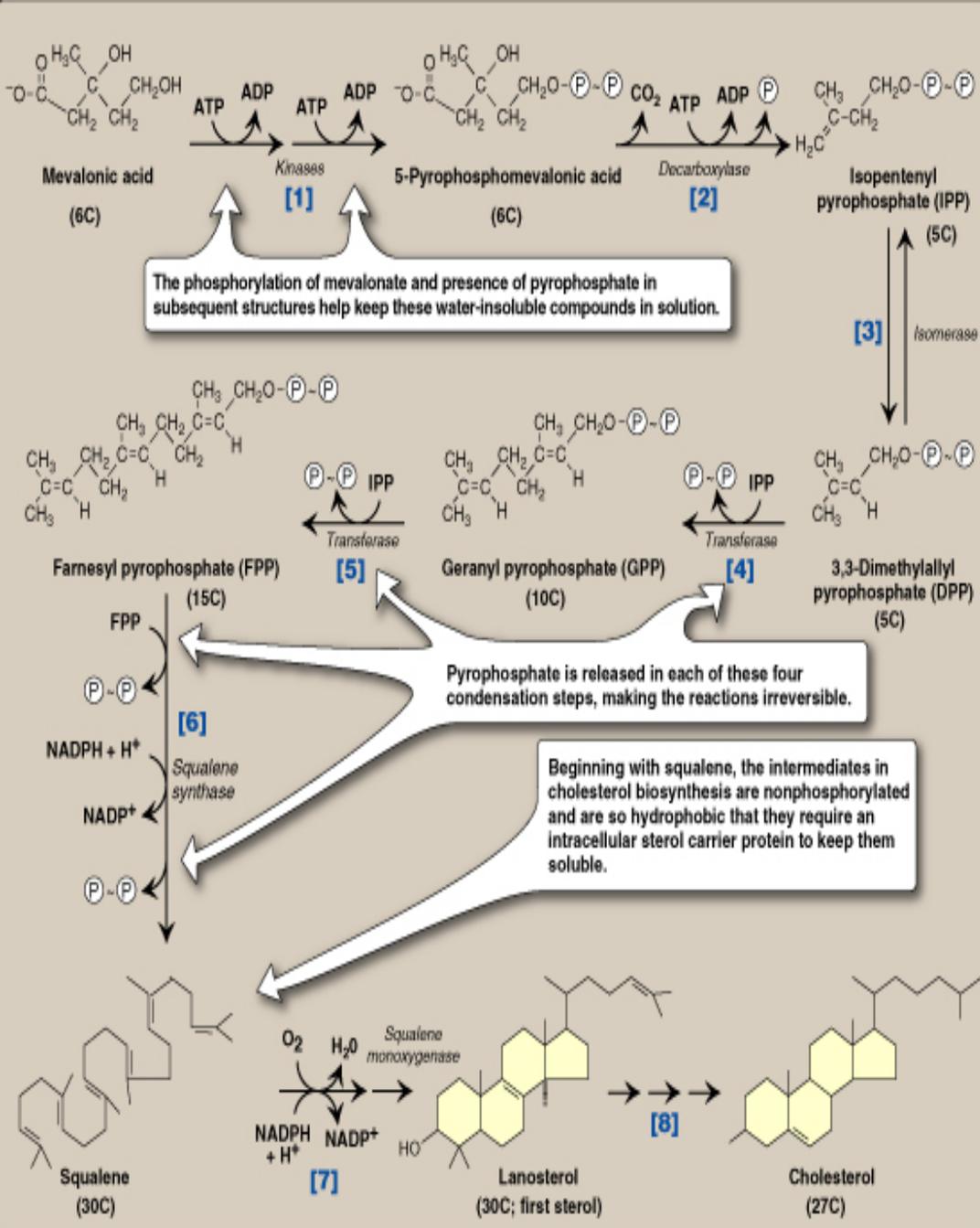


3-Hydroxy-3-methylglutaryl CoA (6C)
(HMG CoA)

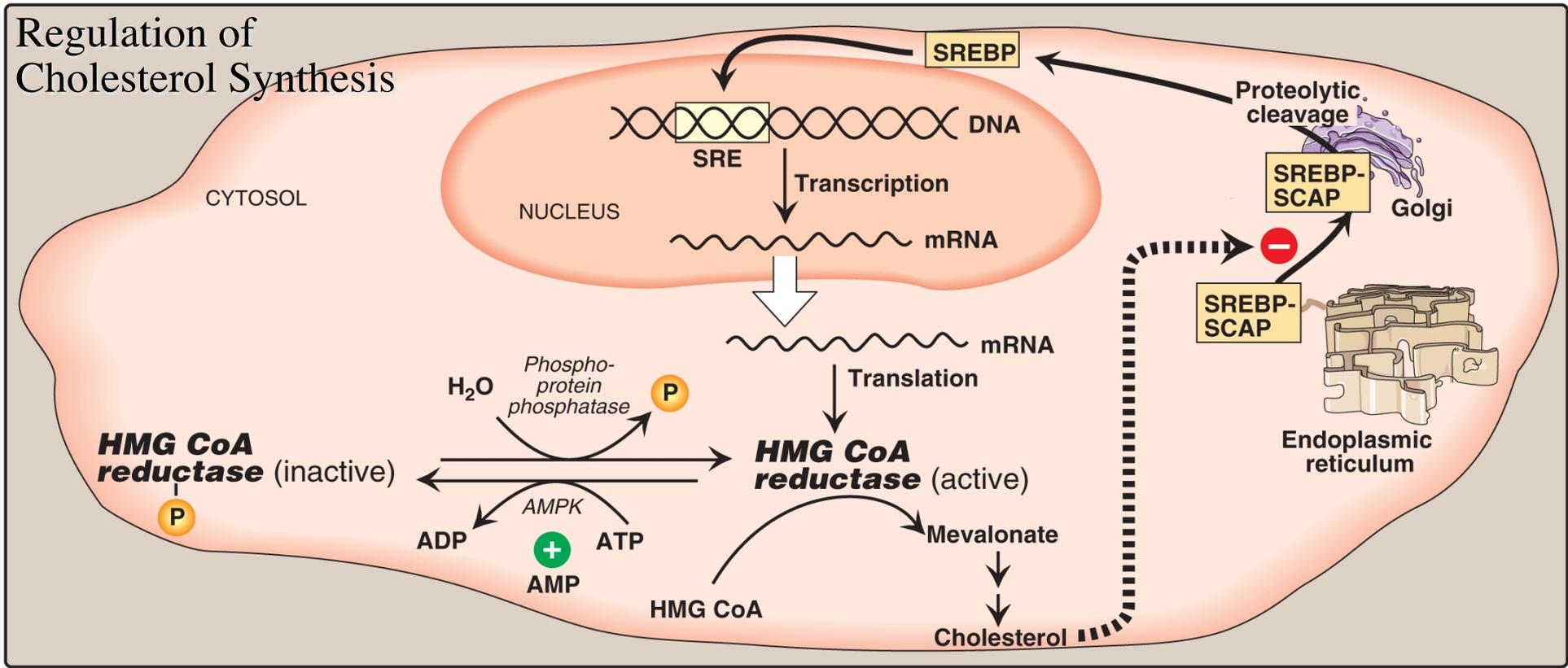
Expression is inhibited by cholesterol



The formation of mevalonic acid is catalyzed by HMG CoA reductase and it is the rate limiting step in Cholesterol synthesis.



1. Mevalonic acid is converted to 5-pyrophosphomevalonate in two phosphorylation.
2. A 5 carbon isoprene unit, isopentenyl pyrophosphate (IPP) is formed by decarboxylation requiring ATP.
3. IPP is isomerized to 3,3-dimethylallyl pyrophosphate (DPP)
4. IPP & DPP condense to form geranyl pyrophosphate (GPP)
5. A second molecule of IPP then condenses with GPP to form farnesyl pyrophosphate (FPP).
6. Two molecules of FPP (15 carbons) combine releasing pyrophosphate (PPi) and are reduced forming 30 carbon compound squalene.
7. Squalene is then converted to lanosterol using O_2 and NADPH. Hydroxylation of squalene triggers the cyclization of lanosterol.
8. The conversion of lanosterol to cholesterol is a multistep process from 30 to 27 carbon, about 19 enzyme reactions in ER.

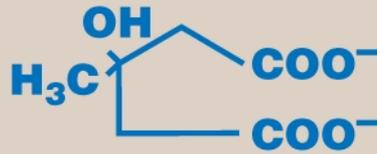


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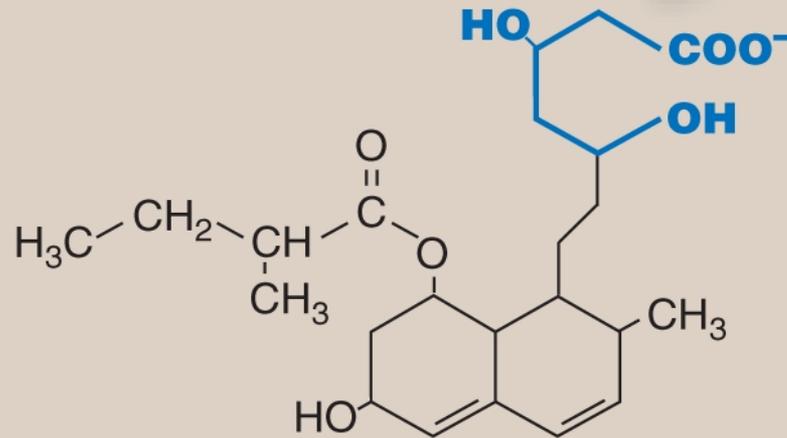
HMG CoA reductase is found in the ER with active sites in the cytosol.

