

9. STEROID HORMONES

STEROIDS

- Steroids are one subclass of a broad group of lipids known as isoprenoids or terpenes.
- Steroids are a group of molecules derived from or having a structural relationship to cholesterol

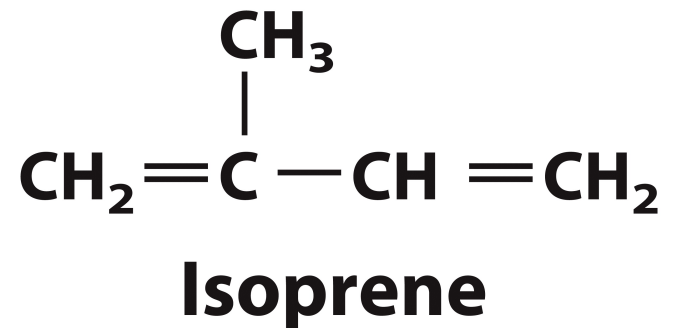
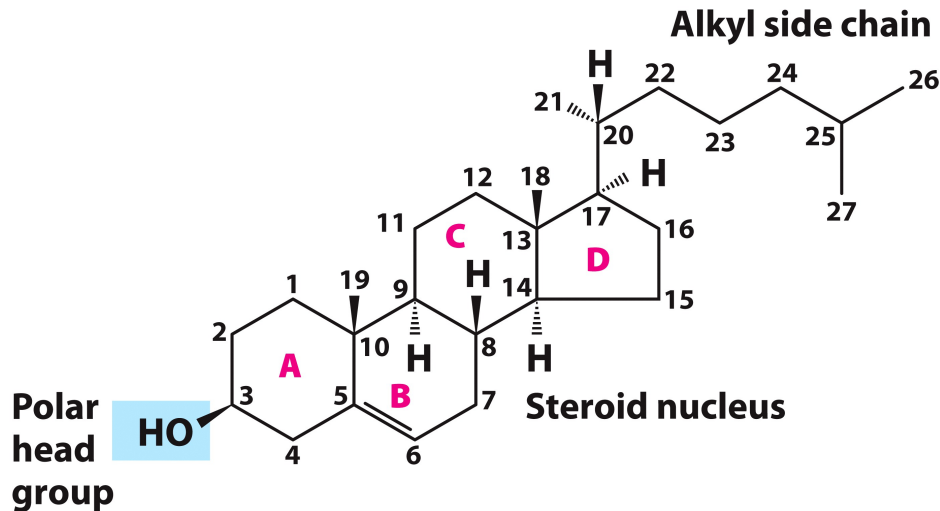


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STEROIDS

- All 27 carbons in cholesterol can be traced to a two-carbon precursor - acetate.

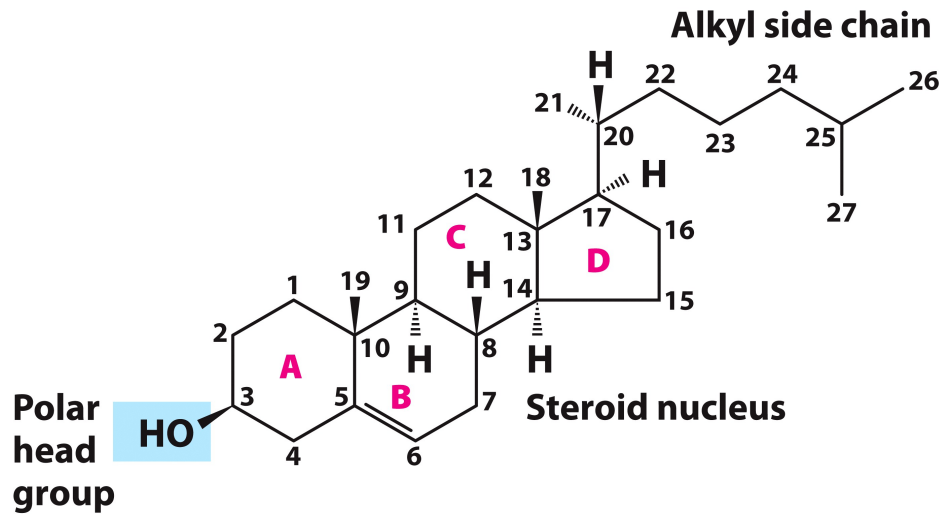


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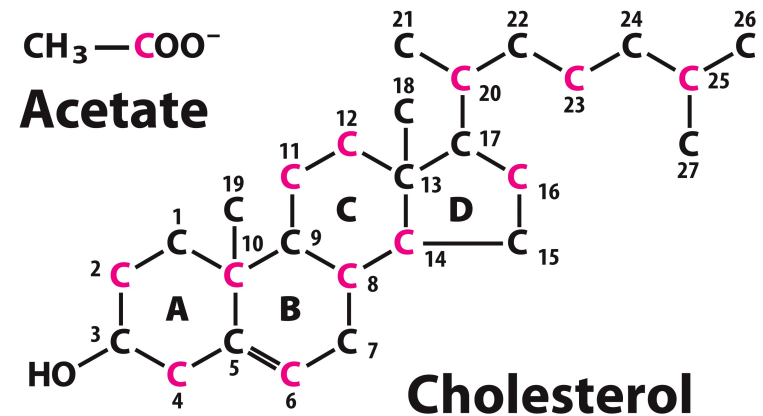


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STEROIDS BIOSYNTHESIS

- Cholesterol biosynthesis springs from a six-carbon intermediate called mevalonate.
- Mevalonate arises, in turn, from linkage of two acetyl-CoAs in the **mitochondrion** to form acetoacetyl-CoA (4 carbons), followed by addition of another acetyl group from a third acetyl-CoA to give 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA).
- This latter compound is reduced by HMG-CoA reductase in the **endoplasmic reticulum**, using two NADPHs, with coincident loss of CoASH.
- HMG-CoA reductase is the major regulatory enzyme in cholesterol biosynthesis.
- HMG-CoA reductase is controlled hormonally by insulin and glucagon and transcription and translation of the enzyme can be suppressed by the presence of cholesterol in cells.
- HMG-CoA reductase is a target for drugs that attempt to lower cholesterol levels in the body. One such drug is lovastatin, which inhibits the enzyme and stops endogenous synthesis of cholesterol

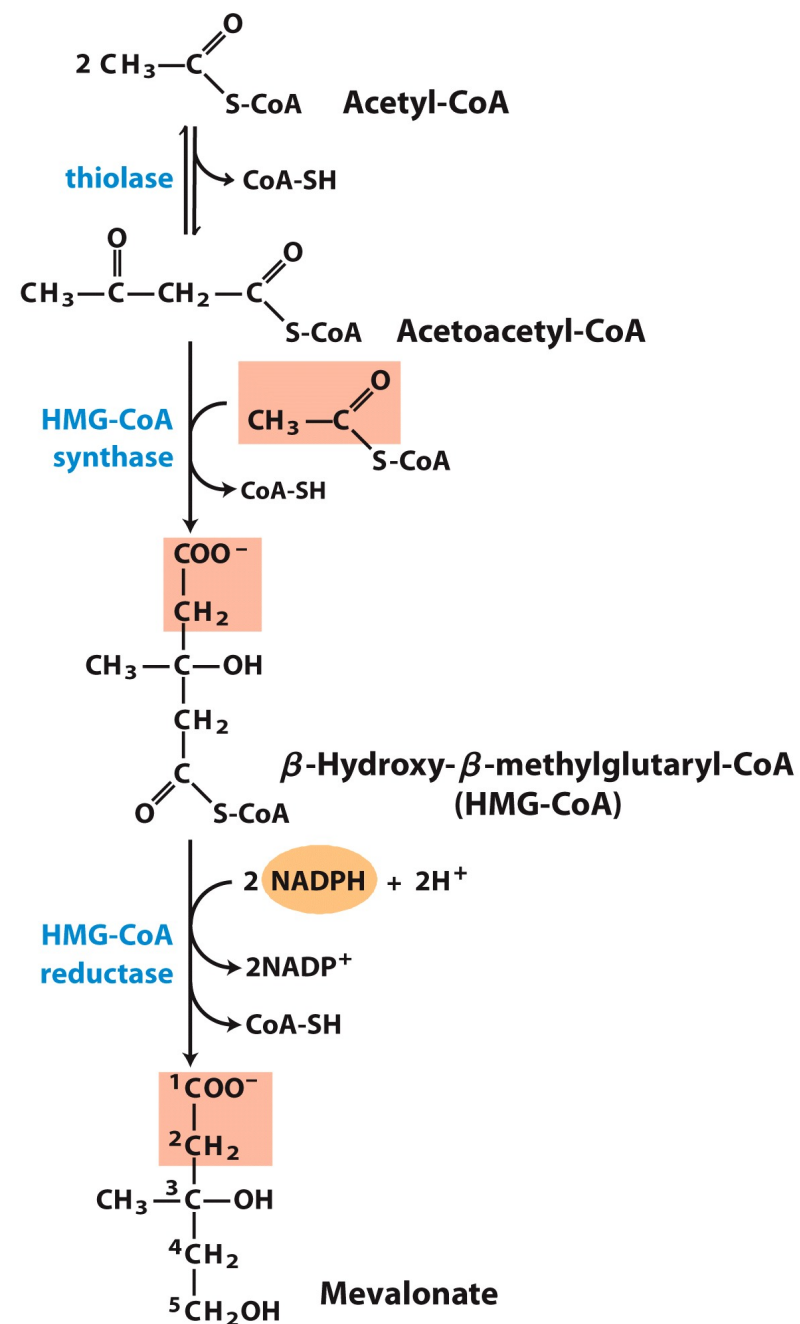


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STEROIDS BIOSYNTHESIS

- Mevalonate is converted in the **cytosol** to the five carbon building blocks of isoprene synthesis - isopentenyl pyrophosphate (IPP) and dimethylallyl pyrophosphate (DPP)

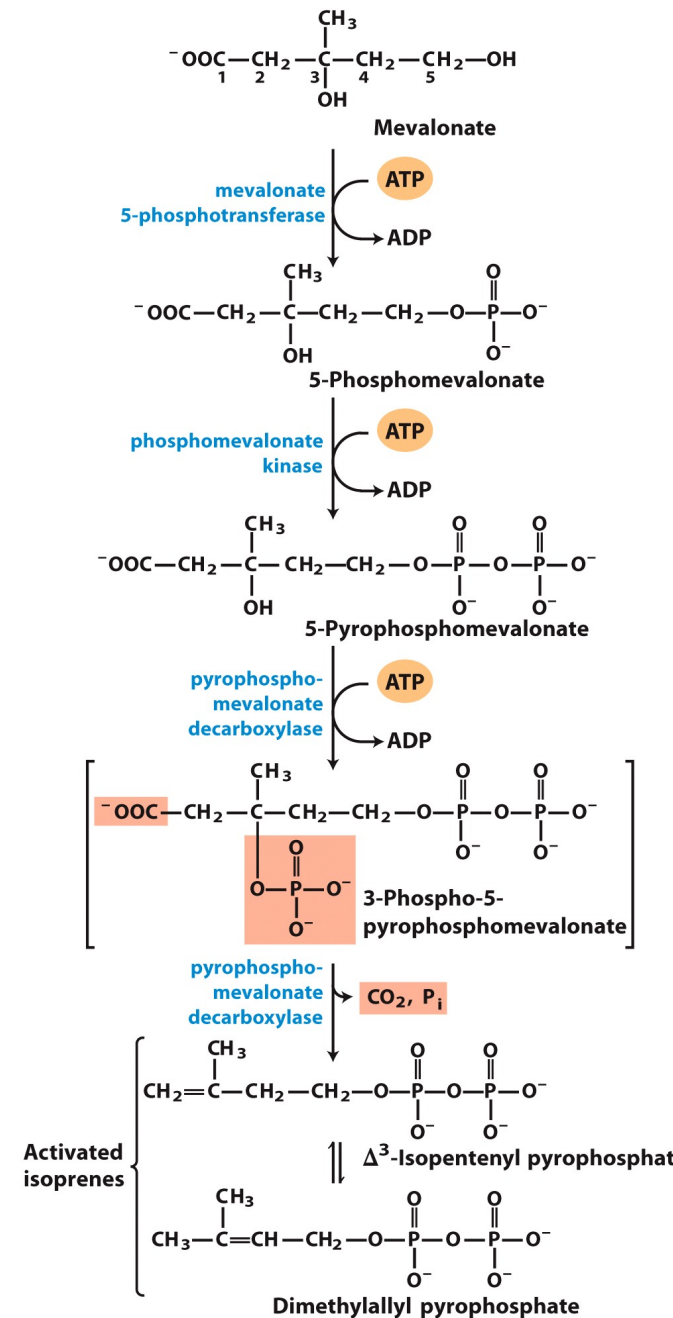


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STEROIDS BIOSYNTHESIS

- Subsequently, IPP and DPP form farnesyl pyrophosphate in the cytosol
- $\text{DPP} + \text{IPP} \rightleftharpoons \text{Geranyl Pyrophosphate} + \text{PPi}$
- $\text{Geranyl Pyrophosphate} + \text{IPP} \rightleftharpoons \text{Farnesyl Pyrophosphate} + \text{PPi}$
- Farnesyl pyrophosphate is then converted to presqualene pyrophosphate in the membrane of the endoplasmic reticulum
- $2 \text{ Farnesyl Pyrophosphate} \rightleftharpoons \text{Presqualene Pyrophosphate} + \text{PPi}$
- Presqualene pyrophosphate is subsequently converted to squalene, also in the membrane of **endoplasmic reticulum**.

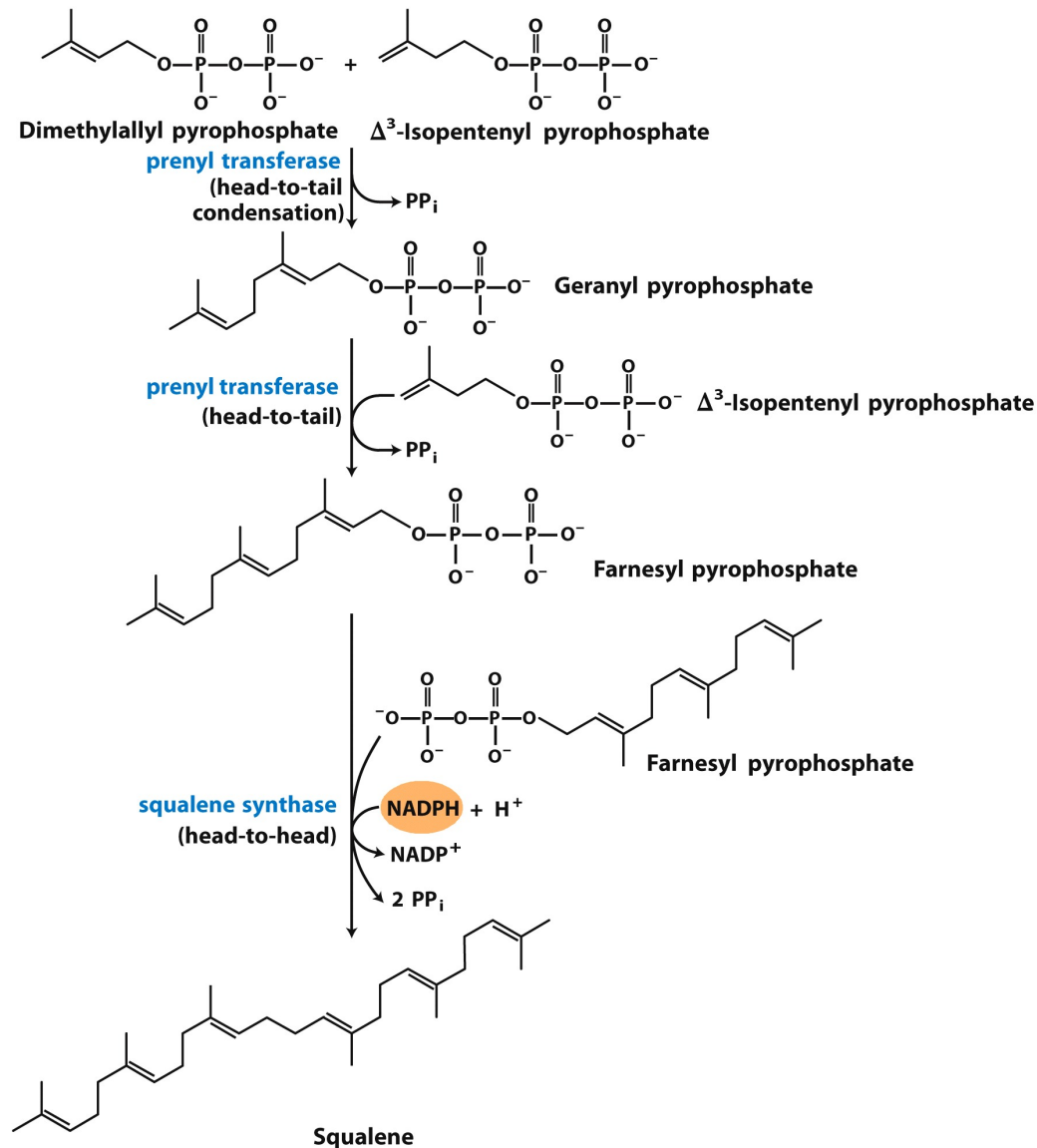


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STEROIDS BIOSYNTHESIS

- Subsequent reactions occur in the **endoplasmic reticulum**. Squalene, for example, is cyclized there to lanosterol, which is subsequently converted to cholesterol.
- Squalene monooxygenase adds oxygen to form an epoxide
- Unsaturated carbons (double bonds) are aligned to allow cyclization and formation of lanosterol