1. Feedback inhibition due to high levels of cholesterol
2. glucagon favor formation of the inactive phosphorylated form of HMG CoA decreasing cholesterol synthesis. In contrast Insulin favors the unphosphorylated form increasing cholesterol synthesis. HMG CoA is also regulated at the level of gene transcription by the internalization of lipoproteins (LDL, HDL). Drugs can inhibit HMG CoA reductase, **Lovastatin** and **mevastatin**

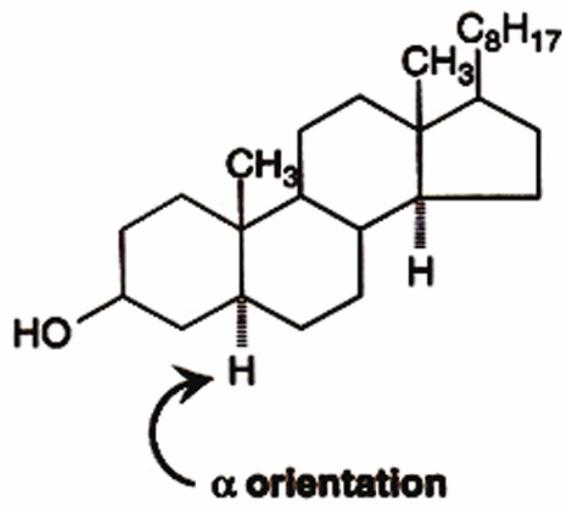
Portions of the statins (shown in blue) clearly resemble HMG-CoA. However, the bulky hydrophobic groups of the inhibitors differ from the CoA moiety of the substrate.



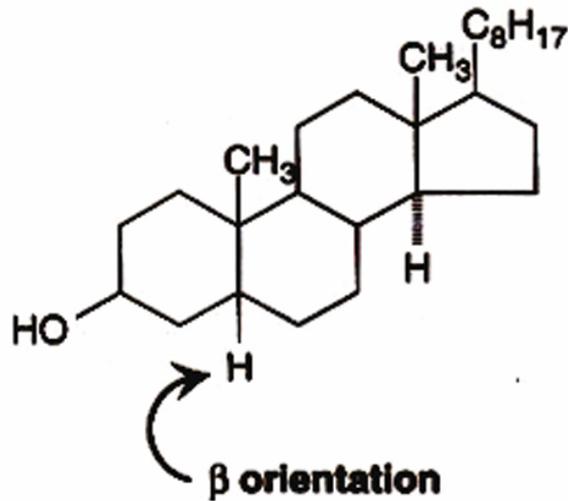
HMG



Pravastatin



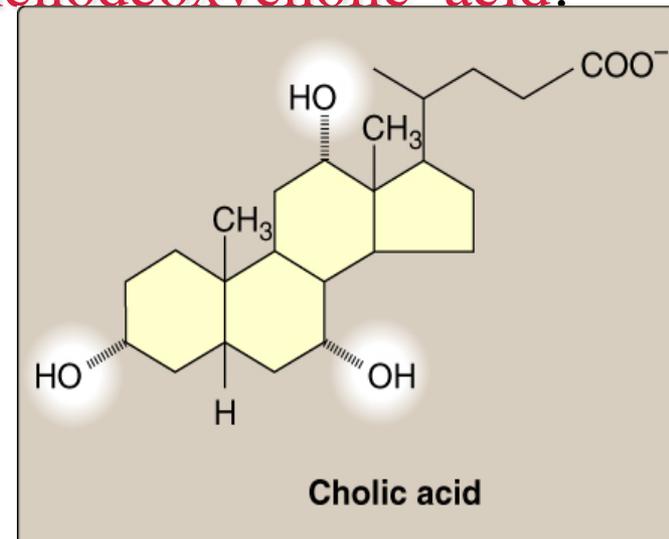
Cholestanol



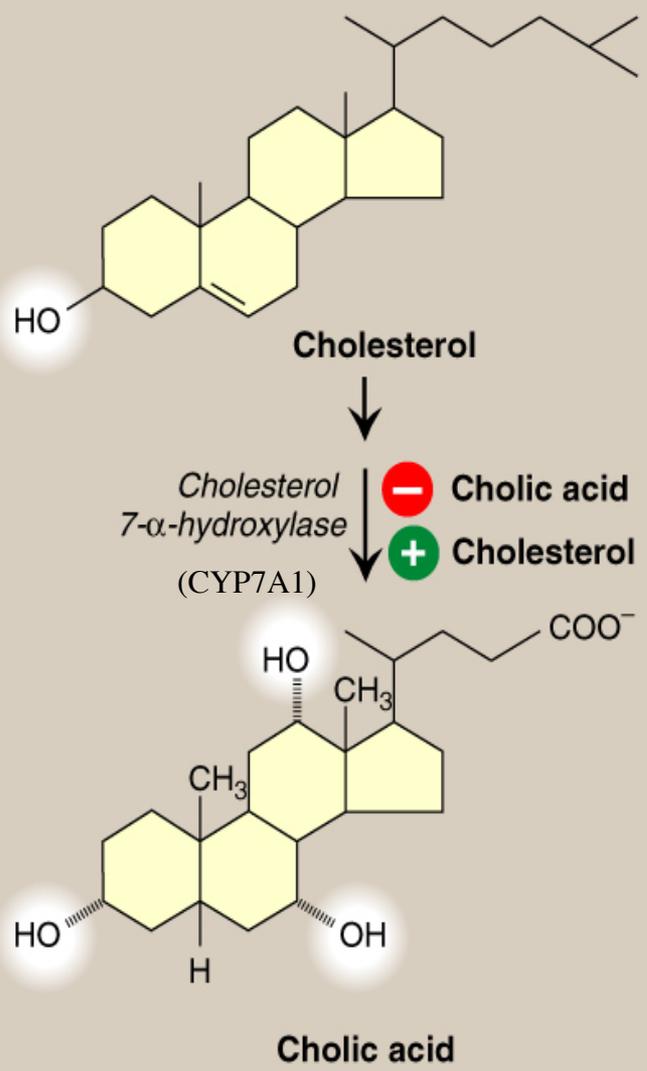
Coprostanol

Cholesterol can not be degraded to CO_2 and H_2O in humans. The sterol ring is removed by the formation of bile salts, Cholesterol is modified by bacteria in the intestine. Primary compounds formed by these bacteria are Coprostanol and cholestanol. Difference is the hydrogen orientation between A and B rings. Bile consists of organic and inorganic compounds. **Phosphatidylcholine** and bile salts are the most important components of bile. The most common bile acids are **cholic acid** and **chenodeoxycholic acid**.

Bile acids have 24 carbons with two or three hydroxyl groups and a side chain with a terminal carboxyl group.