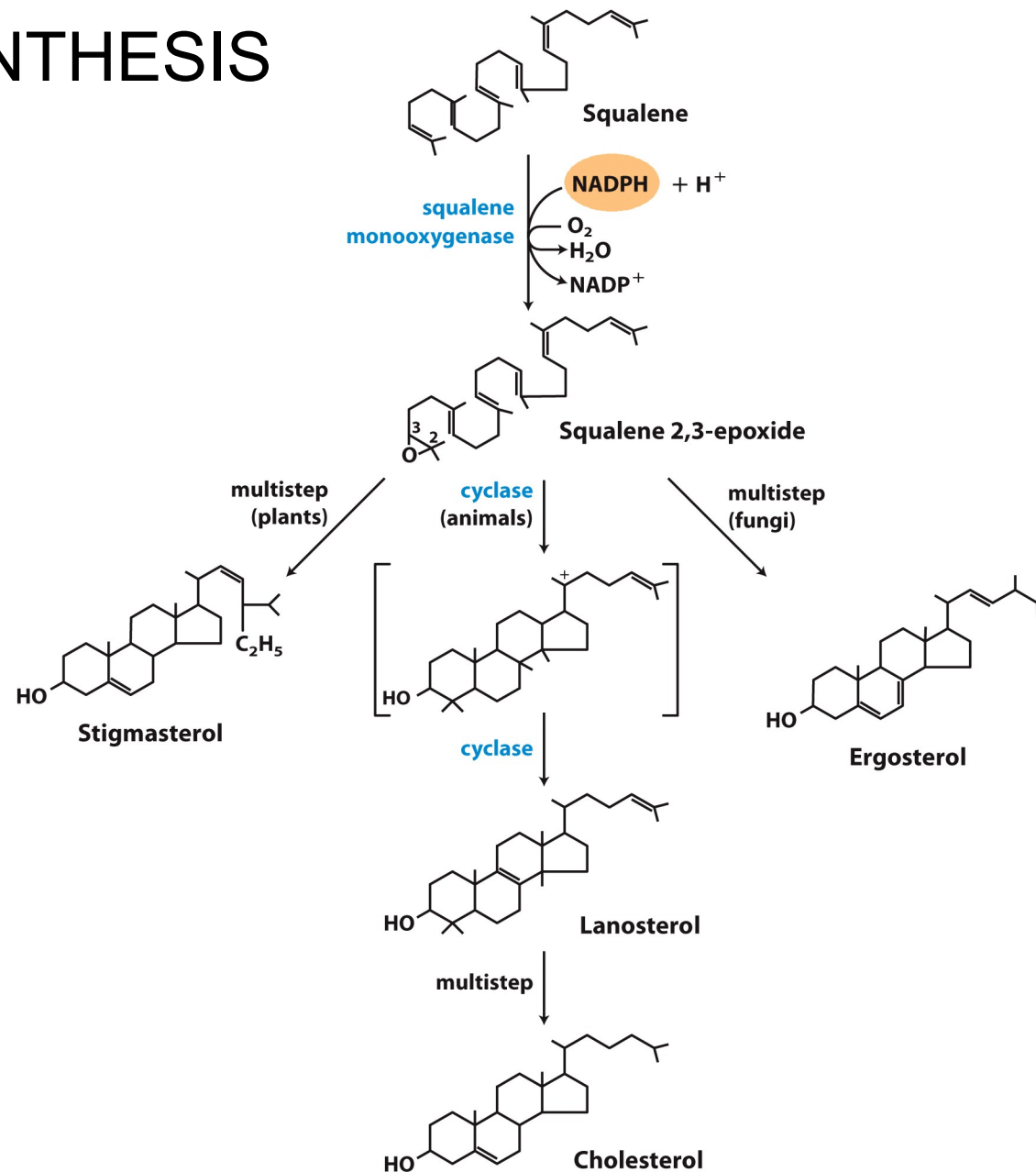


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STEROIDS BIOSYNTHESIS IN SUMMARY

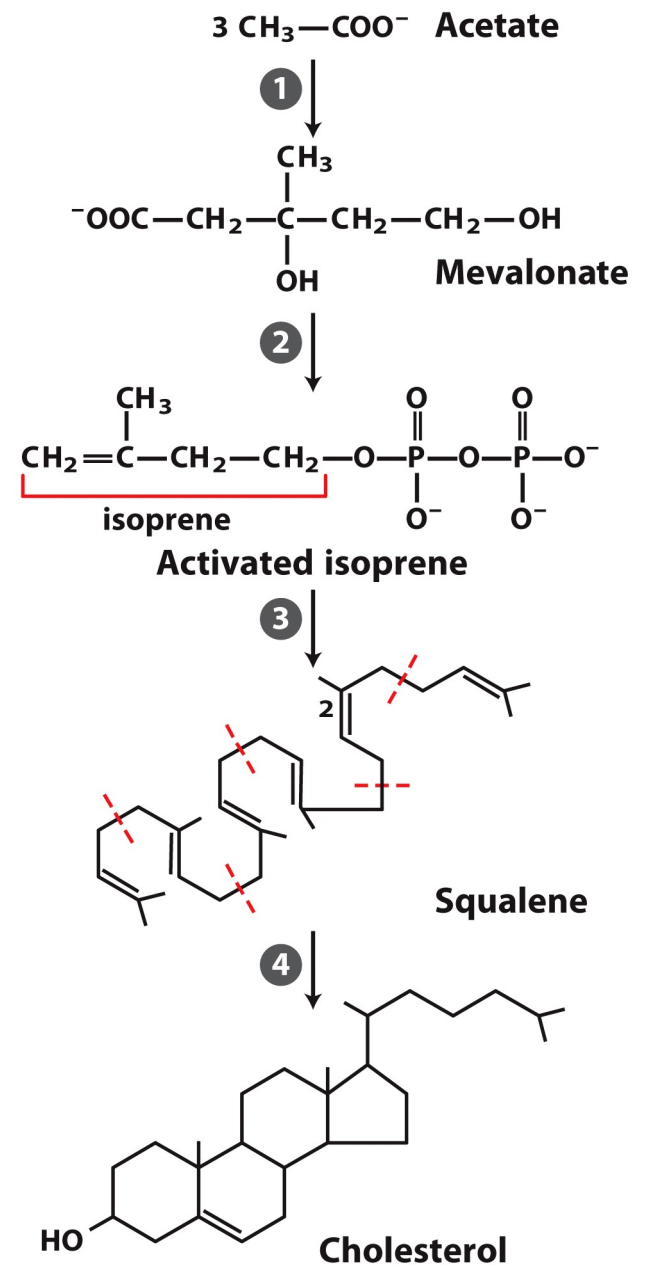
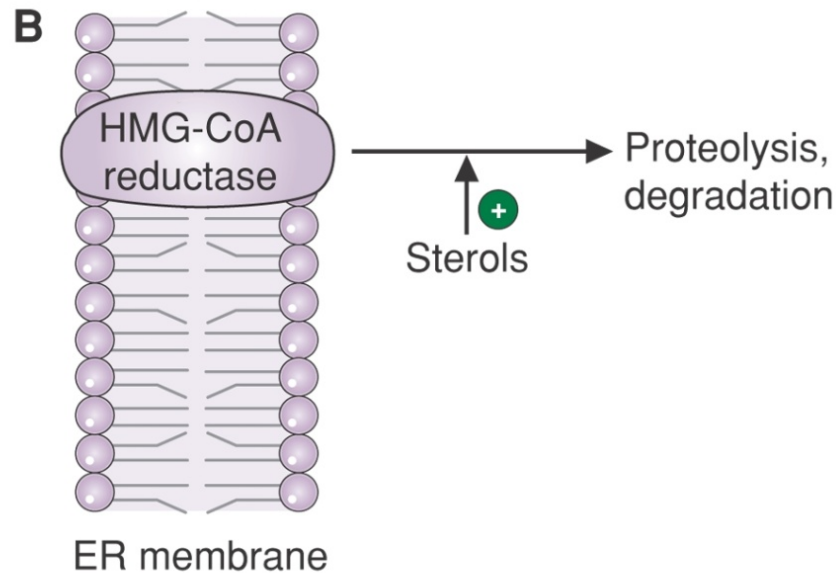


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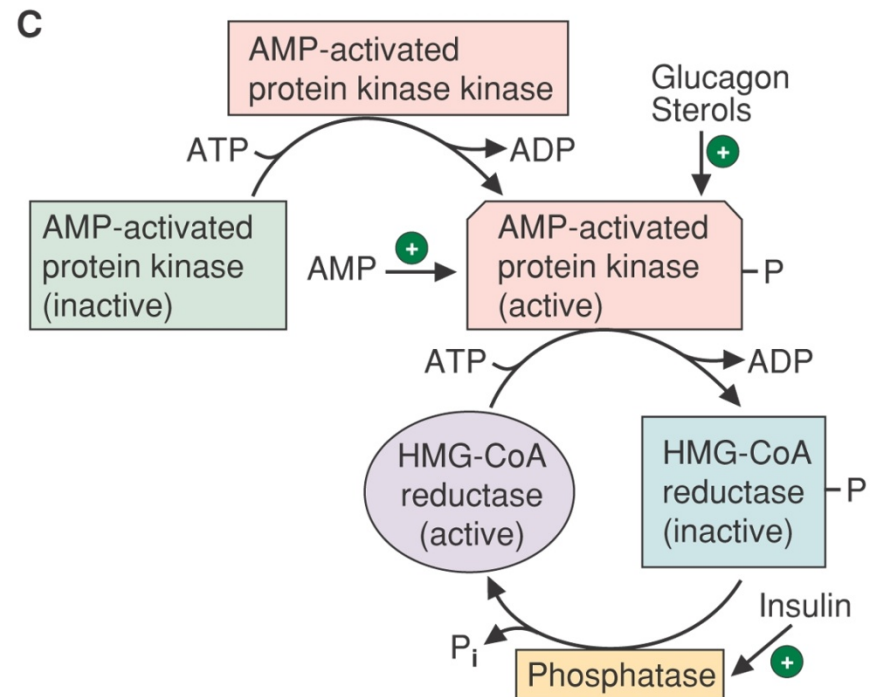
CHOLESTEROL SYNTHESIS: PROTEOLYTIC DEGRADATION OF HMG-CoA REDUCTASE



- When sterol present, enzyme undergoes sterol accelerated ERAD (ER associated degradation)
- HMG-CoA is ubiquitinated and extracted from membrane where it is then degraded by proteasomes

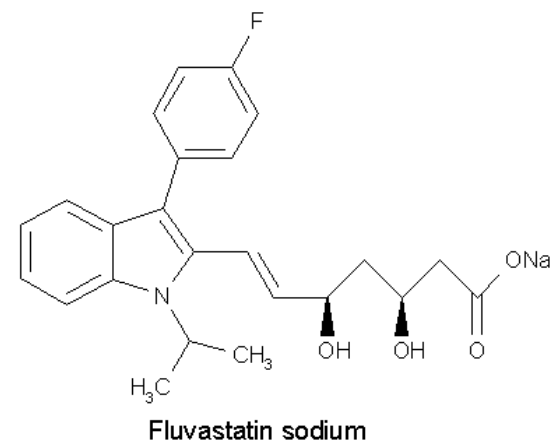
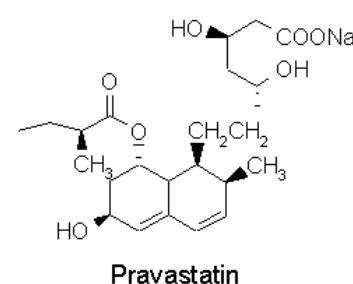
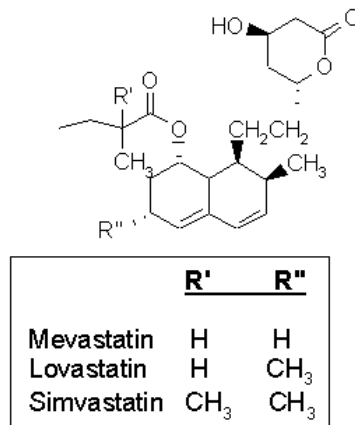
CHOLESTEROL SYNTHESIS: REGULATION BY COVALENT MODIFICATION

- Short-term regulation by phosphorylation and dephosphorylation
- Adenosine monophosphate (AMP) activated kinase phosphorylates HMG-CoA
- Glucagon, sterols, glucocorticoids & low ATP levels inactivate HMG-CoA
- Insulin, thyroid hormone, high ATP levels activate enzyme



CHOLESTEROL SYNTHESIS: REGULATION BY COVALENT MODIFICATION

- HMG-CoA Reductase Inhibitors
 - Statins
 - 18-55% reduction in LDL-C
 - Increases in HDL and decreases in TG
 - Proposed mechanism of action
 - Inhibition of cholesterol synthesis reduces intracellular cholesterol pool and up-regulates LDL-receptors
 - Side effects: myopathy, increased serum hepatic enzymes



Structures of common statin drugs

CHOLESTEROL FATE

- Membranes
- Cholesterol Ester
- Biliary Cholesterol
- Bile Acids
- Steroid hormones

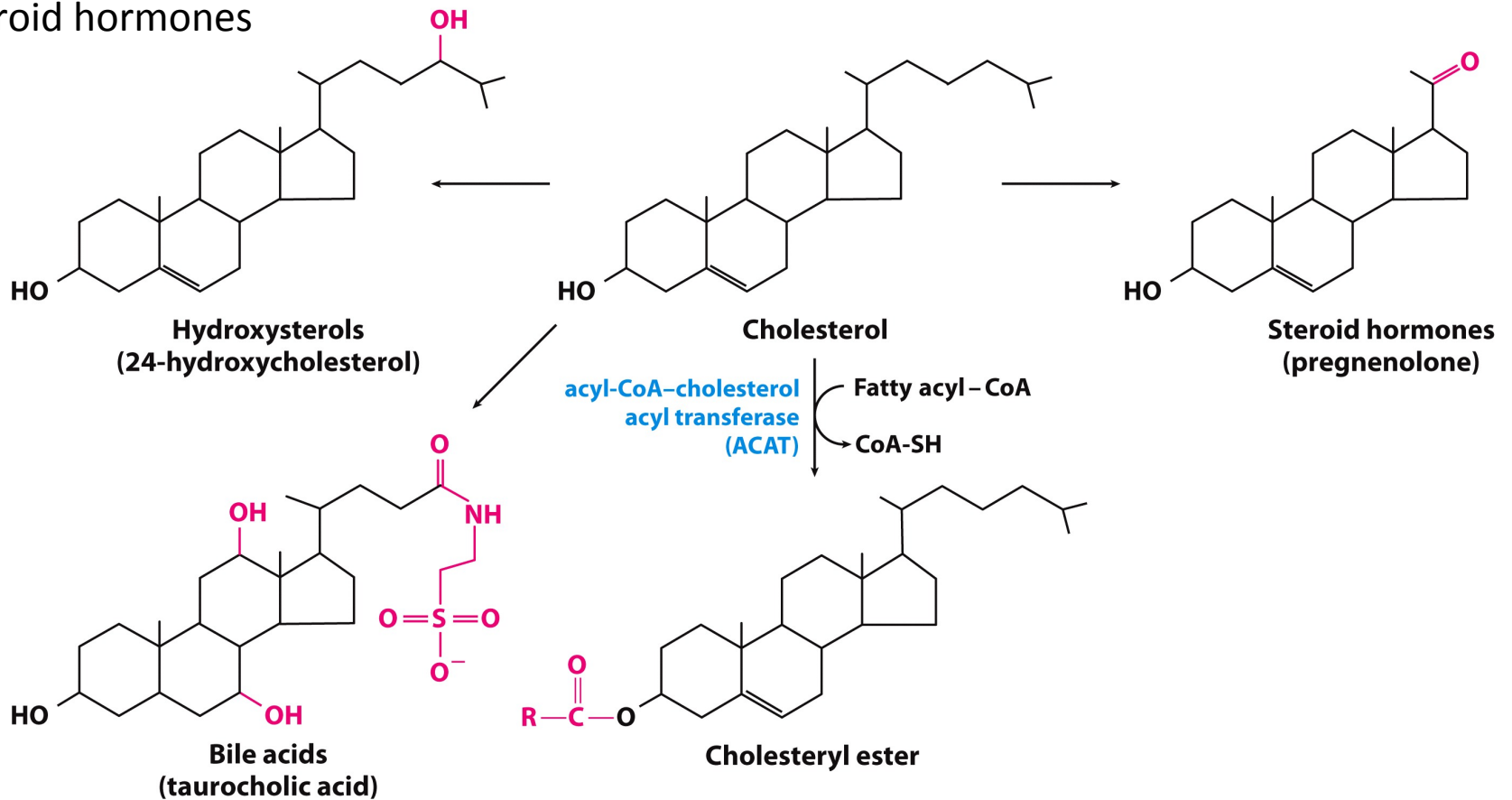


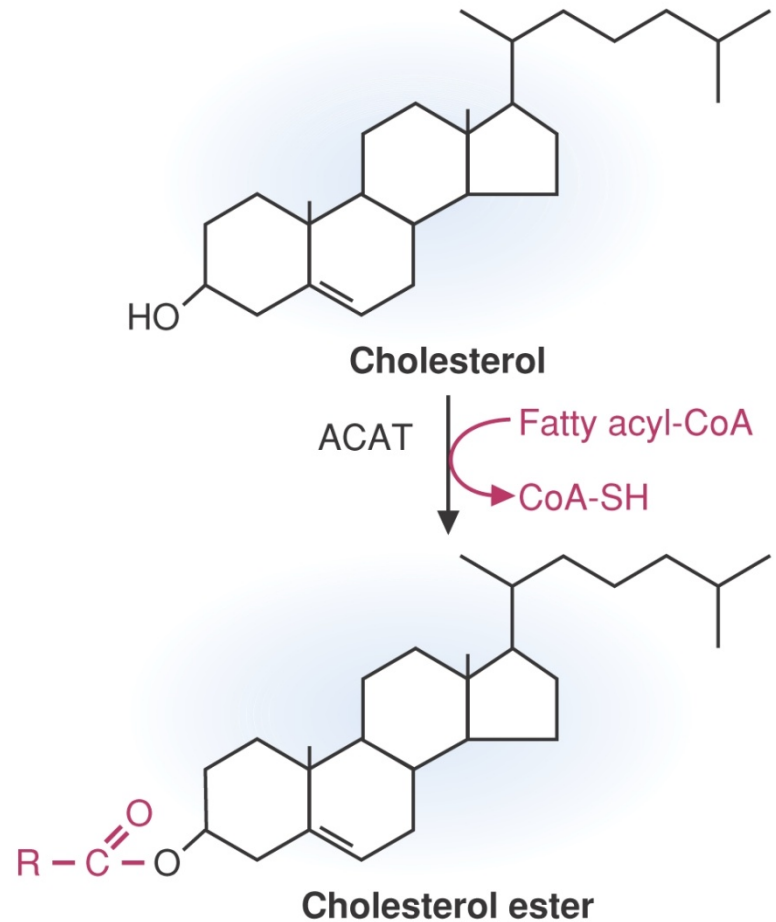
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CHOLESTEROL ESTERS

- Acyl-CoA:cholesterol acyl transferase (ACAT) is an ER membrane protein
- ACAT transfers fatty acid of CoA to C3 hydroxyl group of cholesterol
- Excess cholesterol is stored as cholesterol esters in cytosolic lipid droplets

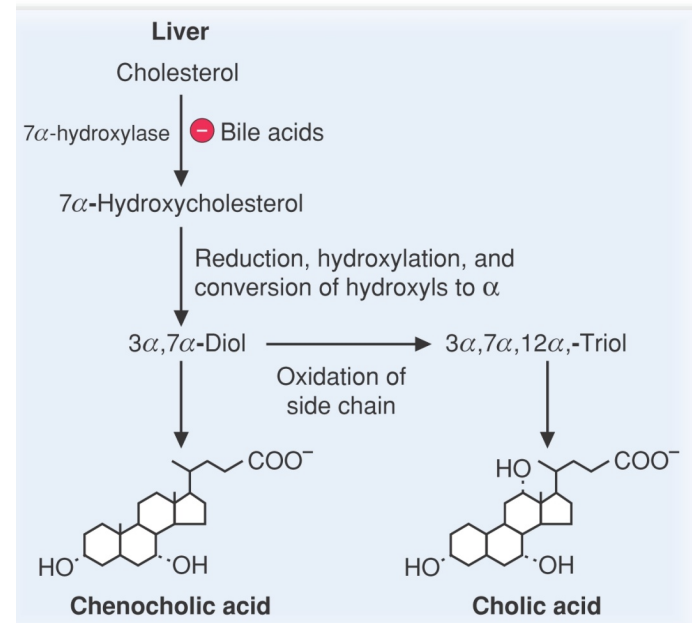
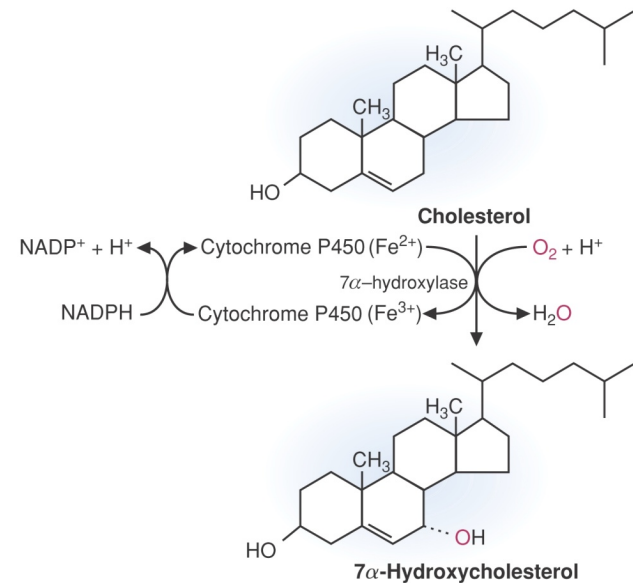


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Fig. 8

BILE SALTS

- Bile acids and salts are effective detergents
- Synthesized in the liver
- Stored and concentrated in the gallbladder
- Discharged into gut and aids in absorption of intraluminal lipids, cholesterol, and fat soluble vitamins
- Bile acid refers to the protonated form while bile salts refers to the ionized form
 - The pH of the intestine is 7 and the pKa of bile salts is 6, which means that 50% are protonated
- These terms are sometimes used interchangeably
- Rate-limiting step performed by the 7 α -hydroxylase (CYP7A1) and is regulated by bile salt concentration
- End product: Cholic acid series and Chenocholic acid series
- Bile salts can be conjugated and become better detergents



FATE OF BILE SALTS

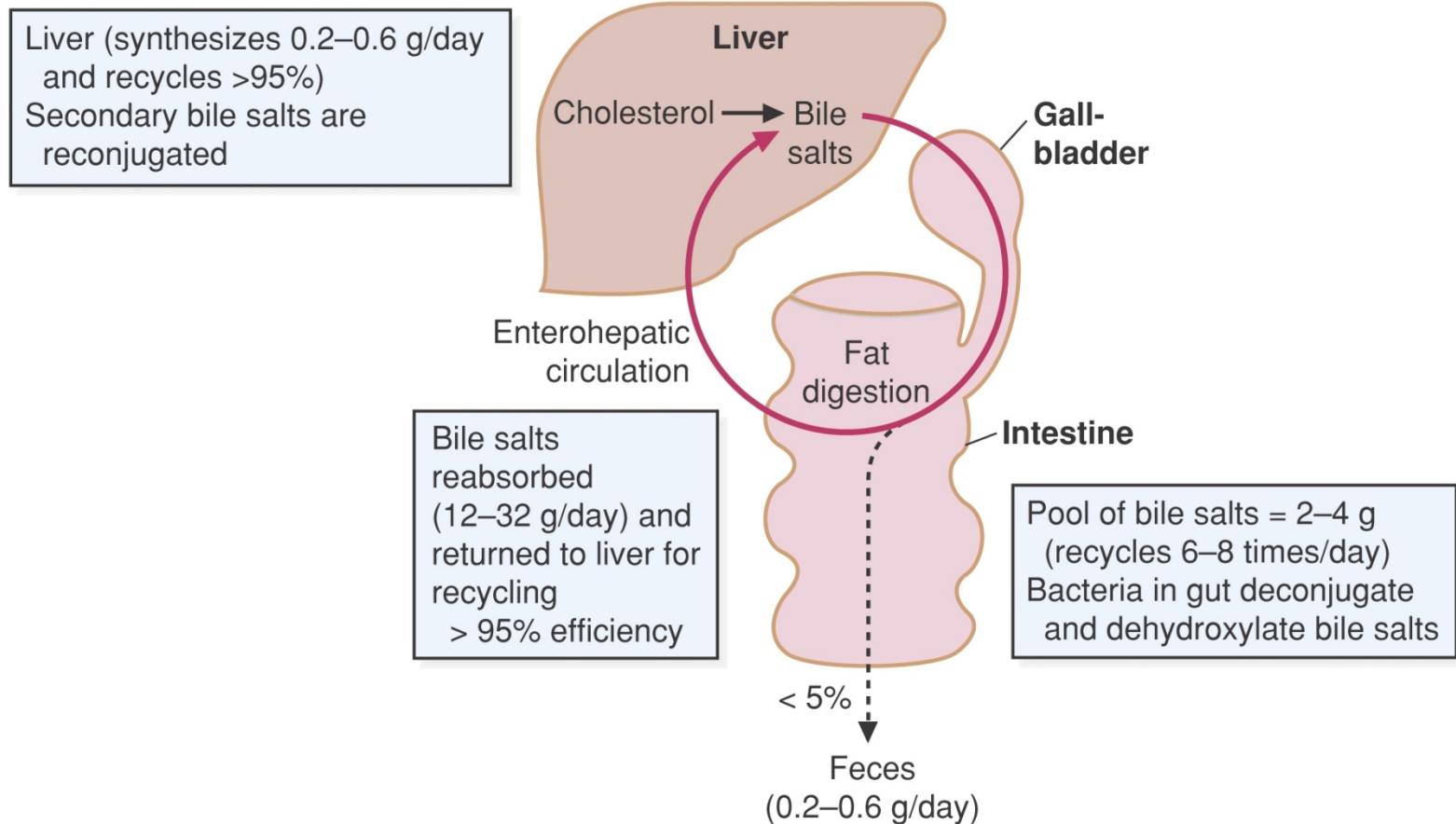
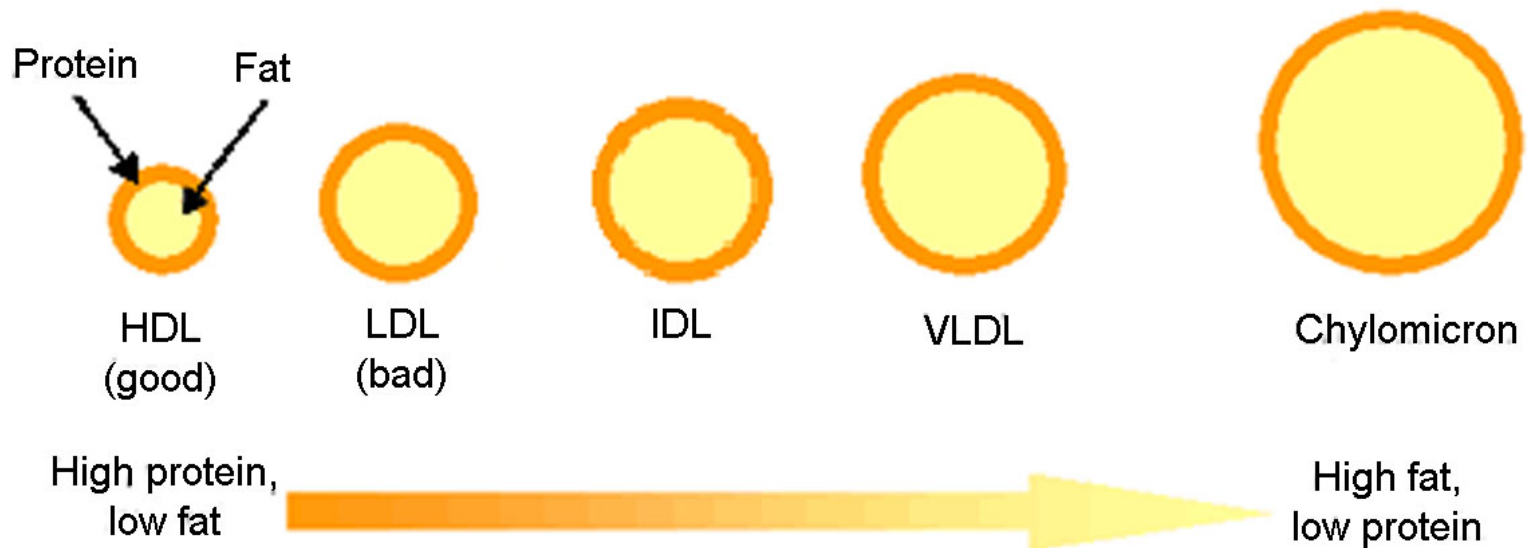


Fig. 12

CHOLESTEROL BACKGROUND (TRANSPORT)

- Cholesterol, cholesterol esters, triacylglycerols, and phospholipids are insoluble and must travel via lipoproteins
- Chylomicrons and VLDL transport cholesterol to other cells through the bloodstream
- Chylomicrons package cholesterol in intestine, while VLDL package in liver
- HDL – reverse cholesterol transport



CHOLESTEROL BACKGROUND (TRANSPORT)

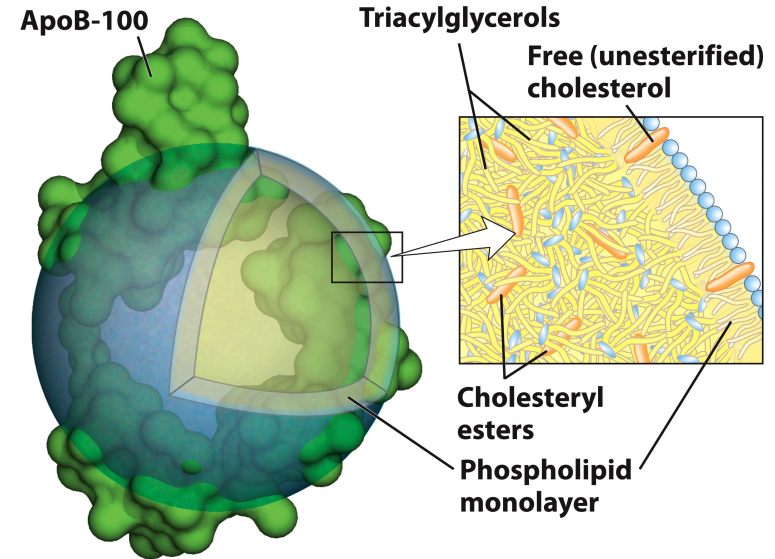


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TABLE 21-1 Major Classes of Human Plasma Lipoproteins: Some Properties

Lipoprotein	Density (g/mL)	Composition (wt %)				
		Protein	Phospholipids	Free cholesterol	Cholesteryl esters	Triacylglycerols
Chylomicrons	<1.006	2	9	1	3	85
VLDL	0.95–1.006	10	18	7	12	50
LDL	1.006–1.063	23	20	8	37	10
HDL	1.063–1.210	55	24	2	15	4

Source: Modified from Kritchevsky, D. (1986) Atherosclerosis and nutrition. *Nutr. Int.* 2, 290–297.

Table 21-1

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CHOLESTEROL BACKGROUND (TRANSPORT)

1. Chylomicrons are synthesized in epithelial cells of intestine from diet fats;
2. Apo C-II activates lipases in capillaries of adipose tissue, heart, mammary gland, and myocyte releasing fatty acids in tissues;
3. Chylomicrons remnants, carrying cholesterol, go to liver where they enter
4. through endocytosis and are degraded by lysosomes;
5. If the diet contains too many fats, they are converted to TAG and cholesterol esters in liver and they are transported through VLDL for example to adipose tissue (insulin promotes this process);
6. VLDL are converted into IDL and LDL while releasing fats but they still contain cholesterol that is transported to periferic tissues (7);
8. LDL transport cholesterol to macrophages or back to the liver (9)

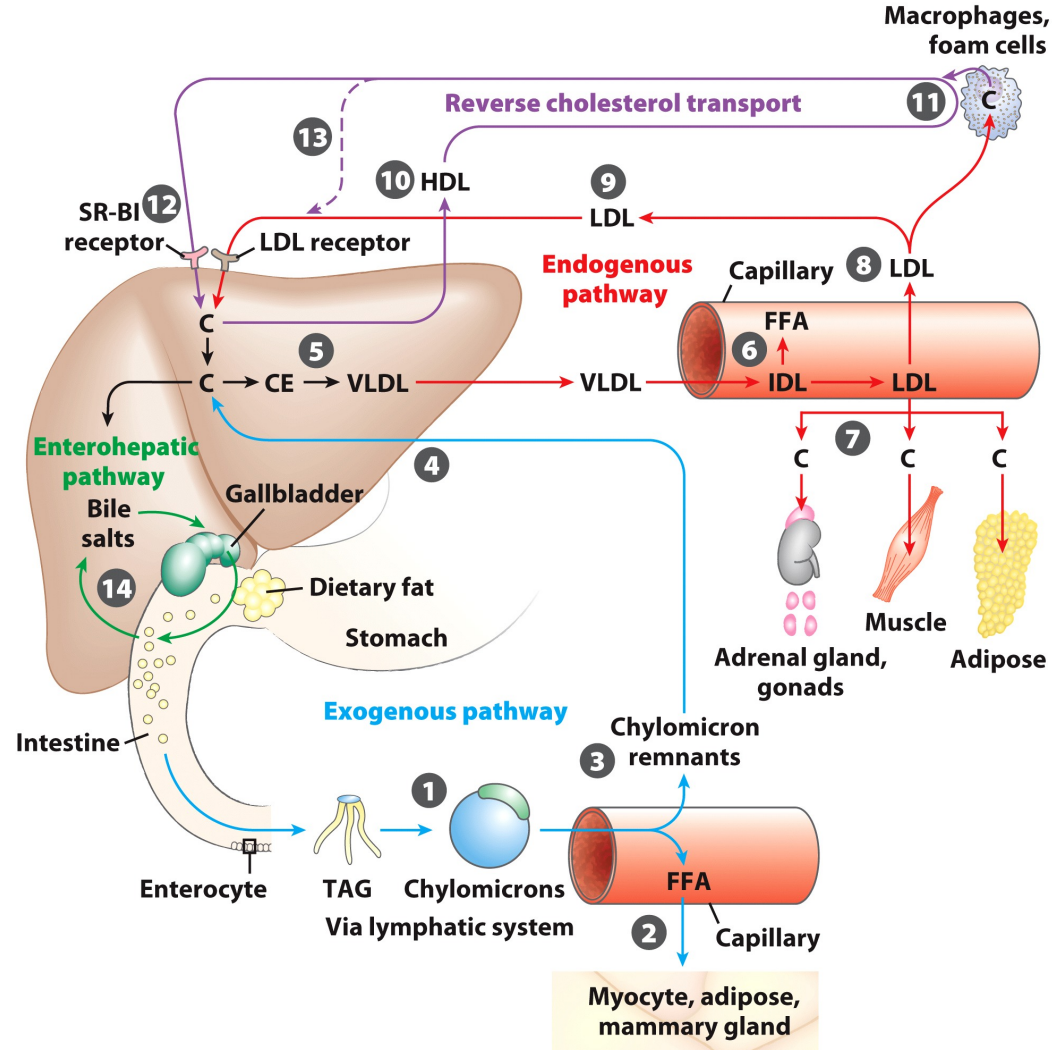


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CHOLESTEROL BACKGROUND (TRANSPORT)