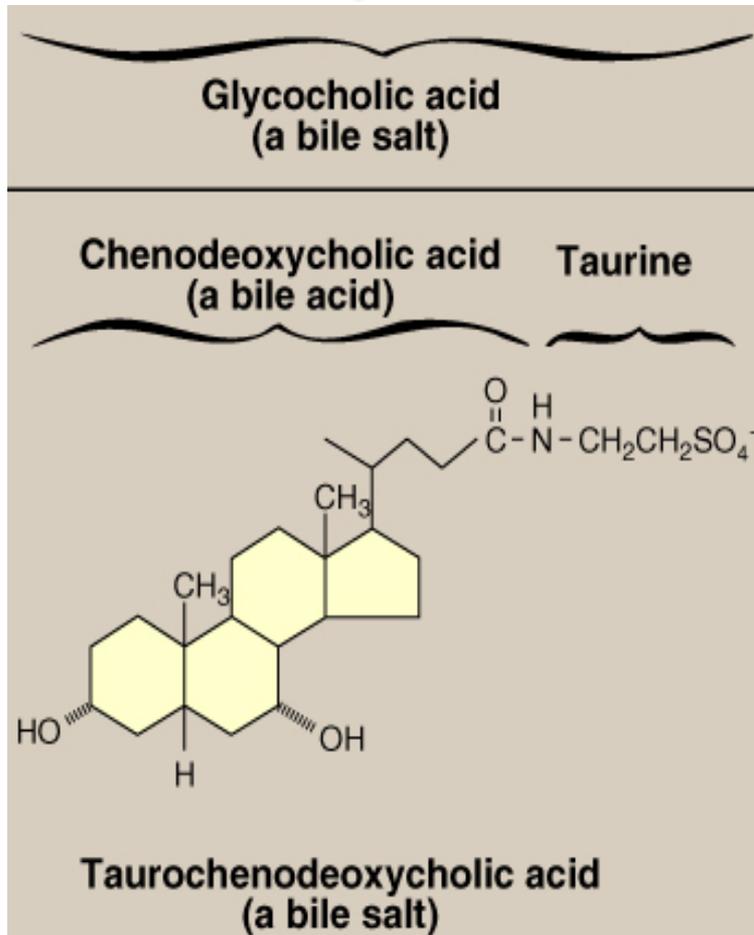


Cholic acid

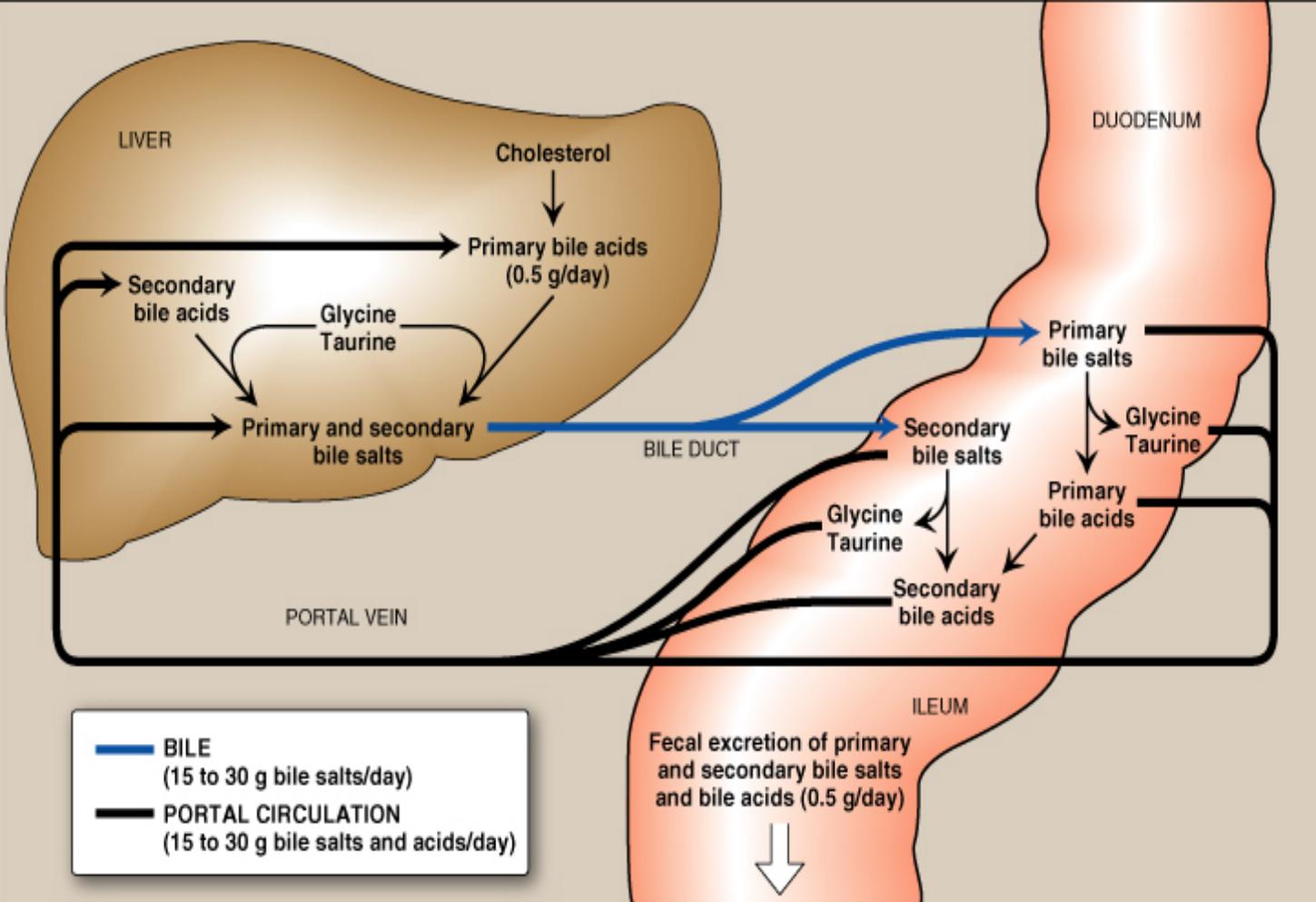


The following bile acids are primary bile acids. The reaction shown is the rate limiting step in the formation of bile acids which is the introduction of hydroxyl group at the carbon 7 of the steroid ring by **7- α -hydroxylase** (CYP7A1) which is inhibited by cholic acid.

Bile acids are conjugated by an amide bond with **taurine** or **glycine** to form bile salts. Glycocholic and glycochenodeoxycholic acids as well as taurocholic

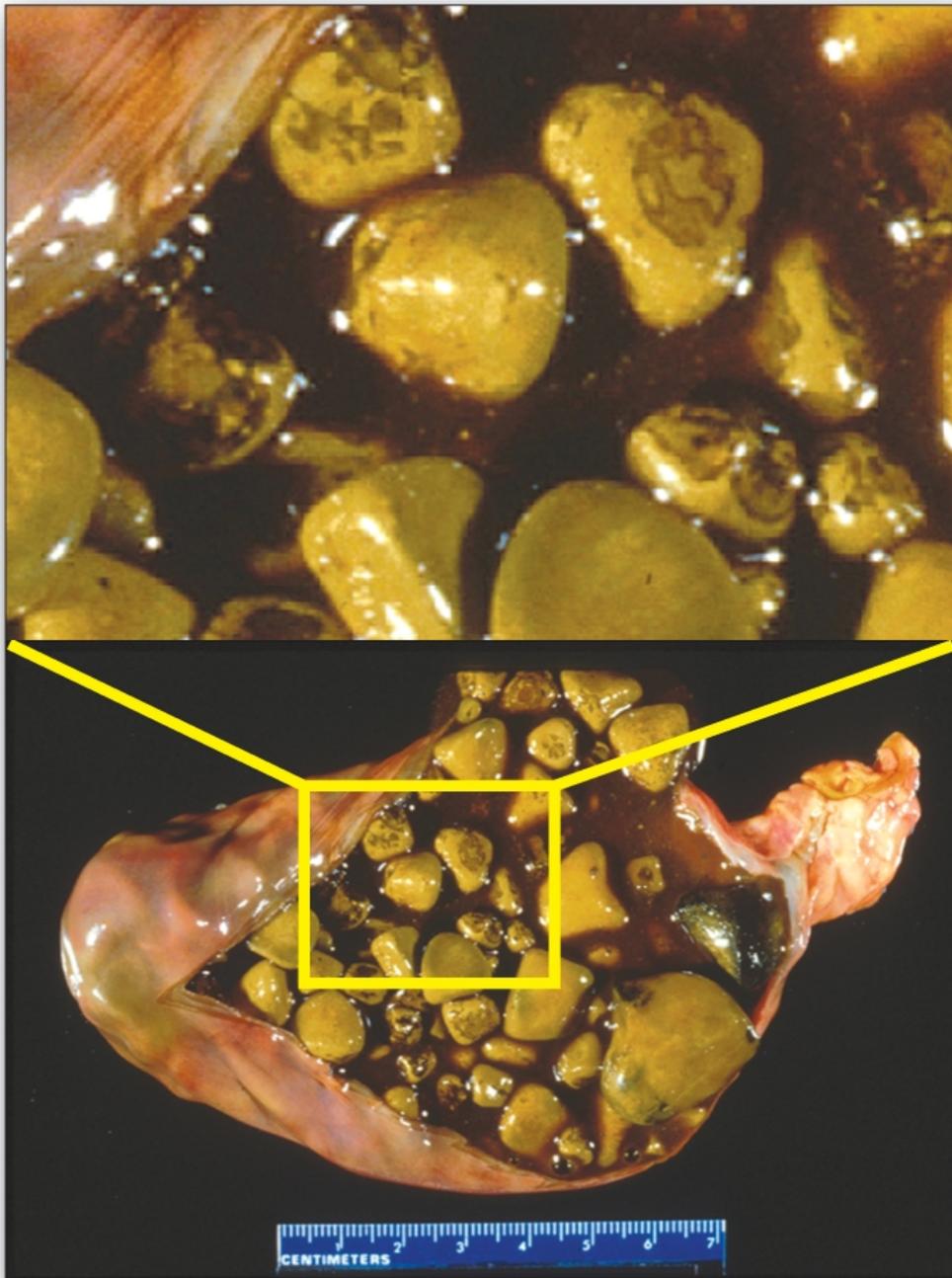


and taurochenodeoxycholic acids. Bacteria in the intestine can remove glycine and taurine from bile salts (deoxycholic acid)



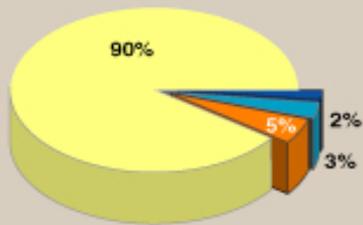
Bile salts secreted to the intestine are reabsorbed. Bile salts are converted to primary or secondary bile acid in the intestine where they are reabsorbed and passed to the

Liver where they are reconverted to bile salts and secreted into the gall bladder or intestine. This cycle is referred to as **enterohepatic circulation**. Between 15 and 30 g of bile salts are secreted from the liver into the duodenum each day, only about 0.5 g is lost daily in the feces. This amount is re-synthesized in the liver to compensate for this lost.



Cholelithiasis: cholesterol gallstone disease. Caused by the malabsorption of bile acids from intestine, obstruction of biliary tract, severe hepatic dysfunction leading to decreased synthesis of bile salts, or excessive feedback suppression of bile acid synthesis. Surgical removal of gallbladder was only treatment, now treatment with chenodiol as supplement of bile acid resulting in gradual dissolution of gallstone.

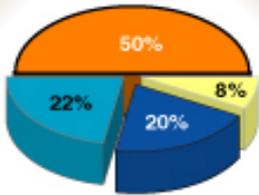
Plasma lipoproteins: these include chylomicrons (CM), very low density lipoprotein (VLDL), low density lipoprotein (LDL) and high density lipoprotein (HDL). The principal lipid carried by lipoprotein are triacylglycerol and cholesterol (free and esterified). Lipoproteins are constantly interchanging lipids and lipoproteins with each other. Relative composition of the various lipoproteins consist of TG, Cholesterol, proteins, and phospholipids. The biggest lipoprotein is the CM yet they are the lowest density HDL is the most dense. Class of lipoproteins range from A-H.



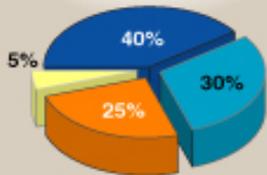
Chylomicron



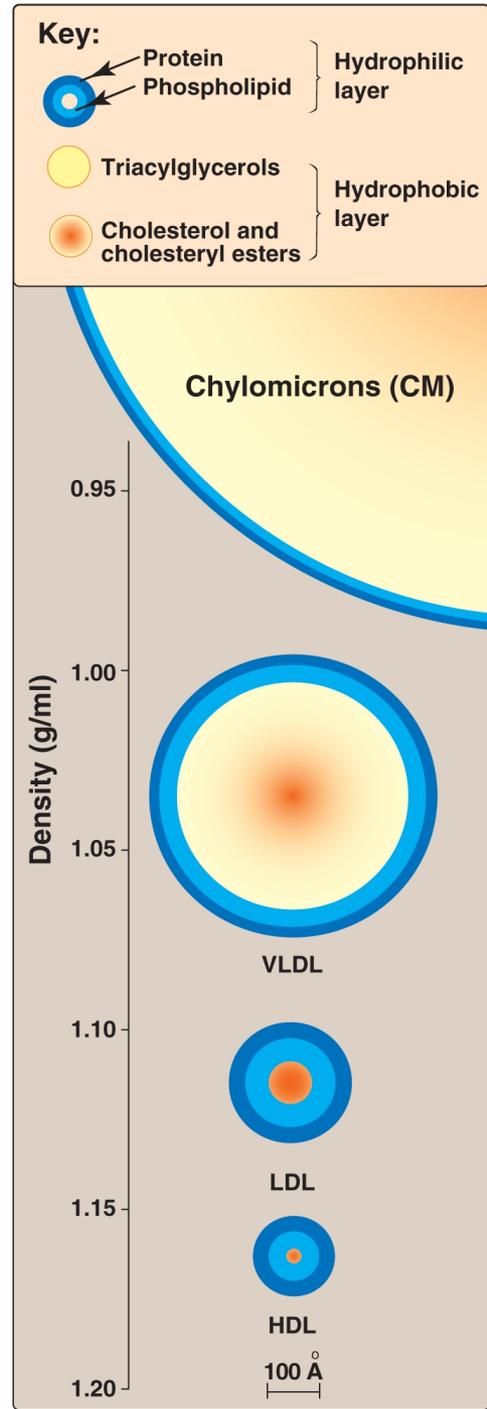
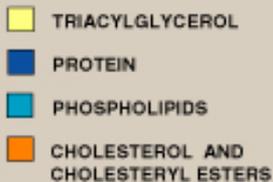
Very-Low-Density Lipoprotein (VLDL)

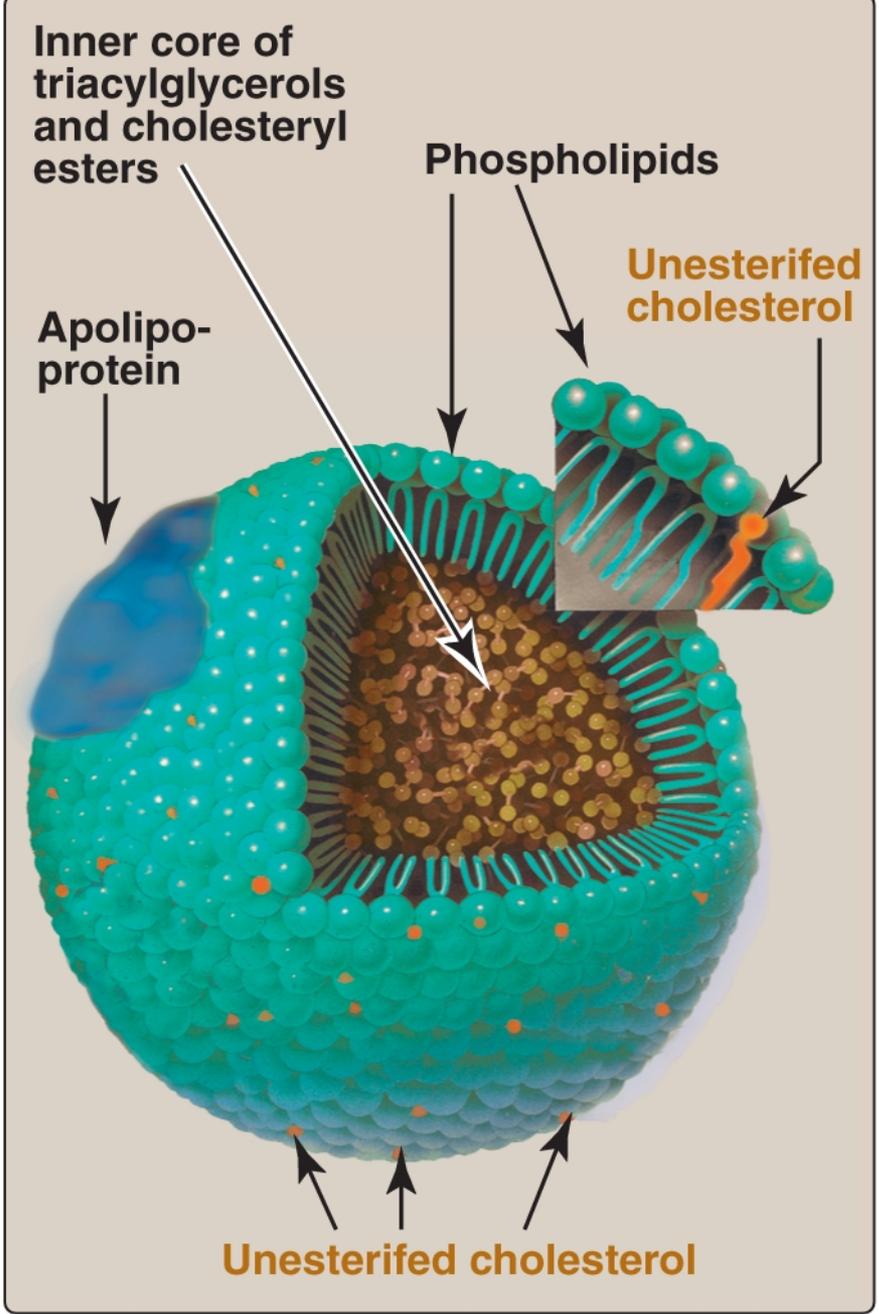
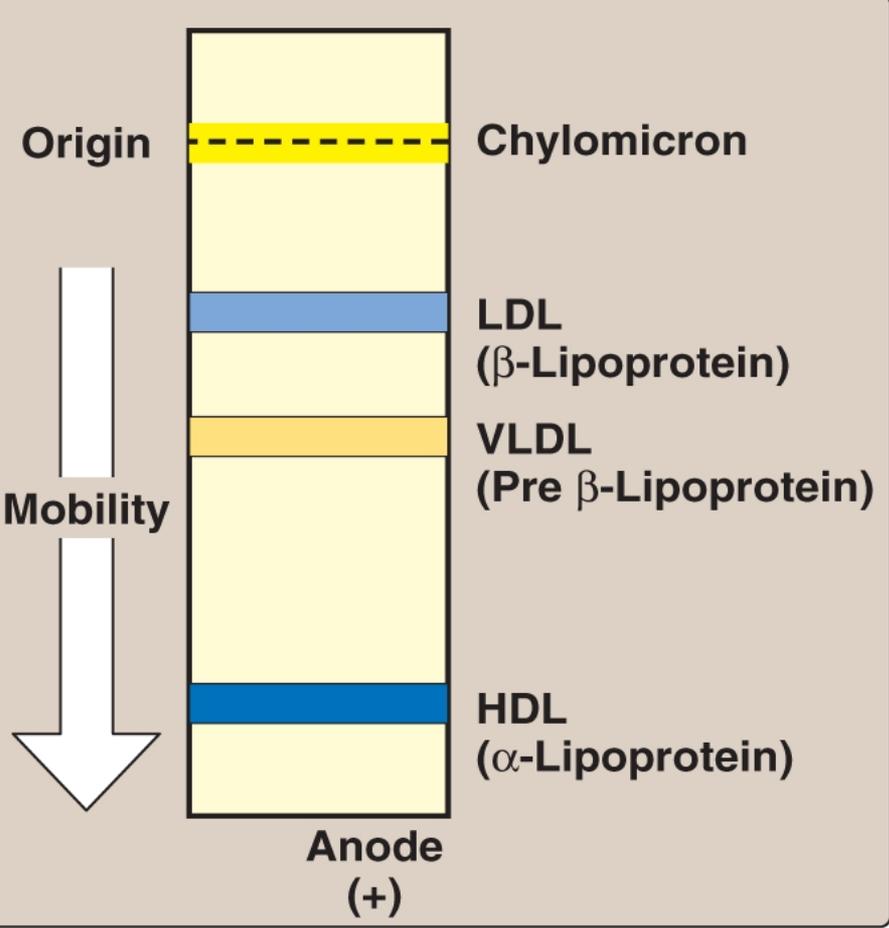


Low-Density Lipoprotein (LDL)