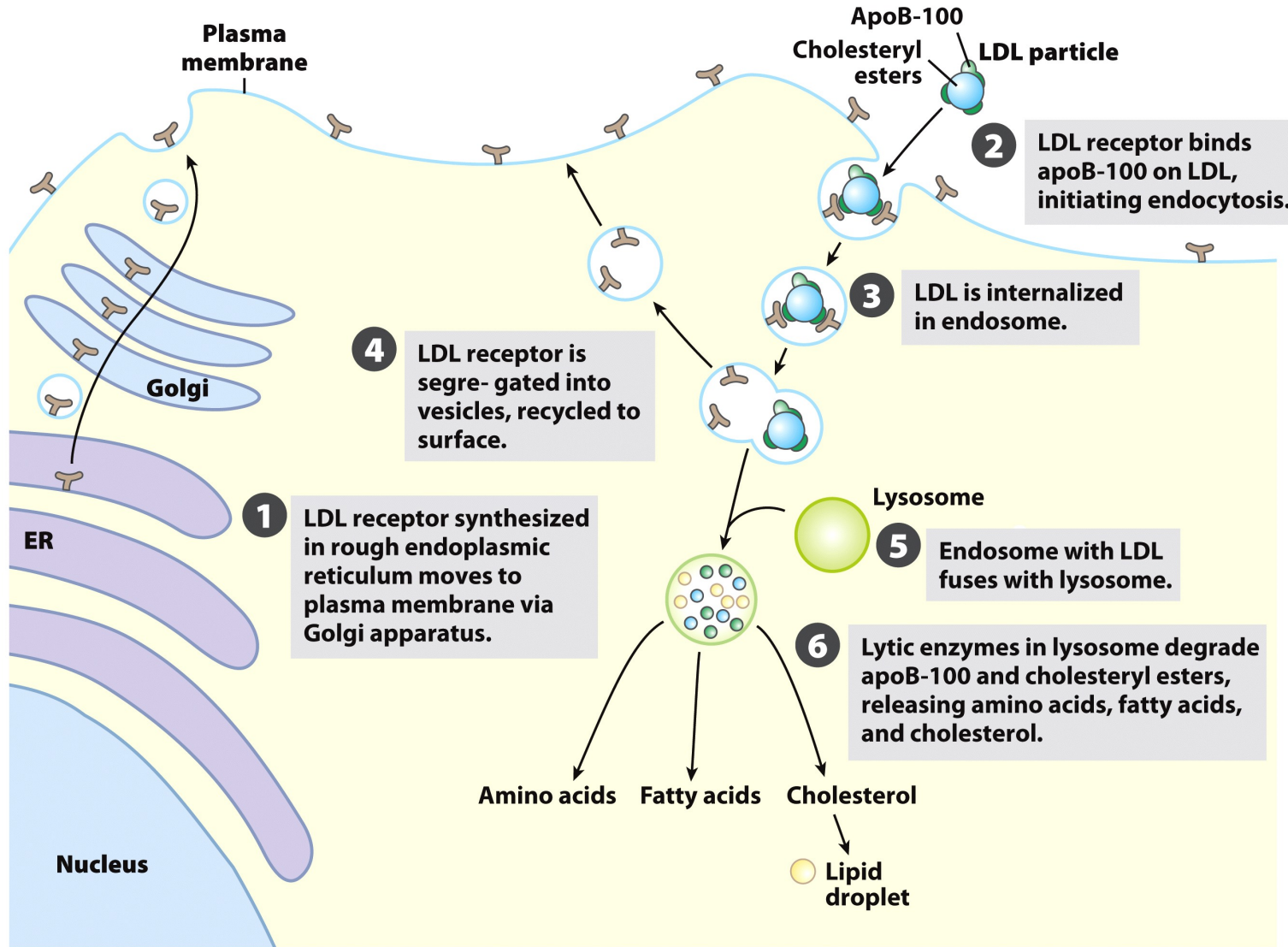


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Cholesterol absorption through receptor-mediate endocytosis

CHOLESTEROL SYNTHESIS: REGULATION

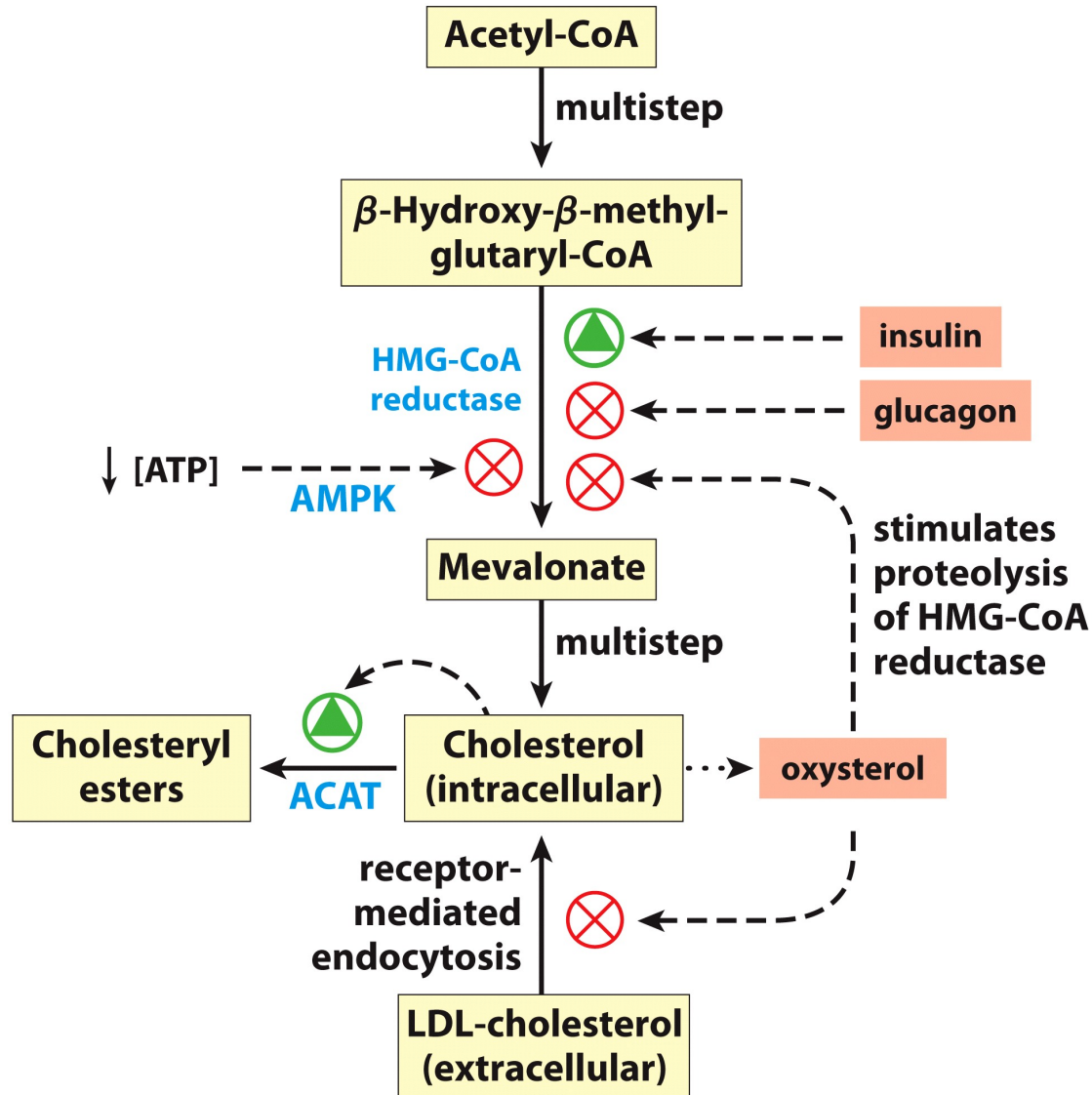
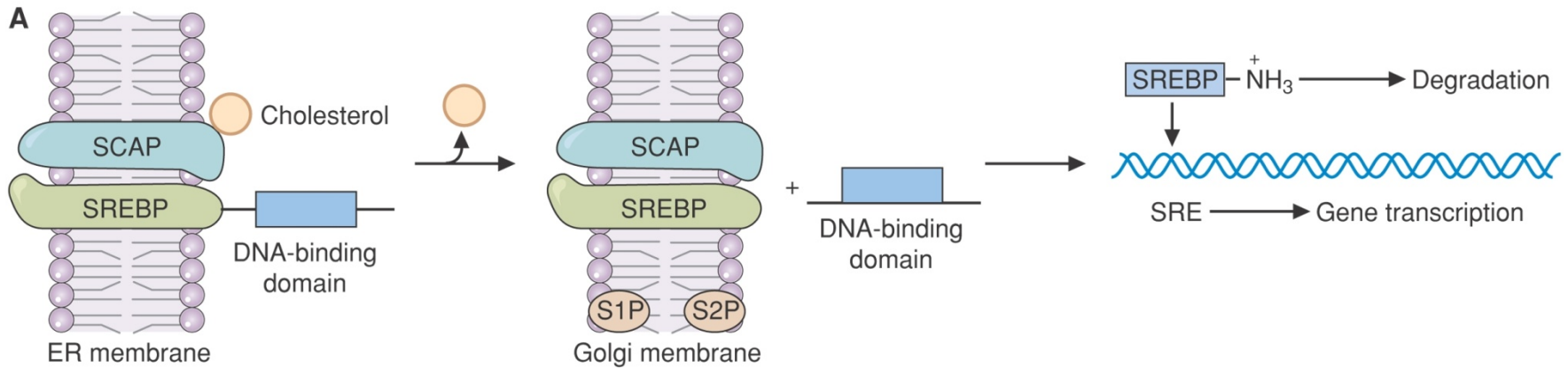


Figure 21-43

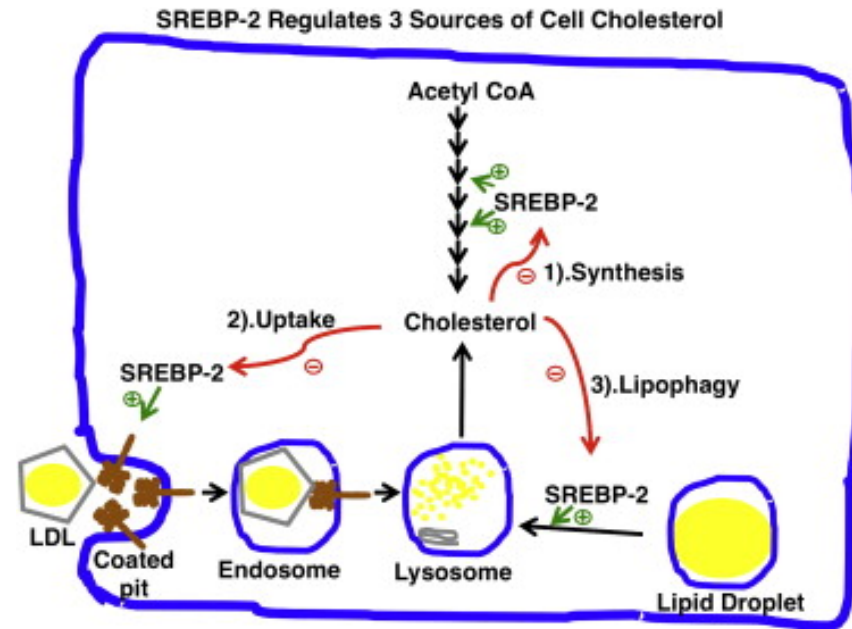
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CHOLESTEROL SYNTHESIS: TRANSCRIPTION CONTROL



- Feedback regulatory system
- Rate of HMG-CoA reductase mRNA synthesis controlled by sterol regulatory element binding protein (SREBP)
- Once in the Golgi, SREBP is cleaved twice by S1P and S2P to release the transcription factor



CHOLESTEROL SYNTHESIS: TRANSCRIPTION CONTROL

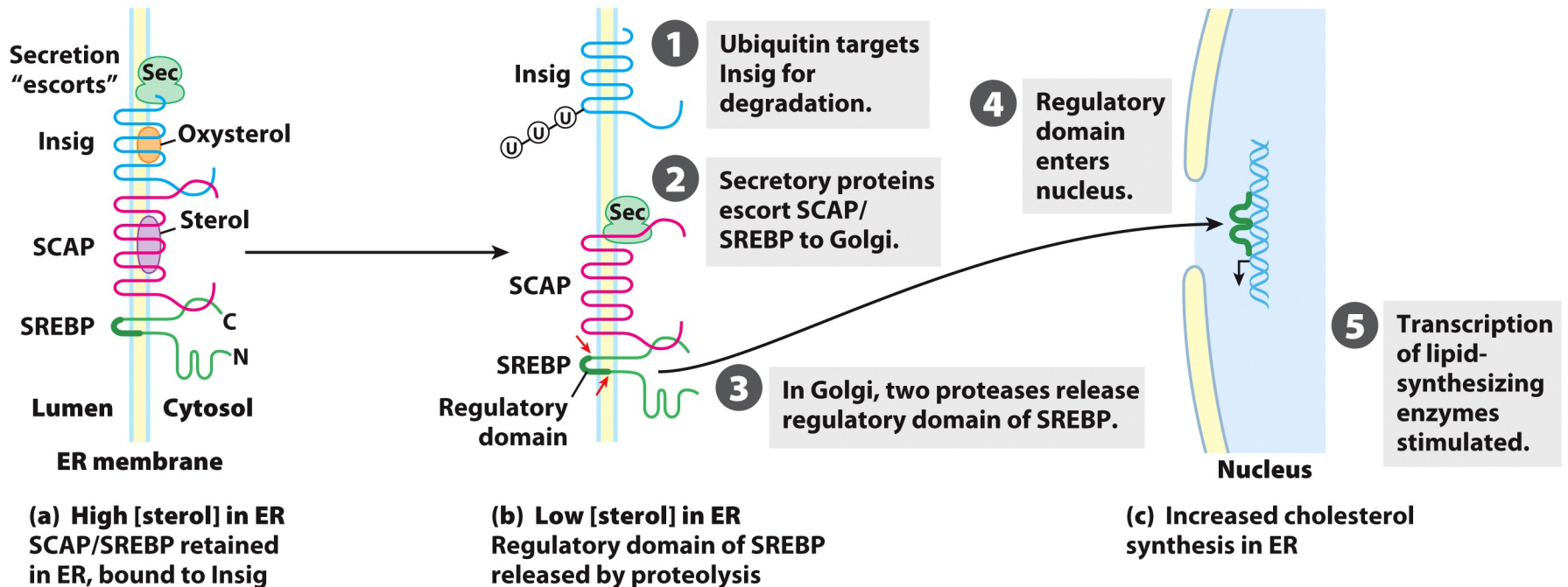


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STEROID HORMONES

- Steroid hormones: produced in the adrenal cortex, testis, ovary, and some peripheral tissues (adipose tissue, the brain!)
- All steroid hormones share a typical (but not identical) ring structure.
- All steroid hormones are derived from cholesterol and differ only in the ring structure and side chains attached to it.
- All steroid hormones are lipid soluble

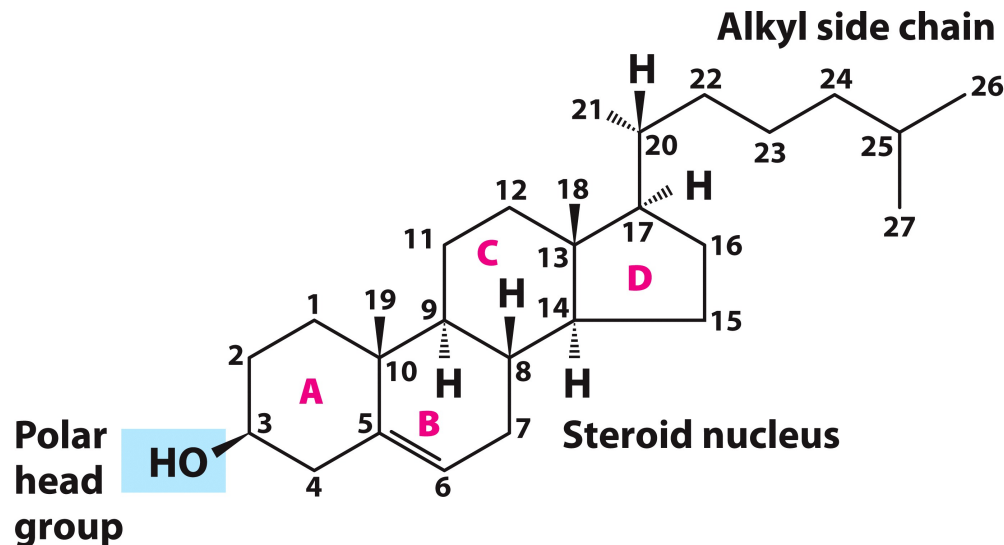
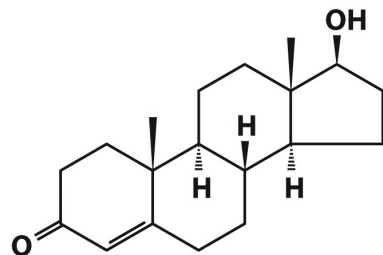
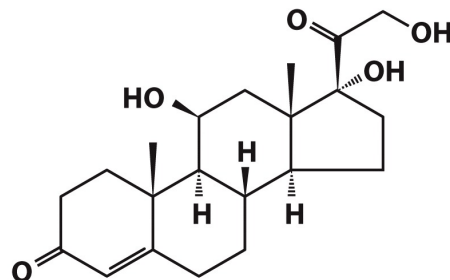


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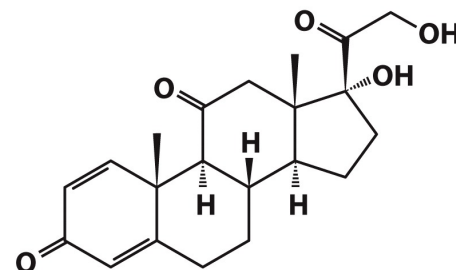
STEROID HORMONES



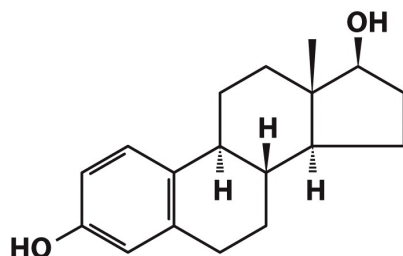
Testosterone



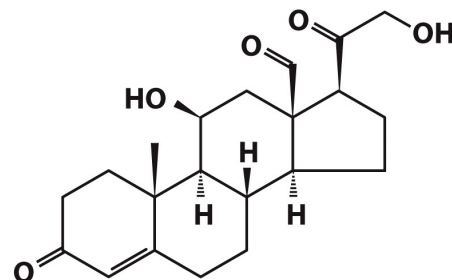
Cortisol



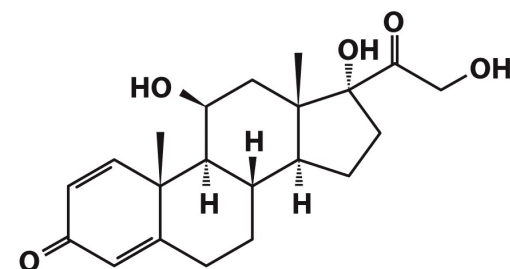
Prednisone



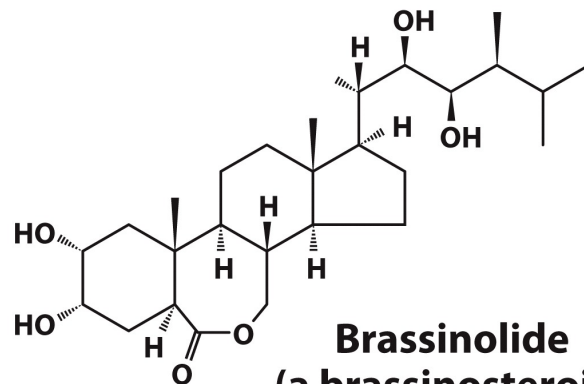
β -Estradiol



Aldosterone



Prednisolone



**Brassinolide
(a brassinosteroid)**

Figure 10-19

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STEROID HORMONES

Adrenal cortex

- Composed of 3 layers (zones):
- **outer zone** (*zona glomerulosa*) produces ***aldosterone*** (mineralocorticoid)
- **middle zone** (*zona fasciculata*) produces ***cortisol*** (glucocorticoid)
- **inner zone** (*zona reticularis*) produces ***androgens***

Corpus luteum and ovary

- produce ***progesteron*** and ***estradiol***

Testes

- produces ***testosterone*** and ***dihydrotestosterone (DHT)***

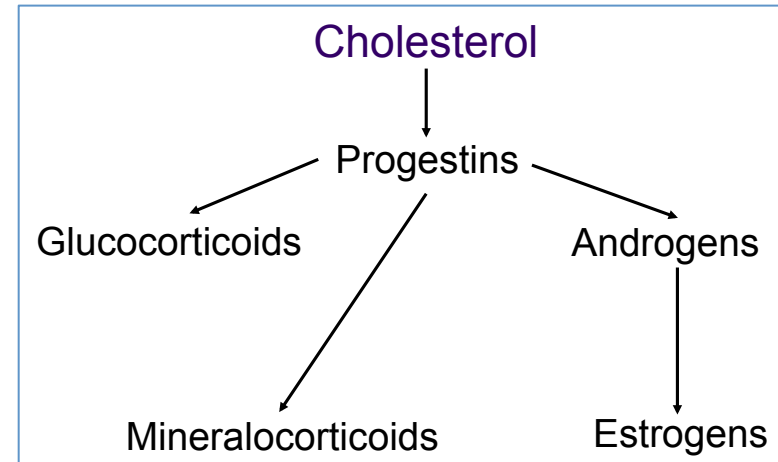
STEROID HORMONES

- Steroid hormones are extracellular messengers elaborated by different organs.
- A general feature of steroid hormones is that **they are not stored** for release after synthesis.
- Levels of circulating hormones are controlled primarily by their rates of synthesis. This, in turn, is often controlled by signals from the brain.
- Are all derived from the same parent compound: cholesterol
- Enzymes which produce steroid hormones from cholesterol are located in mitochondria and smooth ER
- Steroids are lipid soluble and thus are freely permeable to membranes so are not stored in cells

STEROID HORMONES: TYPES AND ROLES

Steroid hormones are classified into five major categories:

- **Glucocorticoids**; cortisol is the major representative in most mammals
- **Mineralocorticoids**; aldosterone being most prominent
- **Androgens** such as testosterone
- **Estrogens**, including estradiol and estrone
- **Progestogens** (also known as progestins) such as progesterone
- Steroid hormones play important roles in:
 - carbohydrate regulation (glucocorticoids)
 - mineral balance (mineralocorticoids)
 - reproductive functions (gonadal steroids)
- Steroids also play roles in inflammatory responses, stress responses, bone metabolism, cardiovascular fitness, behavior, cognition, and mood.

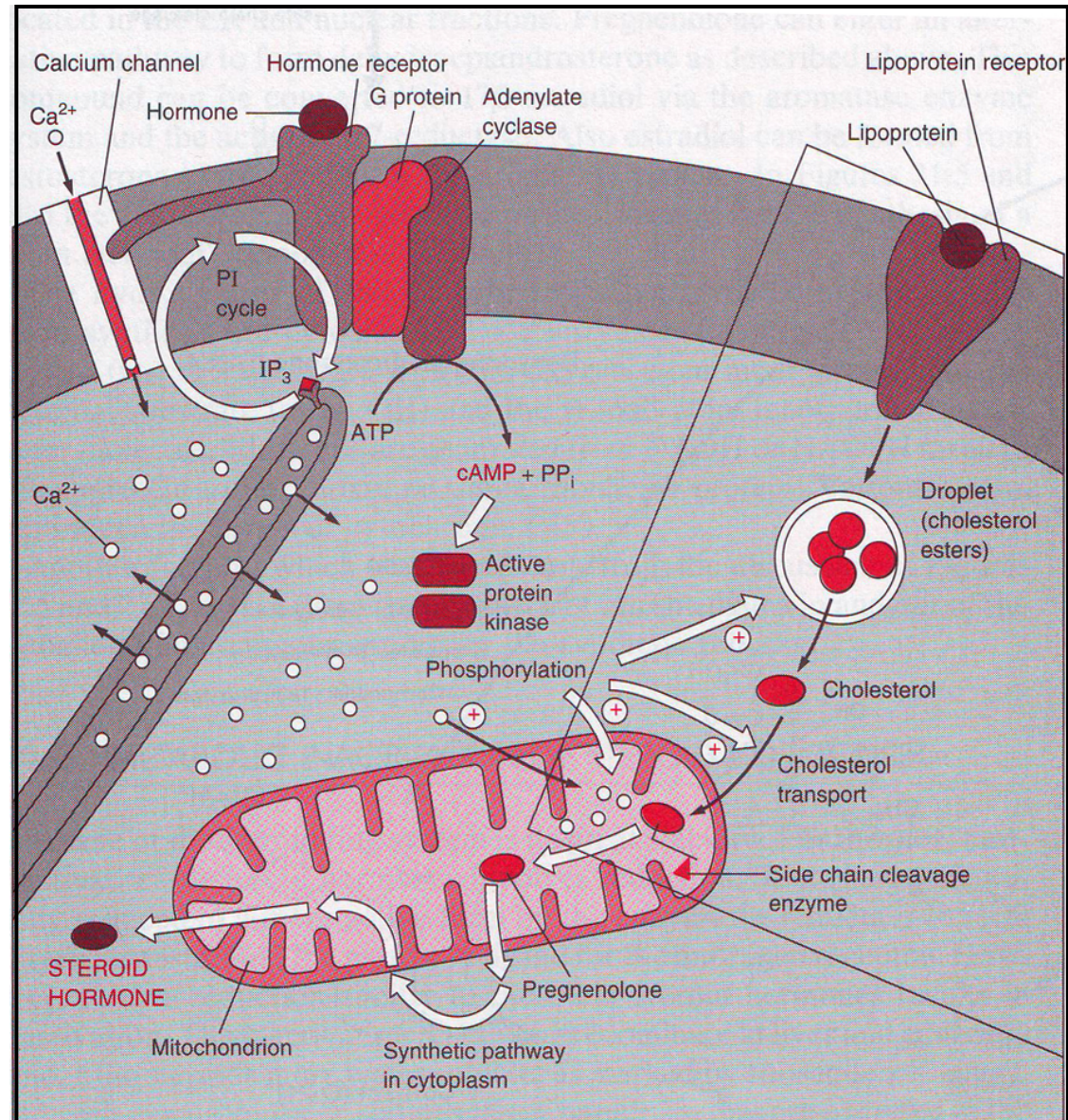


STEROID HORMONES: TYPES AND ROLES

Product	Functions
Progesterone	prepares uterus lining for implantation of ovum
Glucocorticoids (cortisol) (produced in adrenal cortex) (catabolic steroid)	promote gluconeogenesis; favor breakdown of fat and protein (fuel mobilization); anti-inflammatory
Mineralocorticoids (aldosterone) (produced in adrenal glands)	maintains blood volume and blood pressure by increasing sodium reabsorption by kidney
Androgens (strongest = testosterone) (produced in testes primarily but weak androgens in adrenal cortex) (anabolic steroid)	development of male secondary sex characteristics; prevents bone resorption
Estrogen (produced in ovaries primarily but also in adipose cells of males and females)	development of female secondary sex characteristics; prevents bone resorption

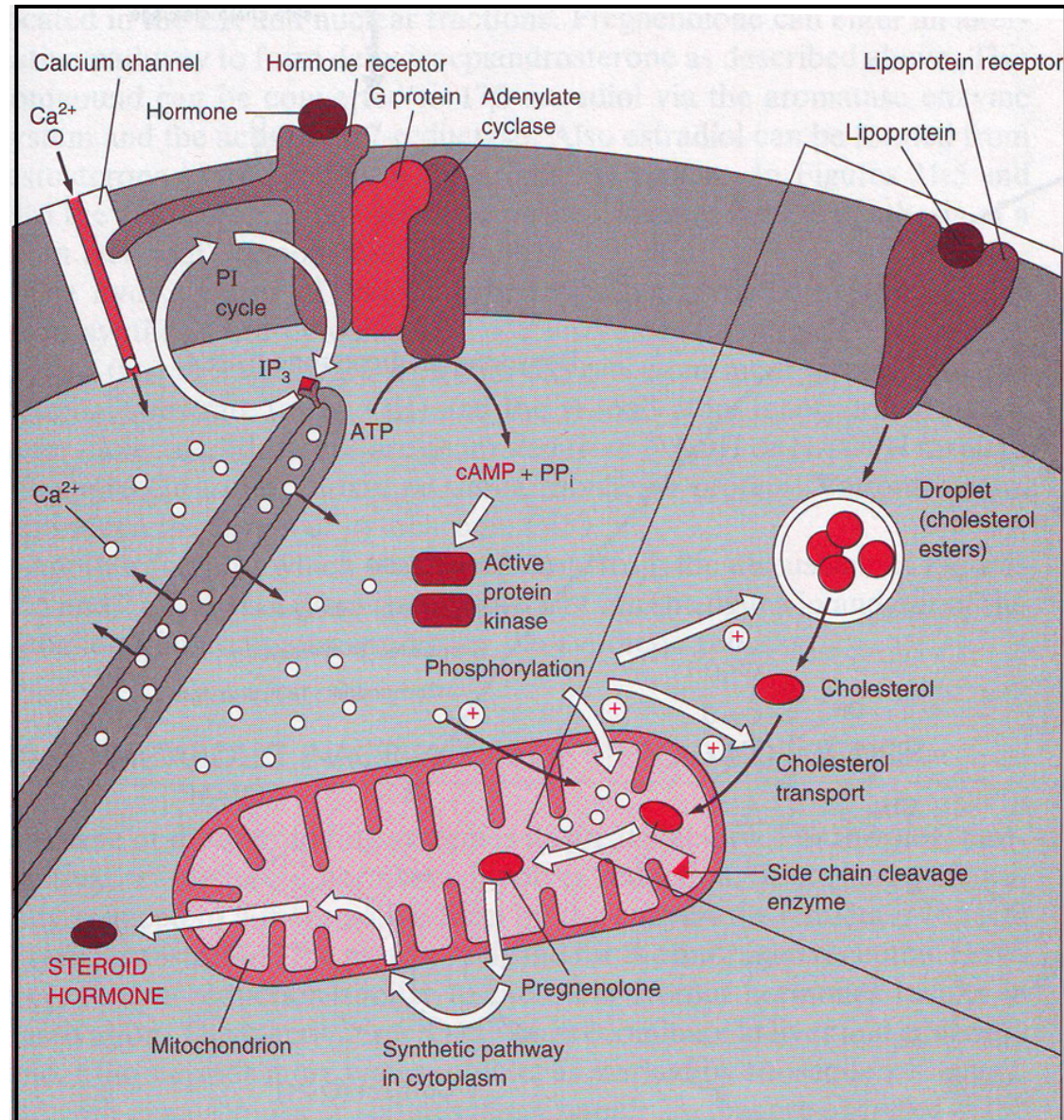
HORMONAL STIMULATION OF STEROID HORMONE BIOSYNTHESIS

- Hormone stimulation depends on the cell type and receptor (ACTH for cortisol synthesis, FSH for estradiol synthesis, LH for testosterone synthesis etc.)
- Hormone binds to cell membrane receptor and activates adenylate cyclase mediated by a stimulatory G protein.
- Receptor, activated by hormone, may directly stimulate a **calcium channel** or indirectly stimulate it by activating the **phosphatidylinositol (PI) cycle**.



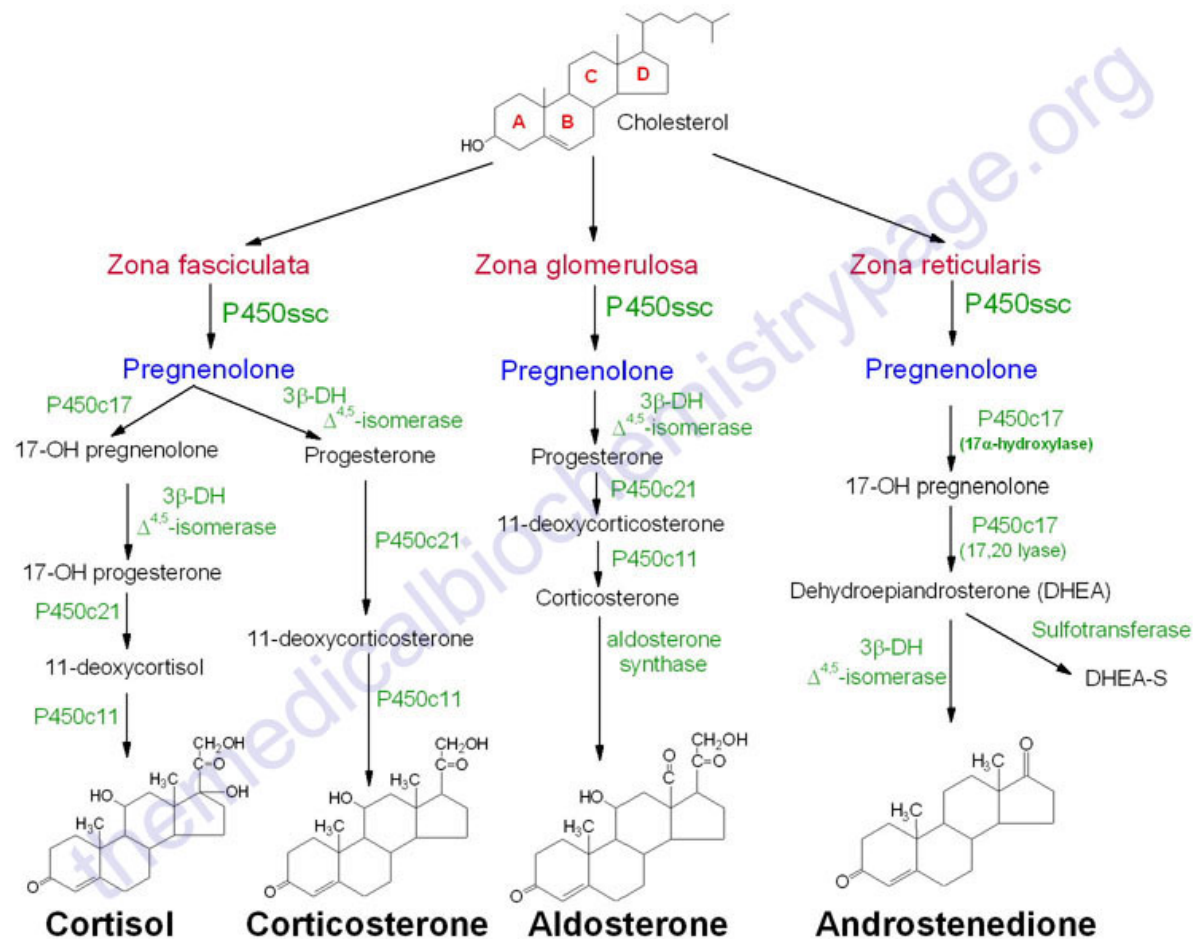
HORMONAL STIMULATION OF STEROID HORMONE BIOSYNTHESIS

- The **increase in cAMP** activates **protein kinase** whose phosphorylations cause **increased hydrolysis of cholesteryl esters** from droplet to free cholesterol and increase cholesterol transport into the mitochondrion.
- Elevated Ca^{2+} levels and protein phosphorylation bring about **induced levels of the side chain cleavage reaction**.
- Steroid is produced, secreted into the extracellular space and circulated to the target tissue in the bloodstream



BIOSYNTHESIS OF STEROID HORMONES

- Critical step is the cell activity in mobilizing cholesterol stored in a droplets, transport of cholesterol to mitochondrion.
- The rate-limiting step is the rate of **cholesterol side chain cleavage** in mitochondrion by enzymes known as the **cytochrome P450 side chain cleavage enzyme complex**.