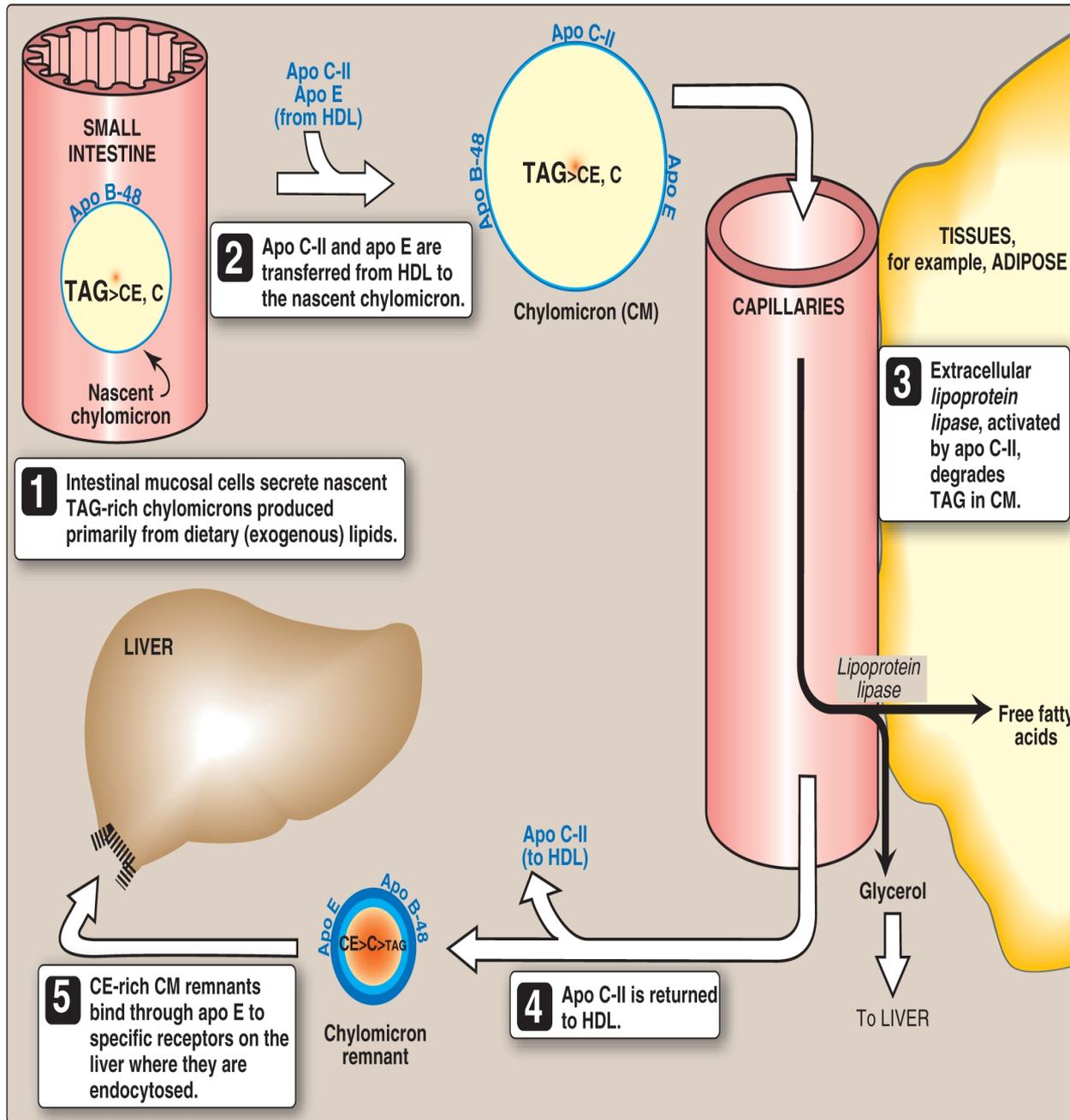
High-Density Lipoprotein (HDL)



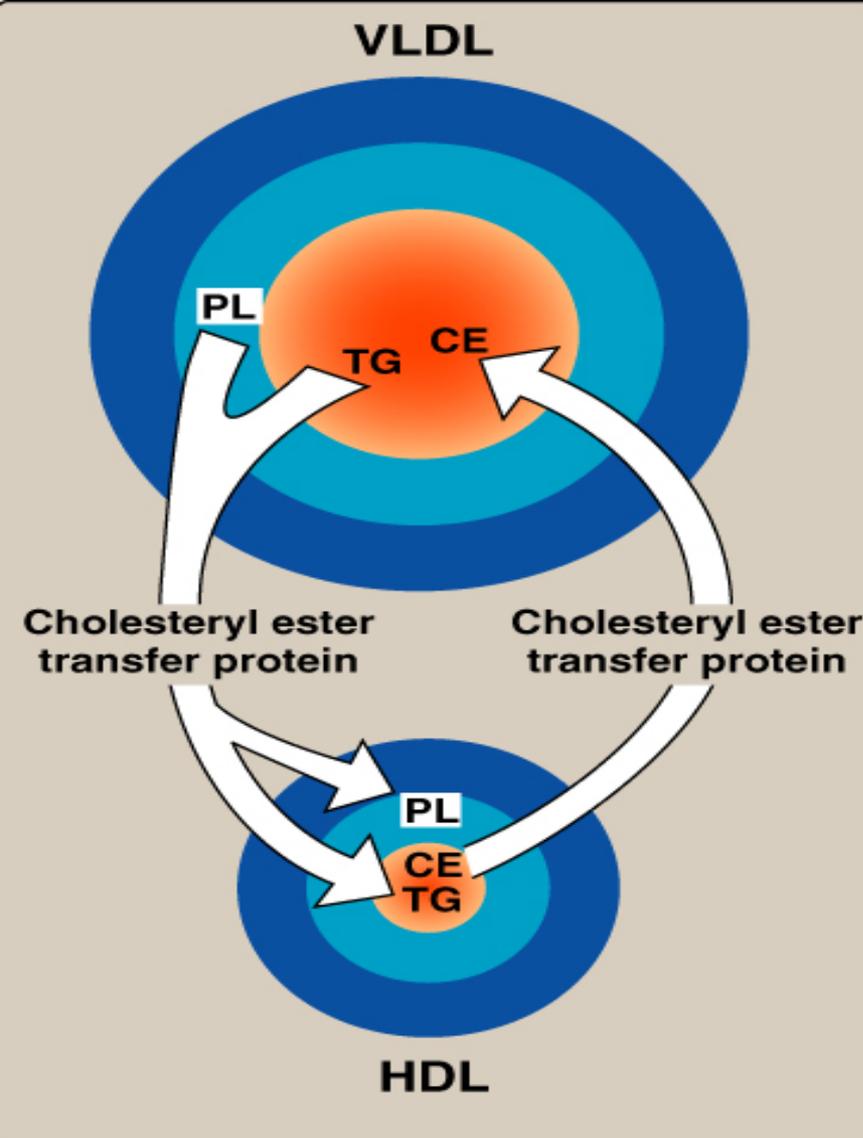


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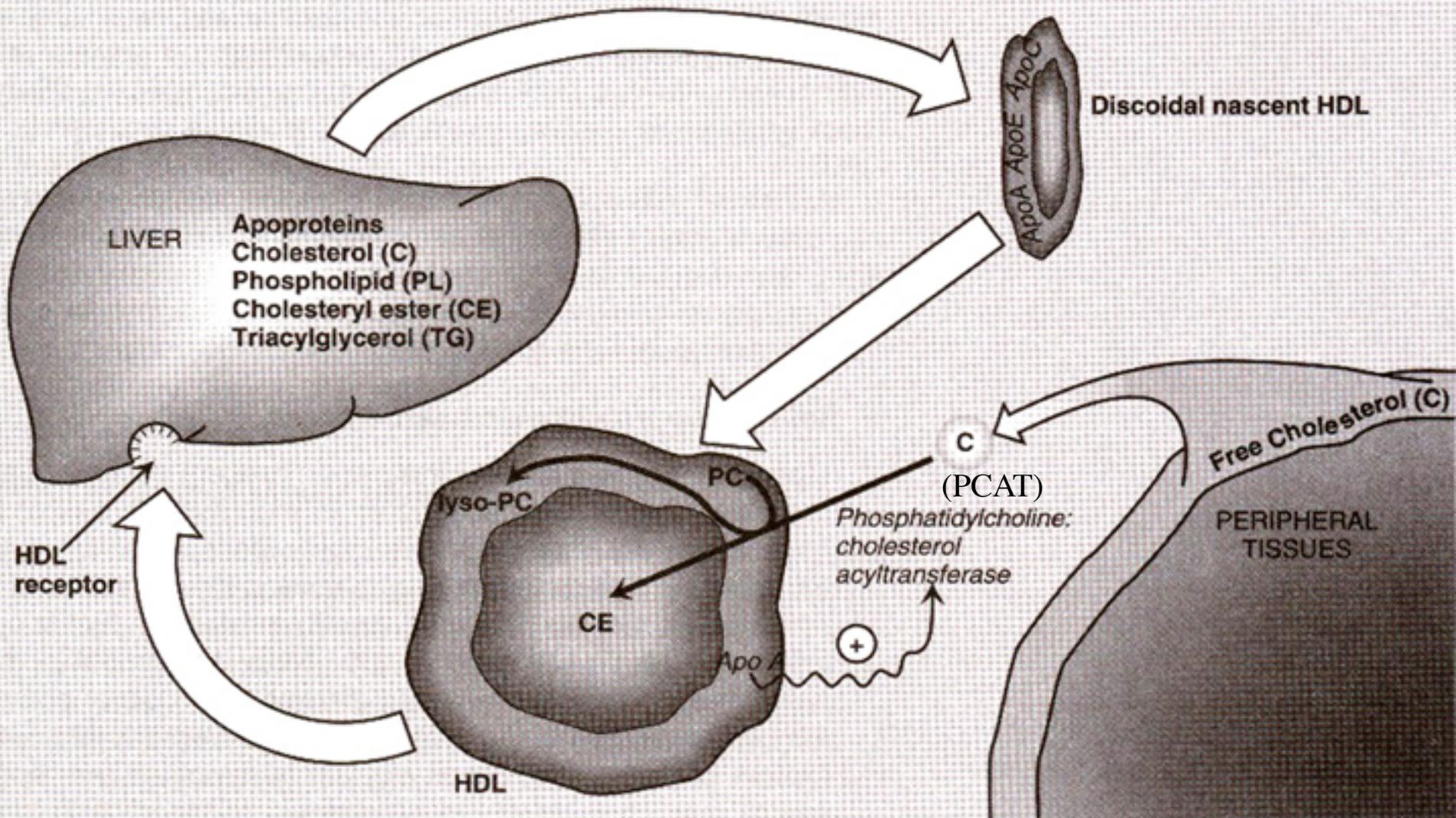


This diagram shows the metabolism of plasma lipoproteins showing the various types of exchange of apolipoproteins and lipids among these particles. Notice how the nascent CM is transformed into the CM remnant transferring ApoCII to HDL and then binding of receptors to the liver where they are endocytosed. VLDL are released from the liver and converted to LDL after releasing TG to tissues by lipoprotein lipase where this enzyme is activated by ApoCII. Receptors for LDL in muscles and liver where they are endocytosed. HDL transfers ApoCII and ApoE to VLDL and CM.

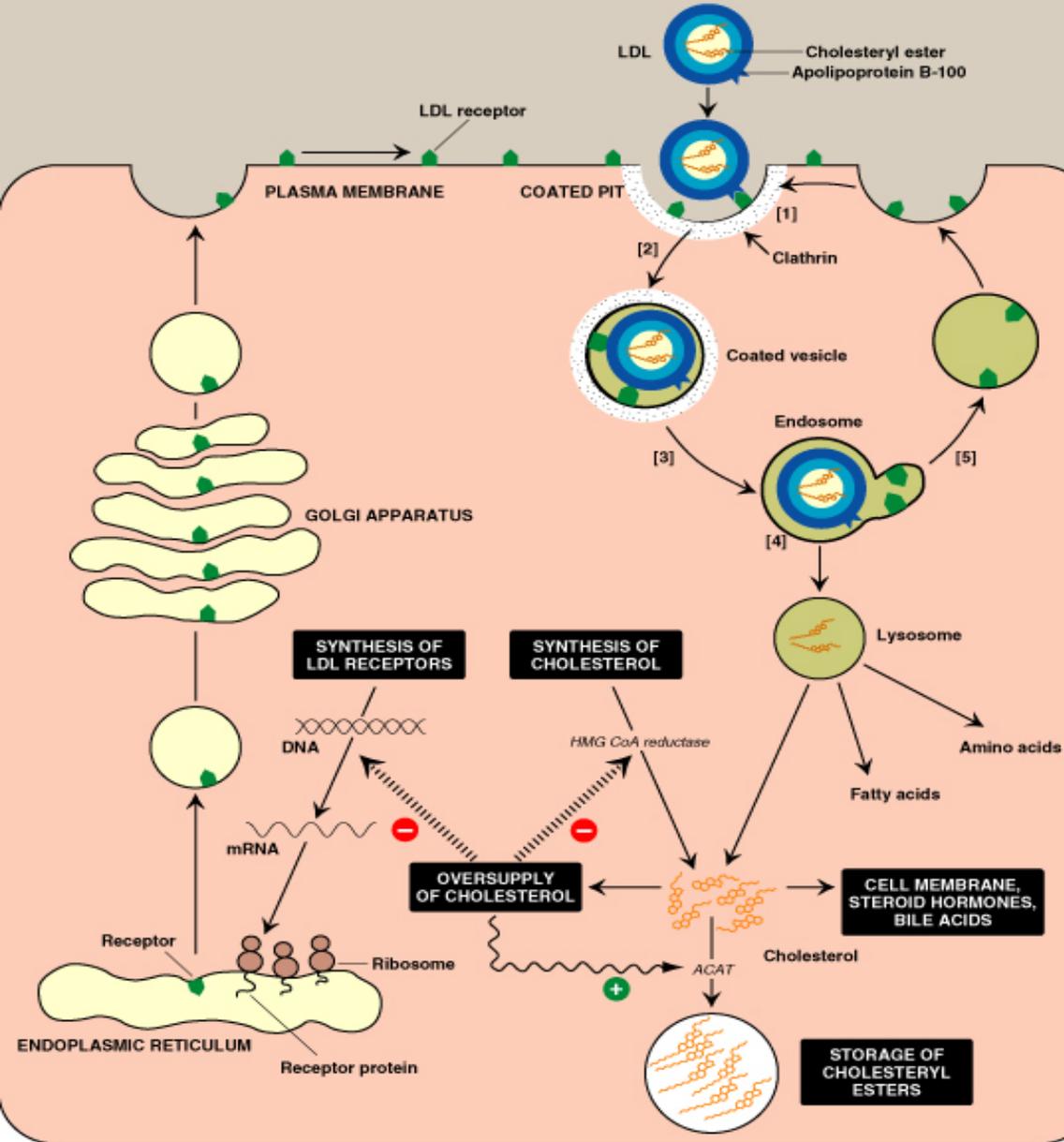


VLDL are released from the liver with ApoB100 and A-1 and need to obtain ApoCII and ApoE from circulating HDL. Triacylglycerol is removed by lipases through the body. Cholesteryl ester (CE) transfer protein exchanges CE from HDL to VLDL while triacylglycerol (TG) and Phospholipids (PL) are transferred from VLDL to HDL. LDL is formed from VLDL, IDL is an intermediate particle between these two.

Lipoprotein lipase deficiency or Apo CII result in a dramatic accumulation of triacylglycerol-rich lipoproteins in plasma type I hyperlipidemia (familial hyperchylomicronemia). ApoB100 is characteristic of LDL and VLDL particles.



HDL is synthesized by the liver (as a discoidal nascent particle) and are released by exocytosis. HDL particles serve as a circulating reservoir of ApoC-II, transferring cholesteryl ester to VLDL and LDL in exchange for triacylglycerol, carrying CE to the liver, removing free cholesterol from extrahepatic tissues and esterifying it using PCAT activated by ApoA-1. About 2/3 of cholesterol in plasma is esterified.



LDL particles are commonly referred to as the bad cholesterol. These particles retain ApoB100 and have high concentrations of cholesterol and CE. LDL provides cholesterol to peripheral tissues. LDL are transported inside cells by endocytosis via a membrane receptor that recognizes **ApoB100** in a pit area on the surface of cells coated with **clathrin** (protein). Deficiency on the function of LDL receptor causes an increase in plasma LDL, cholesterol and the chances of **atherosclerosis**. Endosomes are formed after vesicles loose their clathrin coat. Lysosome enzymes degrade the remnants of the lipoprotein releasing cholesterol fatty acids and amino acids. If cholesterol is not needed immediately it is

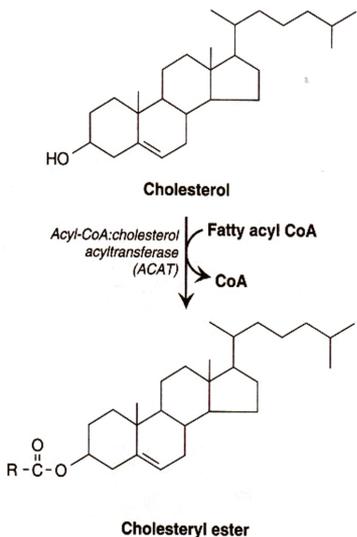
stored as CE by acyl CoA-cholesterol acyltransferase (ACAT), HMG CoA reductase is inhibited and synthesis of cholesterol is stopped. In addition LDL receptor protein is lowered by decreasing transcription of the LDL gene.