STERIOD HORMONE SYNTHESIS

- The rate-limiting step in this process is the transport of free cholesterol from the cytoplasm into mitochondria. This step is carried out by the Steroidogenic Acute Regulatory Protein (StAR)
- StAR is important in transferring cholesterol, the precursor for all steroid hormones, from the outer to inner mitochondrial membrane where P450scc is located
- P450scc is a side chain cleavage enzyme which converts cholesterol to pregnenolone, and is the rate-limiting enzyme in steroidogenesis

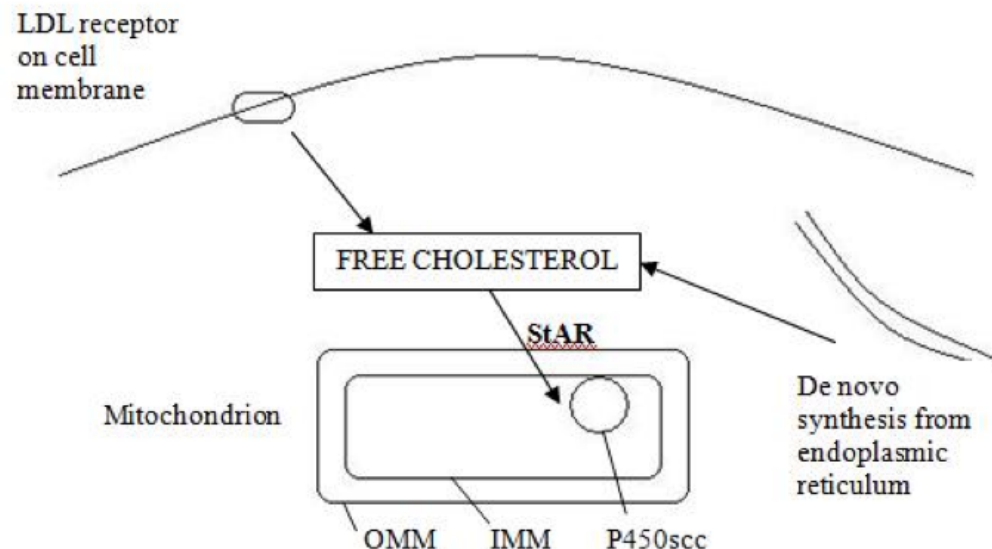
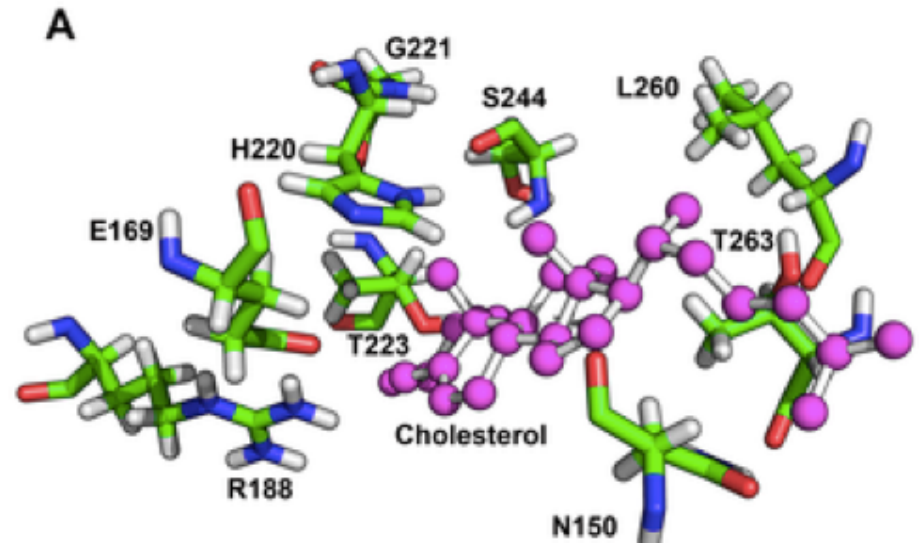
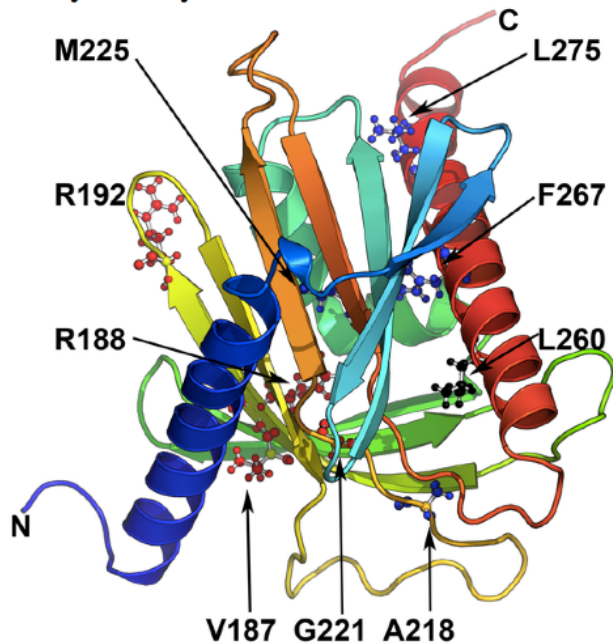


Figure 1: Simplified diagram showing the movement, synthesis and destination of cholesterol within a cell (Source: Redrawn from Miller, 2007). OMM – outer mitochondrial membrane, IMM – inner mitochondrial membrane, LDL receptor – low density lipoprotein receptor, P450scc – cholesterol side chain cleavage enzyme.

STEROID HORMONE SYNTHESIS

- StAR acts exclusively on the outer mitochondrial membrane to bind cholesterol, and is inactivated when imported into the mitochondria
- This process is important in the regulation of steroidogenesis.



The binding pocket of StAR. Cholesterol is represented in pink, and the interacting amino acids are also shown.

STEROID HORMONE SYNTHESIS

- Many signalling pathways have been identified to be involved in regulating the transcription of StAR.
- The figure shows how the signalling molecules interact with each other. cAMP is the main regulator, promoting both expression and phosphorylation.
- Phosphorylation of serine 195 increases activity

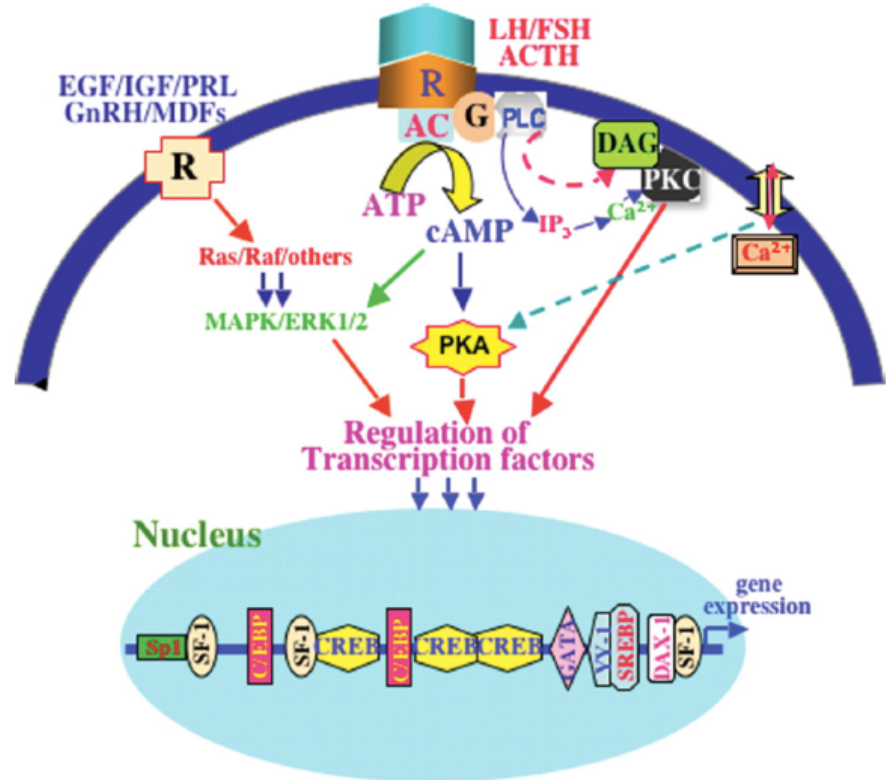


Figure 4: Schematic showing the different signalling pathways that regulate the transcription of StAR (Source: Manna *et al.*, 2009)

STEROID HORMONE SYNTHESIS

- The essentiality of StAR was demonstrated by studying patients with congenital lipid adrenal hyperplasia. Mutations in StAR were found in these patients, showing that this protein is necessary for gonadal and adrenal steroidogenesis

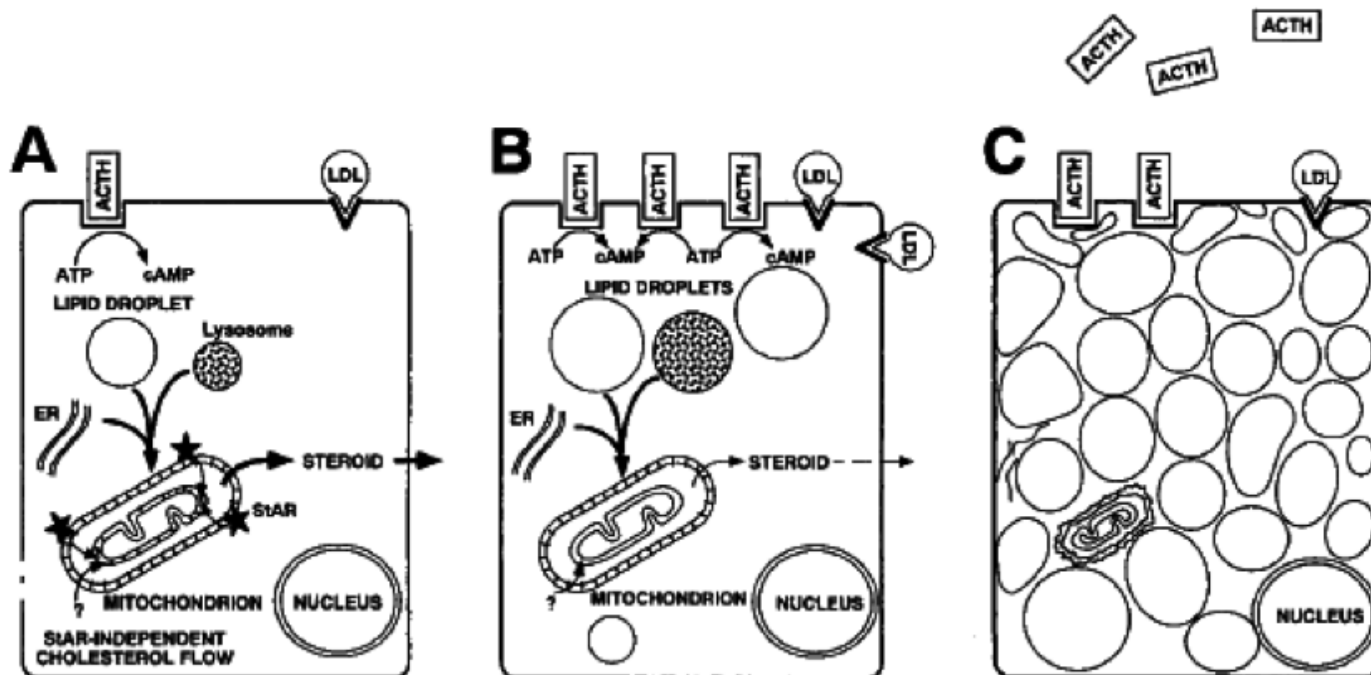


Figure 6: A – a normal adrenal cell stimulated by ACTH produces steroids. B – this cell has no StAR but some steroid is still produced by independent mechanisms. This would be a placental cell or in early congenital lipid hyperplasia. C – lipid droplets accumulate and damage the cell structure. Stimulation continues as there is no negative feedback.

STEROID HORMONE SYNTHESIS

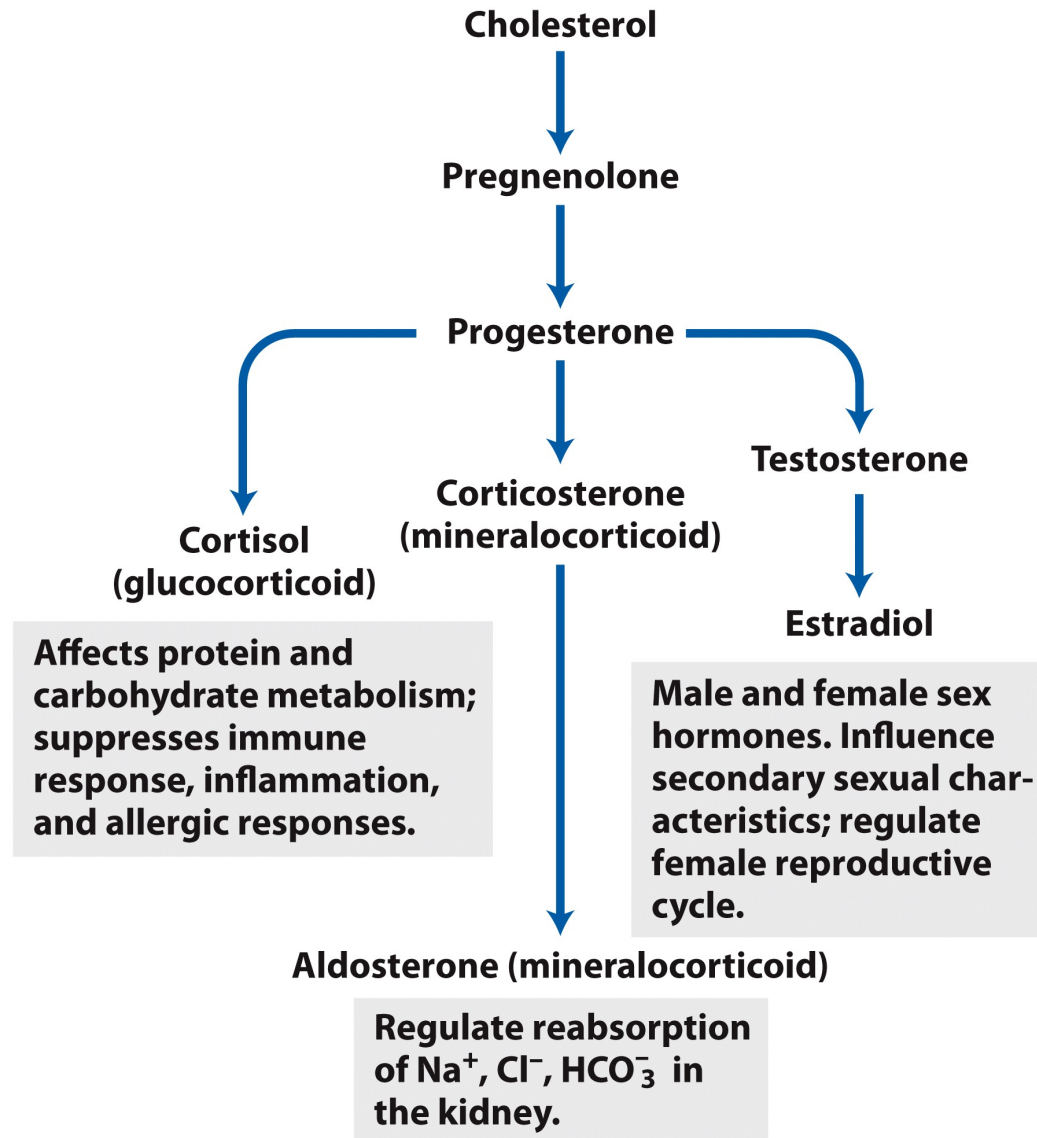
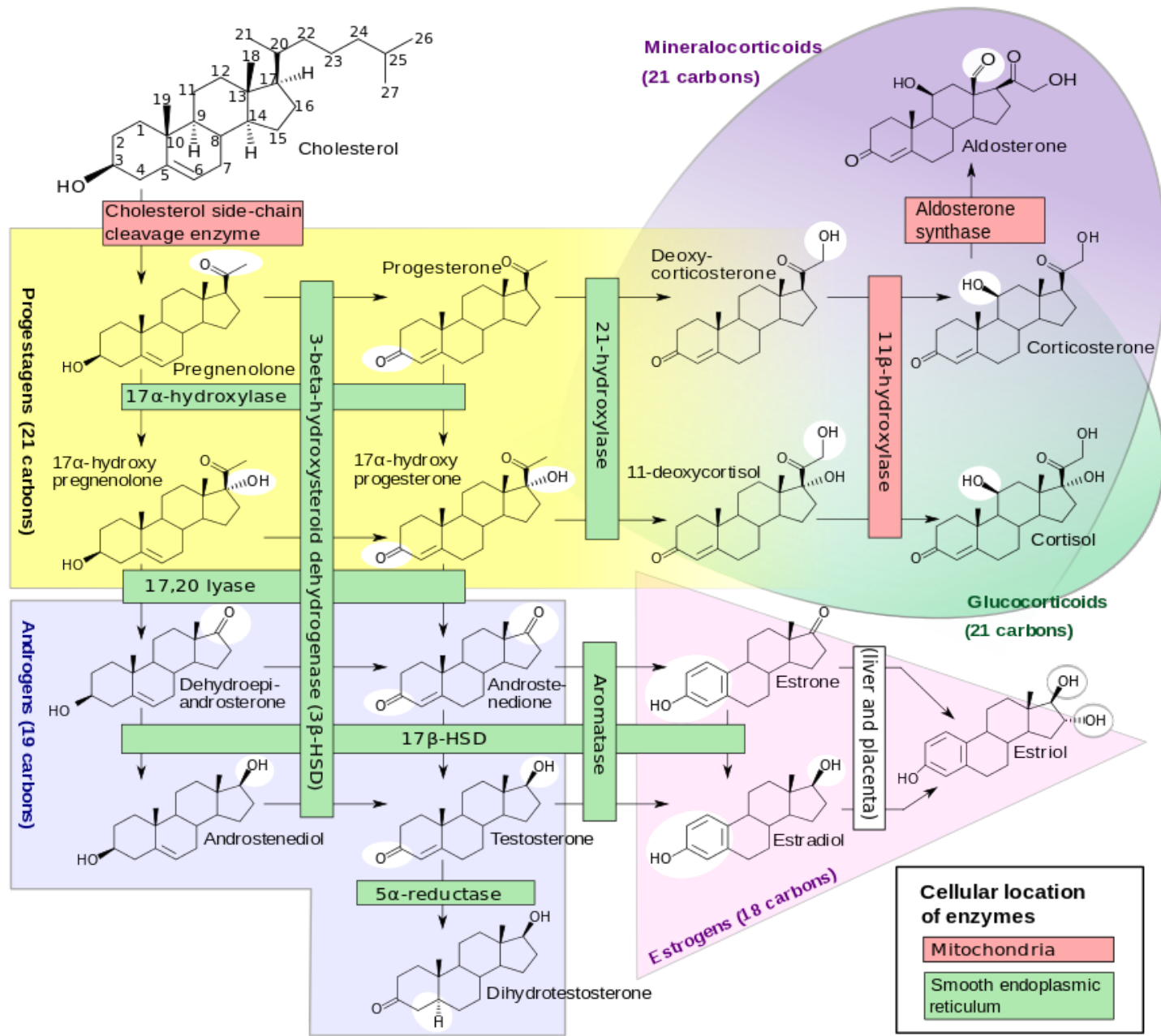


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STEROID HORMONE SYNTHESIS



STEROID HORMONE SYNTHESIS

- Pregnenolone is derived from cholesterol and is the precursor of all other steroid hormones.
- For example, pregnenolone is converted to progesterone by oxidation of the hydroxyl group to a ketone and isomerization of a double bond

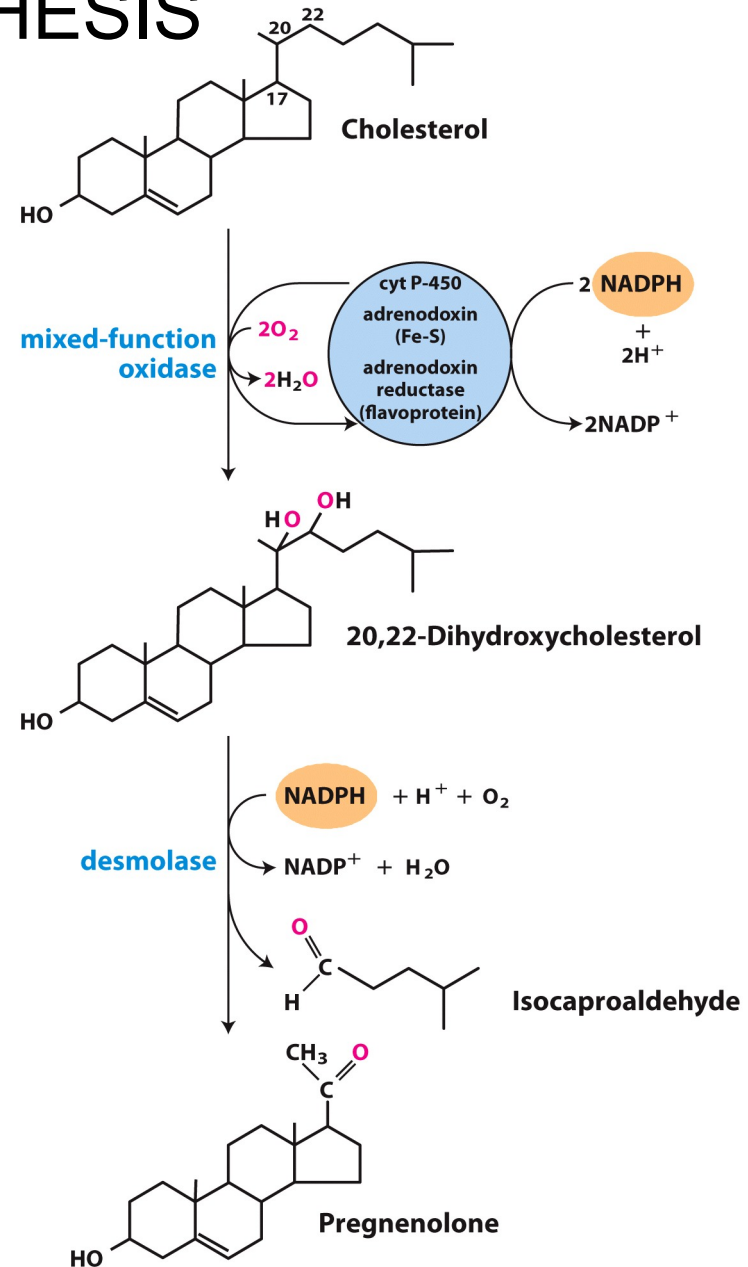


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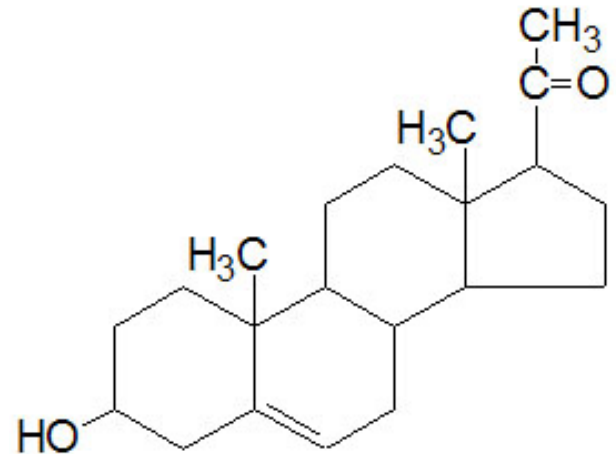
STEROIDOGENIC ENZYMES

Common name	"Old" name	Current name
Side-chain cleavage enzyme; desmolase	P450 _{SCC}	CYP11A1
3 beta-hydroxysteroid dehydrogenase	3 beta-HSD	3 beta-HSD
17 alpha-hydroxylase/17,20 lyase	P450 _{C17}	CYP17
21-hydroxylase	P450 _{C21}	CYP21A2
11 beta-hydroxylase	P450 _{C11}	CYP11B1
Aldosterone synthase	P450 _{C11AS}	CYP11B2
Aromatase	P450 _{aro}	CYP19

STEROID HORMONES

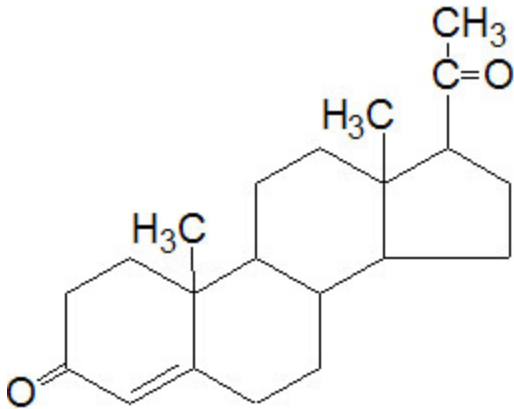
Pregnenolone (C-21)

produced directly from cholesterol, the precursor molecule for all C₁₈, C₁₉ and C₂₁ steroids



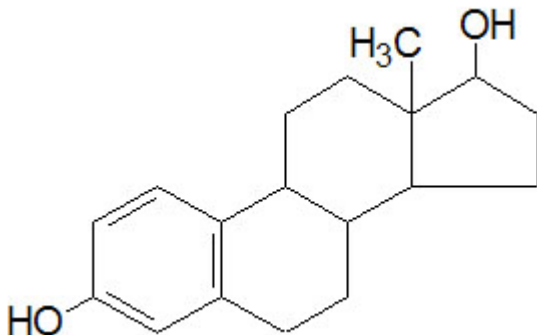
STEROID HORMONES

Progesterone (C-21)



- A progestin, produced directly from pregnenolone.
- Secreted from the ***corpus luteum***.
- Maintains (with estradiol) the uterine endometrium for implantation.
- Differentiation factor for mammalian glands.

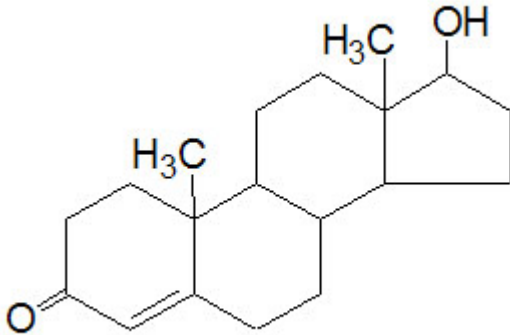
Estradiol (C-18)



- Female: regulates gonadotrope secretion in ovarian cycle.
- Maintains (with progesterone) uterine endometrium.
- Differentiation of mammalian gland.
- Responsible for secondary female sex characteristics.
- Male: negative feedback inhibitor of Leydig cell synthesis of testosterone.

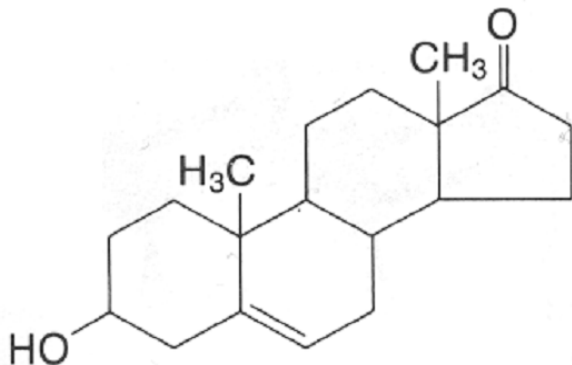
STEROID HORMONES

Testosterone (C-19)



- After conversion to dihydrotestosterone, production of sperm proteins in Sertoli cells.
- Responsible for secondary male sex characteristics.
- Produced from progesterone.

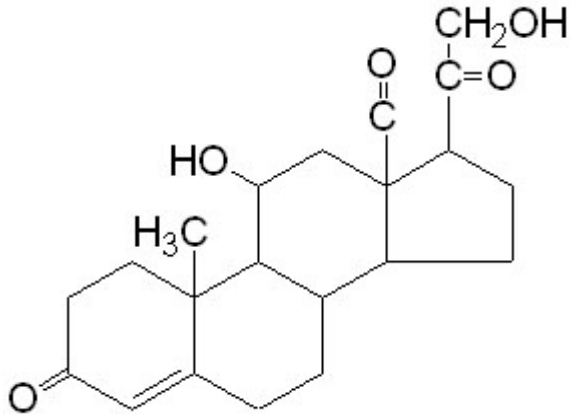
Dehydroepiandrosterone



- Weak androgen, which can be converted to estrogen.
- Various protective effects. It may play a role in the aging process.
- Regulates NAD⁺ coenzymes.

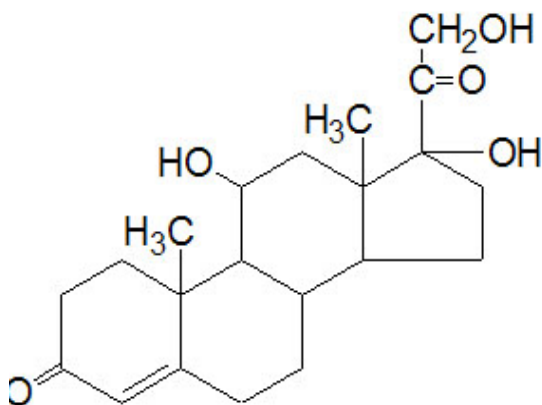
STEROID HORMONES

Aldosterone (C-21)



- The principal mineralocorticoid.
- Produced from progesterone in the **zona glomerulosa** of adrenal cortex.
- Causes sodium ion uptake via conductance channel.
- Occurs in high levels during stress. Rises blood pressure and fluid volume.

Cortisol (C-21)

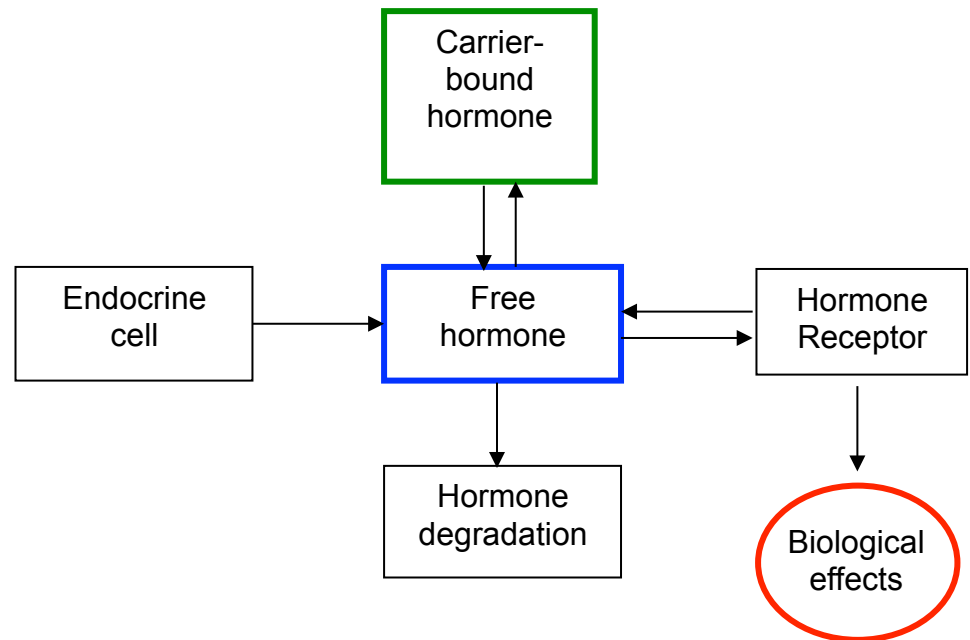


- Dominant glucocorticoid in humans, synthesized from progesterone in the **zona fasciculata** of the adrenal cortex.
- Stress adaptation through various cellular phenotypic expression, stress adaptation.
- Slight elevation of liver glycogen. Numerous effects on the immune system, killing effect on certain T cells in high doses.
- Na⁺ uptake in epithelia lumen.

STEROID HORMONES TRANSPORT

- Are not water soluble so have to be carried in the blood complexed to specific binding globulins.
- Corticosteroid binding globulin carries cortisol.
- Sex steroid binding globulin carries testosterone and estradiol.
- In some cases a steroid is secreted by one cell and is converted to the active steroid by the target cell: (androgen is secreted by the gonad and converted into estrogen in the brain).

- Albumin
- Corticosteroid binding globulin (CBG) or transcortin
- Sex hormone binding globulin (SHBG)
- Androgen binding protein (ABP)

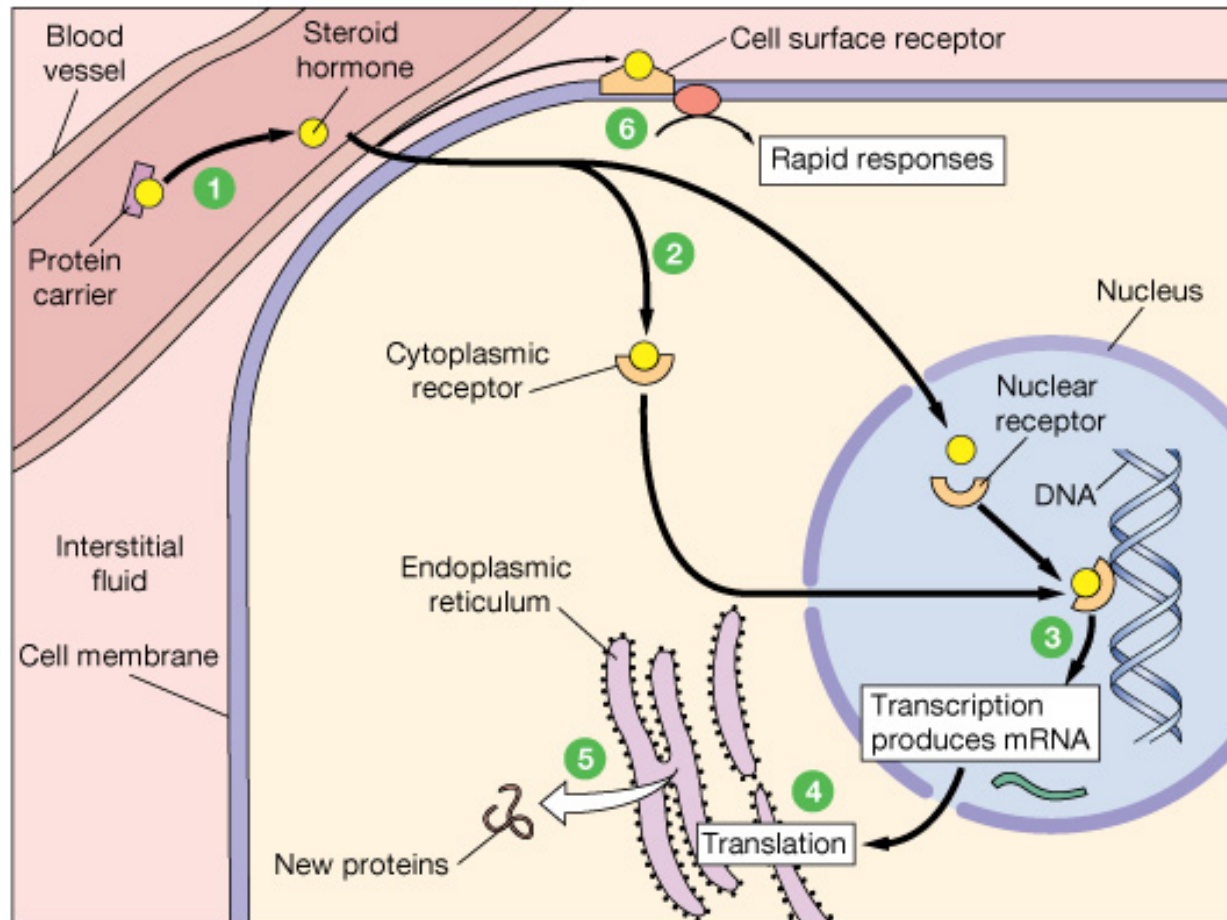


Only the free fraction is biologically active usually less than 10%

HORMONE HALF LIFE

- **Steroids and thyroid hormone**, which are bound to plasma proteins, have a long half life (~ **hours**)
- **Peptides and catecholamines** are water-soluble, they are transported dissolved in plasma, generally have a very short half life (~ **seconds to minutes**)