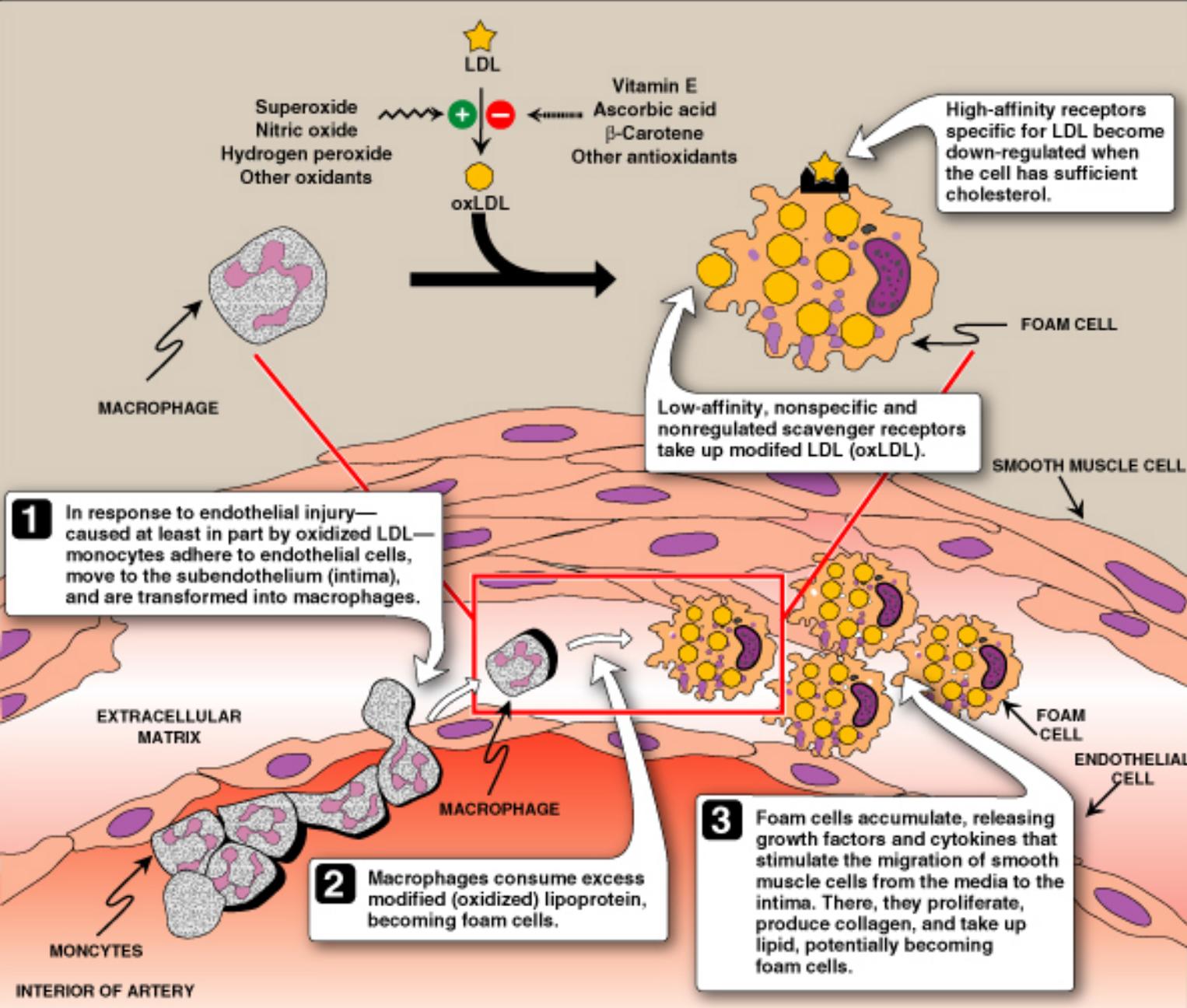
SUMMARY OF LIPASES

ENZYME	ORIGIN	SITE OF ACTION	FUNCTION	SPECIAL PROPERTIES
<i>Gastric lipase</i>	Stomach	Stomach	Degrades dietary triacylglycerols containing short-chain fatty acids	Acid-stable
<i>Pancreatic lipase</i>	Pancreas	Small intestine (lumen)	Degrades dietary triacylglycerols (removes fatty acids from carbon 1 and 3, leaving 2-monoacylglycerol)	Requires pancreatic colipase for stabilization
<i>Lipoprotein lipase</i>	Extrahepatic tissues	Surface of endothelial cells lining the capillaries	Degrades triacylglycerols circulating in chylomicrons or VLDL, releasing non-esterified fatty acids and glycerol	Can be released into plasma by heparin; activated by apoprotein C-II
<i>Hormone-sensitive lipase</i>	Adipocytes	Adipocytes (cytosol)	Degradation of stored triacylglycerols	Activated by <i>cyclic AMP-dependent protein kinase</i>
<i>Acid lipase</i>	Most tissues	Lysosomes	Removes fatty acids from lipids taken into cells during phagocytosis	Acid pH optimum

Summary of lipases and functions.

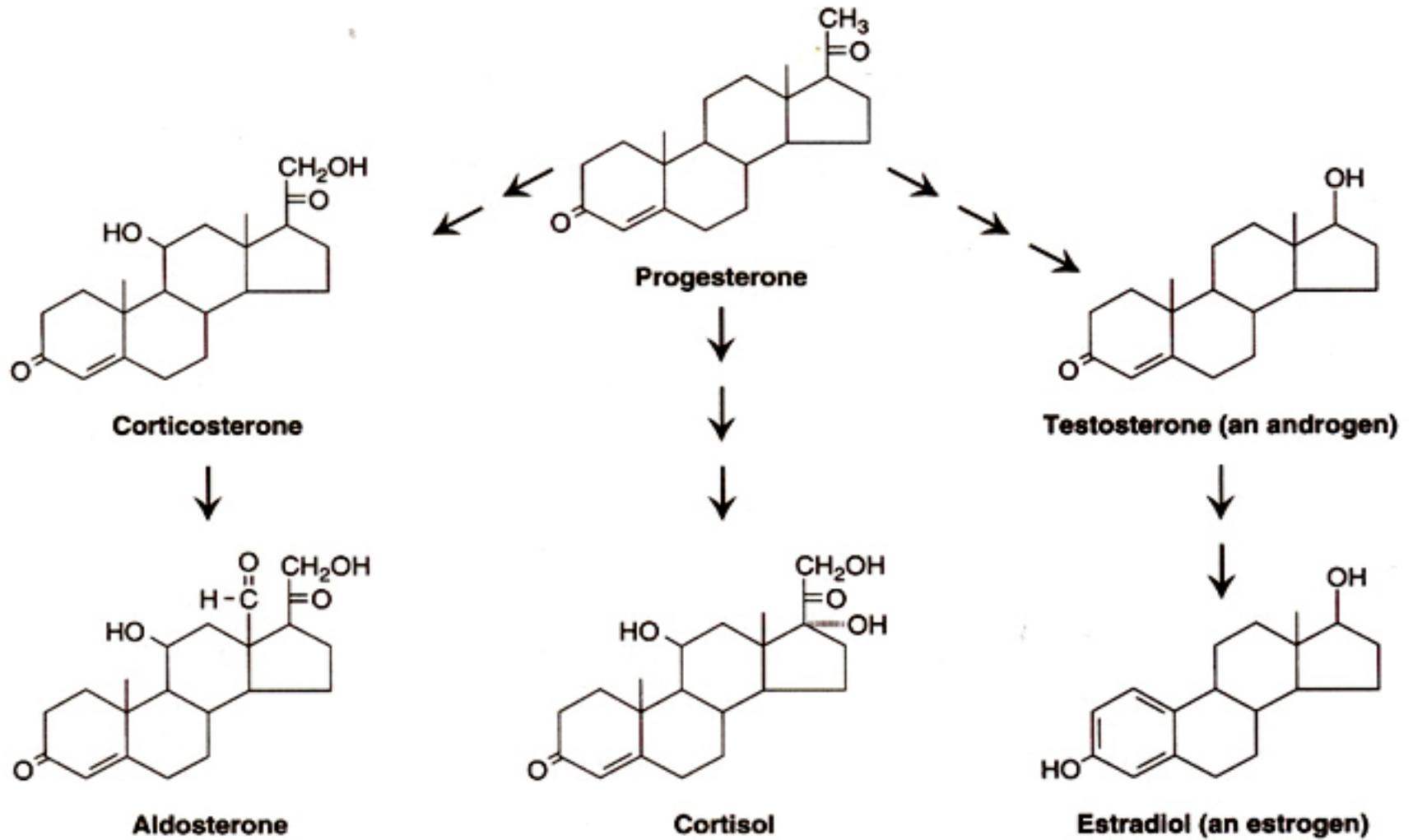
ACAT enzyme reaction which converts cholesterol to CE when cholesterol levels are high.





In addition to LDL uptake by its specific receptor, macrophages possess high levels of scavenger (see figure) receptor. Chemically modified LDL are recognized by scavenger receptors. Peroxidation of polyunsaturated fatty acids in LDL lipids can bring about acetylation or oxidation of ApoB. Since oxLDL can not

regulate intracellular cholesterol levels in macrophages excessive accumulation of cholesterol induces the formation of foam cells that leads to atherosclerosis plaques.



Cholesterol is the precursor of 5 classes of steroid hormones (see figure): glucocorticoids (cortisol), mineralocorticoids (aldosteron), androgens, estrogens and progestins. Synthesis occurs in the adrenal cortex (cortisol, aldosteron), ovaries and corpus luteus (estrogens progestins) and testes (testosterone). Specific hormone carrier proteins are transcortin (cortisol, corticosterone) sex hormone binding protein (sex steroids).

CONGENITAL ADRENAL HYPERPLASIAS (CAH)

STEROID HORMONE SYNTHESIS

3-β-HYDROXYSTEROID DEHYDROGENASE DEFICIENCY

- Virtually no glucocorticoids, mineralocorticoids, or active androgens, or estrogens.
- Marked salt excretion in urine.
- All patients have female genitalia.

17-α-HYDROXYLASE DEFICIENCY

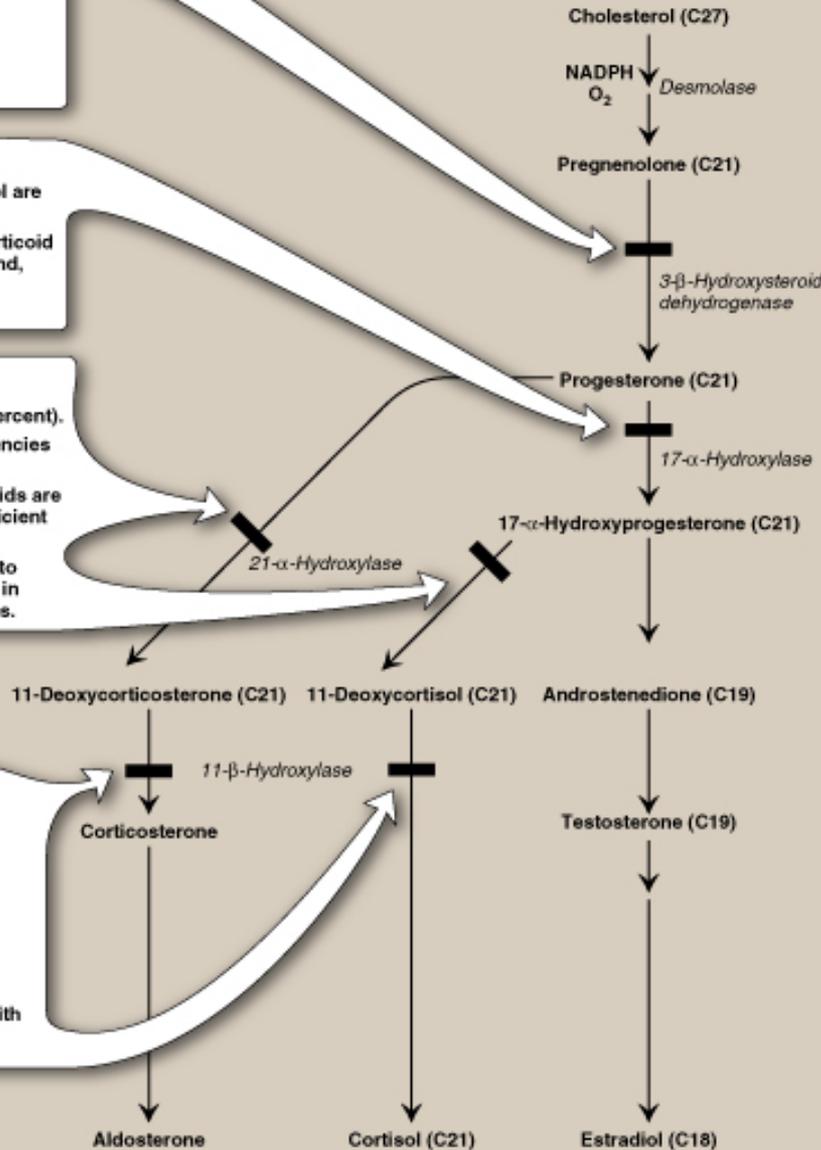
- Virtually no sex hormones or cortisol are produced.
- Increased production of mineralocorticoid causes sodium and fluid retention and, therefore, hypertension.
- All patients have female genitalia.

21-α-HYDROXYLASE DEFICIENCY

- Commonest form of CAH (>ninety percent).
- Partial and virtually complete deficiencies are known.
- Mineralocorticoids and glucocorticoids are virtually absent (classic form) or deficient (non-classic form).
- Overproduction of androgens leads to masculinization of external genitalia in females and early virilization in males.

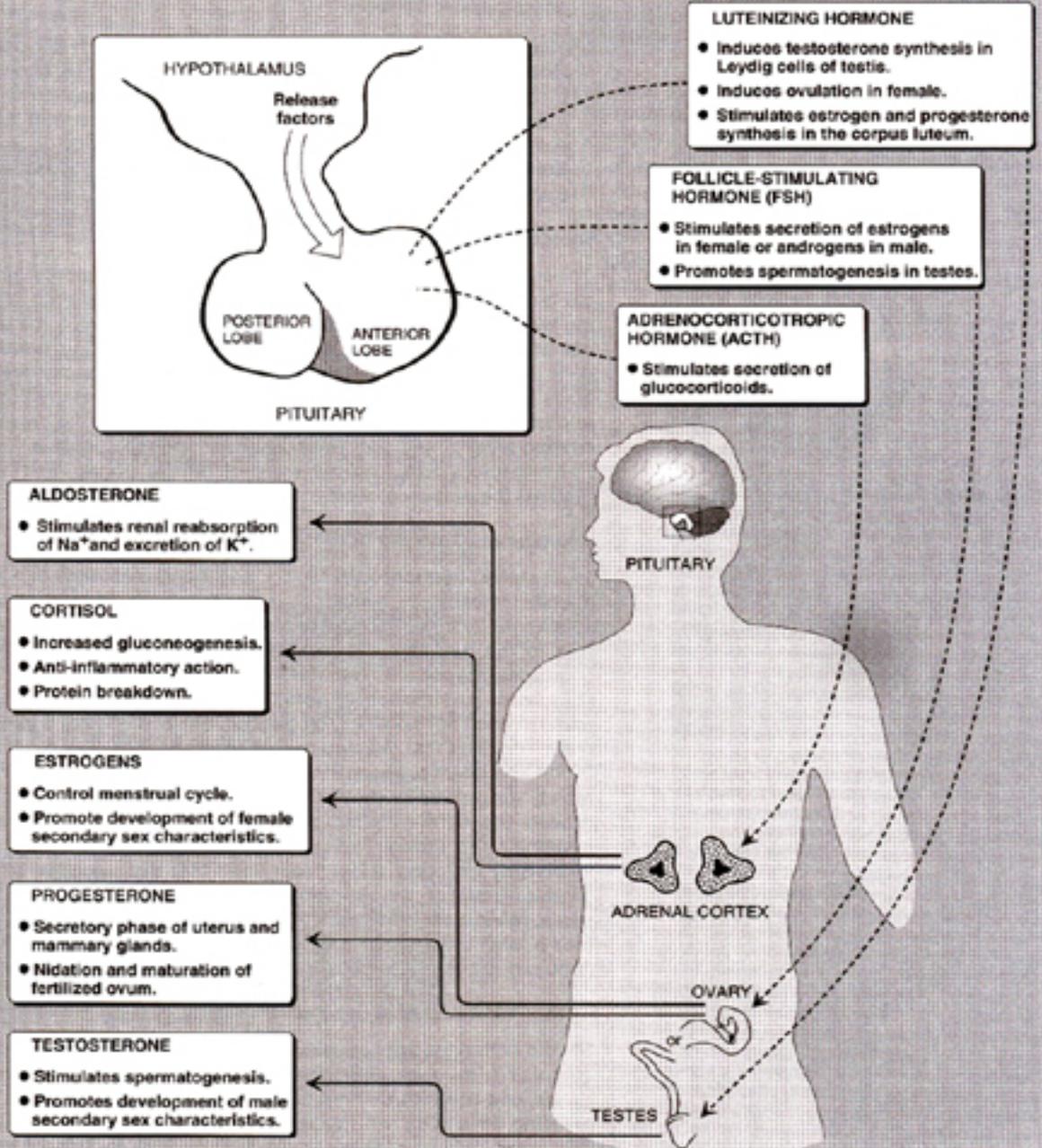
11-β-HYDROXYLASE DEFICIENCY

- Decrease in serum cortisol, aldosterone, and corticosterone.
- Increased production of deoxycorticosterone causes fluid retention. Because this hormone suppresses the renin/angiotensin system, it causes low-renin hypertension.
- Masculinization and virilization as with 21-α-hydroxylase deficiency.



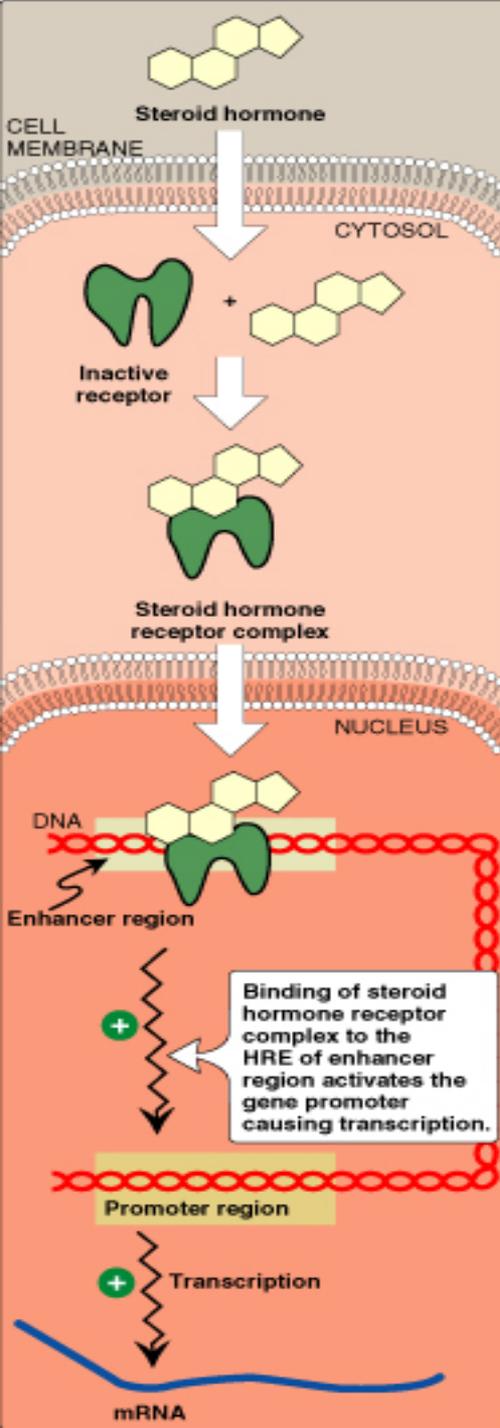
Some hormone related diseases are shown in this figure indicating the enzyme deficiency involved.

Hormone synthesis from cholesterol to pregnenolone is performed by the desmolase complex (cytochrome P450_{scc} side chain cleavage enzyme is included in this complex) This is the rate limiting step in steroid synthesis (NADPH and O₂ required). Pregnenolone is oxidized and isomerized to progesterone. Progesterone is further hydroxylized (by mixed function oxidases MFO) to other steroid hormones. Serious metabolic imbalances can occur if enzymes are deficient (see figure)



Adrenal cortical hormone is controlled by the hypothalamus which releases CRF and induces ACTH at the anterior lobe of the pituitary. ACTH is often called the stress hormone. ACTH stimulates the adrenal cortex to synthesize and secrete corticosteroids (mineralocorticoids and glucocorticoids). A summary of secretions and actions of steroid hormones is shown in the diagram. Cortisol is secreted in times of stress and generally stimulates degradation of proteins to amino acids in muscle and promotes gluconeogenesis. Aldosterone is secreted in

response to Na^+/K^+ ratios and by angiotensin (octapeptide produced by renin from angiotensinogen) secreted by kidneys. It stimulates Na retention and K excretion.



GRH stimulates the pituitary to release LH and and FSH glycoproteins. LH stimulates the testes to produce testosterone and the ovaries to produce progesterone and estrogens. FSH stimulates testicular spermatogenesis and growth of follicles.

Each hormone binds to specific receptors in the cytosol or nucleus (HRE) causing either stimulation or inhibition of activities of genes (see adjacent diagram). The effect of regulation by hormones can last for relatively long periods (hours, days). For example the uterine wall is prepared for implantation of embryo by estrogens. Many of these steroid hormones function in similar way.

Many of these hormones are converted into metabolic excretion products in the liver. Reduction of unsaturated bonds and further oxidation adding hydroxyl groups and conjugation with sulfates and glucuronic acids makes them water soluble so they can be excreted in the feces and through the kidneys.