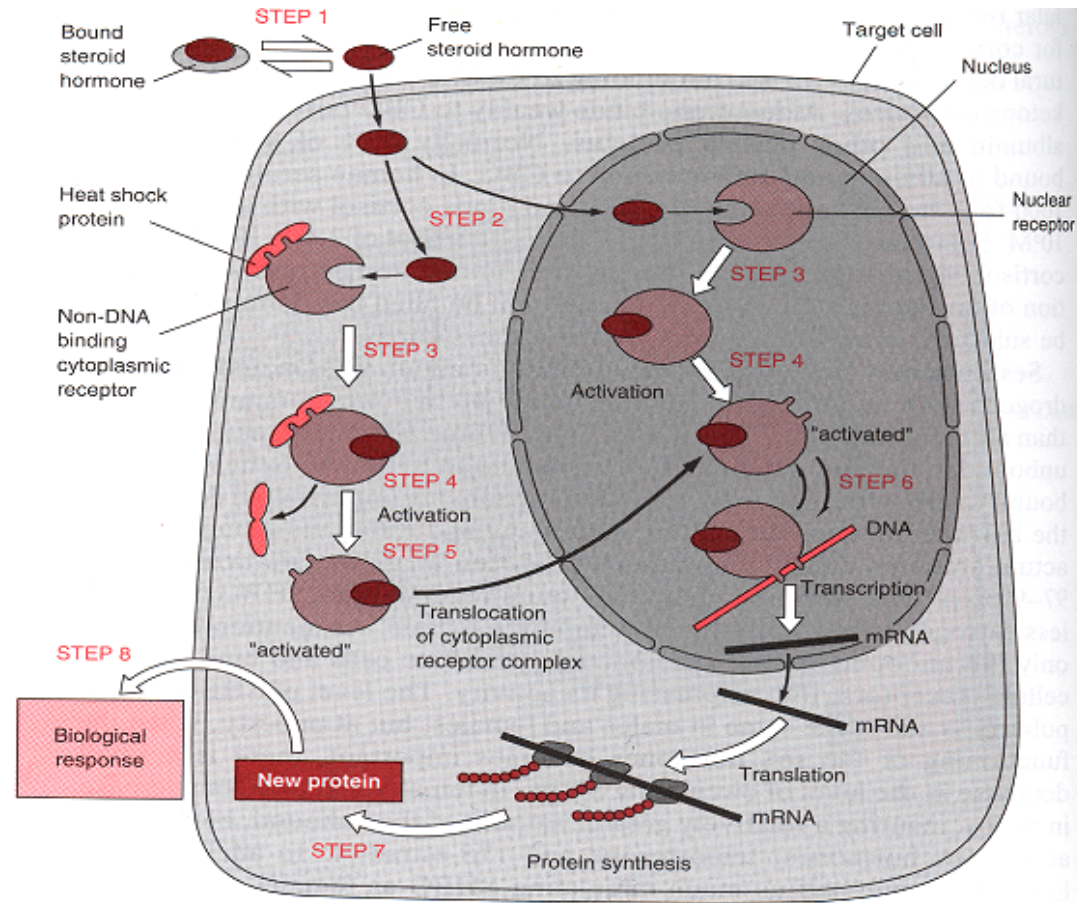
STEROID HORMONES: MOLECULAR ACTION



- 1 Most hydrophobic steroids are bound to plasma protein carriers. Only unbound hormones can diffuse into the target cell.
- 2 Steroid hormone receptors are in the cytoplasm or nucleus.
- 3 The receptor-hormone complex binds to DNA and activates or represses one or more genes.
- 4 Activated genes create new mRNA that moves back to the cytoplasm.
- 5 Translation produces new proteins for cell processes.
- 6 Some steroid hormones also bind to membrane receptors that use second messenger systems to create rapid cellular responses.

STEROID HORMONES: MOLECULAR ACTION

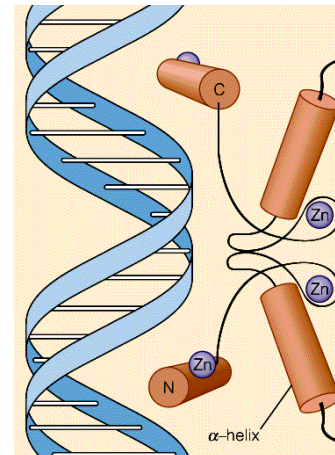
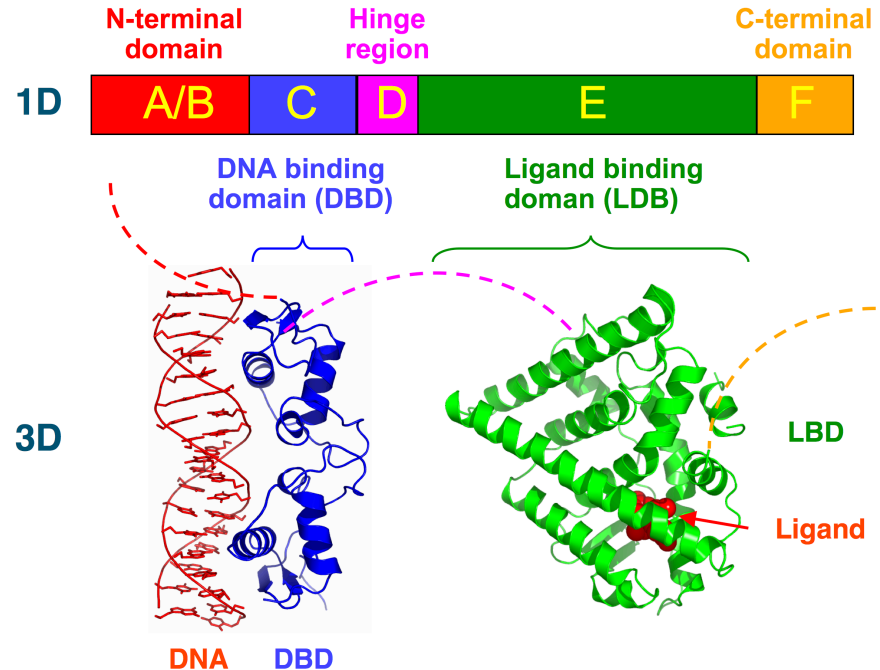
- Steroid hormones are soluble in the plasma membrane and readily enter the cytosol.
- Steroids bind to intracellular receptor either in the cytosol or in the nucleus.
- The hormone-receptor complex acts as a transcription factor which turns on / turns off the genes.
- Messenger RNA is transcribed, leaves the nucleus, and is translated into a specific protein by ribosome.
- The specific proteins then carry out function in the target cell.
- Because steroid hormones initiate protein synthesis their effects are produced more slowly, but are more long-lasting than those produced by other hormones.



STEROID HORMONES: MOLECULAR ACTION

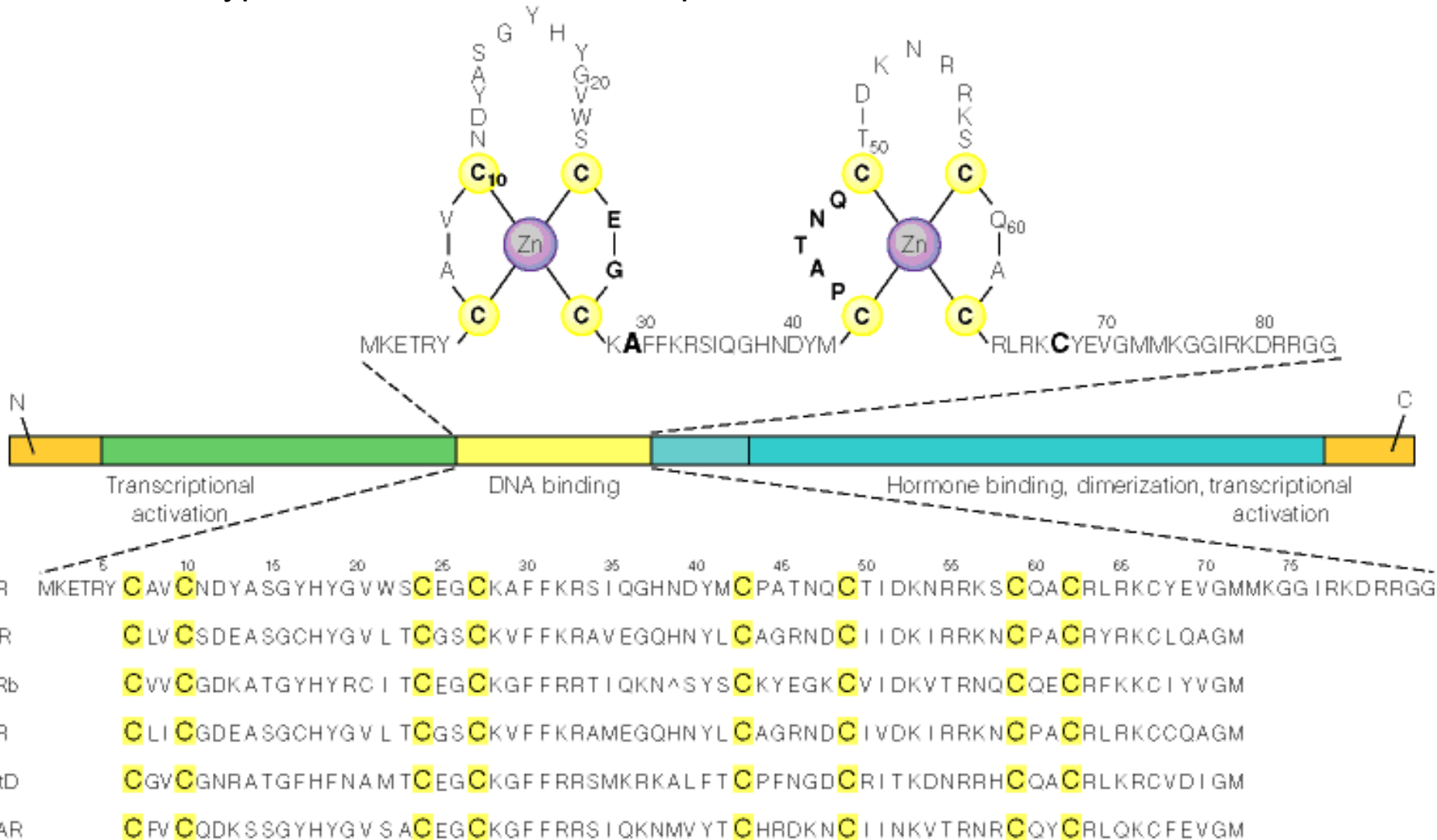
Structural Organization of Nuclear Receptors

- cDNA sequence analysis of intracellular hormone receptors has revealed structural similarities among steroid receptors. Unambiguous identification of domains of function within the receptor molecule has also been performed.
- All of the known receptors in this family contain bound zinc, which is essential for DNA binding. Furthermore, the DNA-binding sequences show a completely conserved distribution of cysteine residues.
- Zinc atoms are probably complexed by the cysteine sulfurs in a pattern akin to the "zinc finger" structural motif of other eukaryotic transcriptional regulatory proteins.



STEROID HORMONES: MOLECULAR ACTION

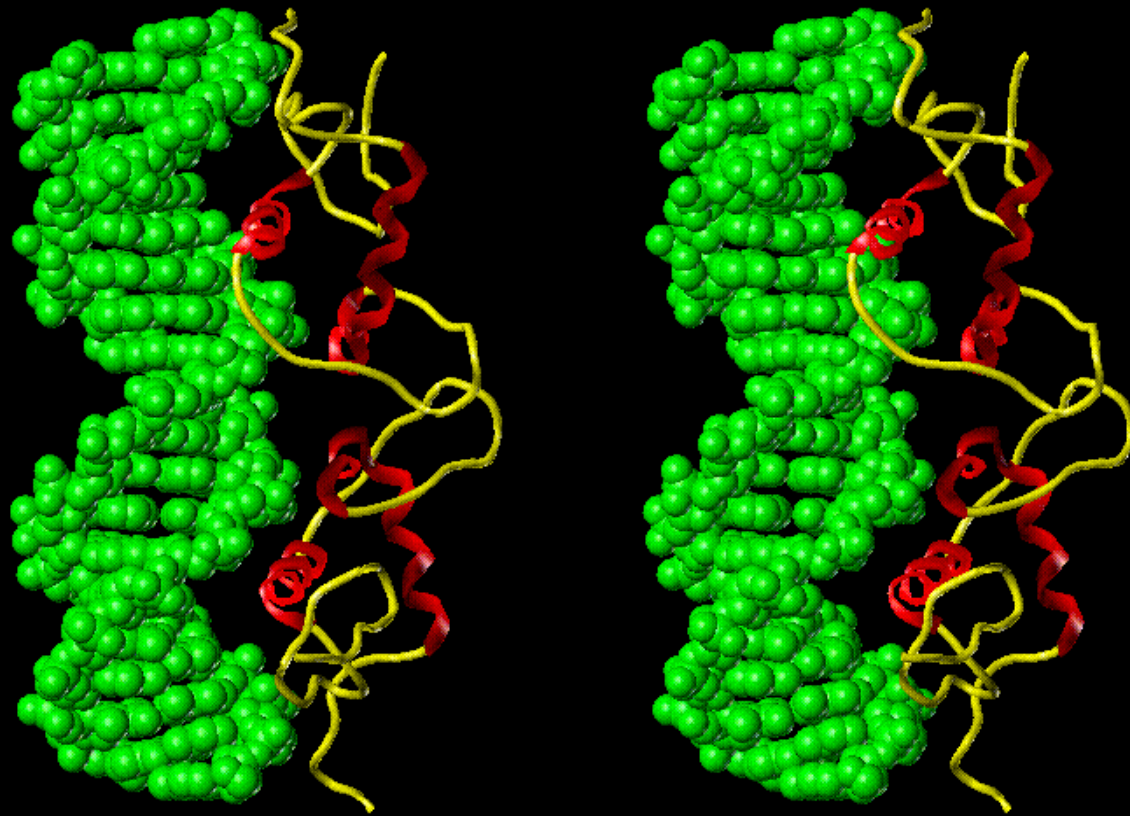
Model of typical steroid hormone receptor



<http://www.aw-bc.com/mathews/ch23/fi23p16.gif>

STEROID HORMONES: MOLECULAR ACTION

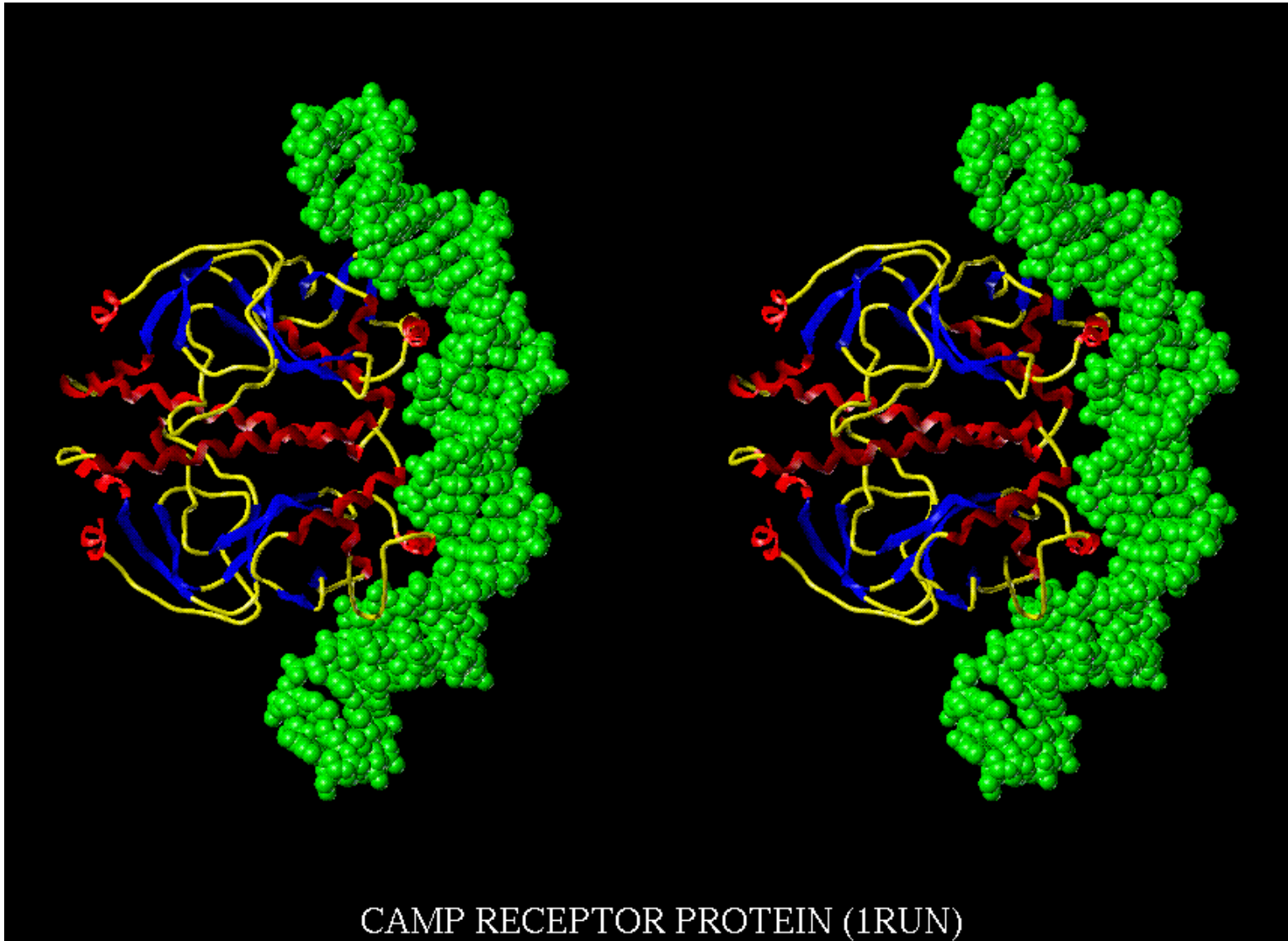
Steroid Receptors Bind HREs as Homo- or Heterodimers



GLUCOCORTICOID RECEPTOR COMPLEX WITH DNA (1GLU)

STEROID HORMONES: MOLECULAR ACTION

Receptor Binding to HREs Can Bend DNA & Alter Transcription



STEROID HORMONES: MOLECULAR ACTION

- The utility of a set of long-term-acting regulators is evident the estrogens and progesterone that regulate the female reproductive cycle. In humans these hormones interact over a 4-week cycle to prepare the uterus for implantation of a fertilized ovum.
- The actions of glucocorticoids are comparable, in that control of the synthesis of particular proteins allows for long-term metabolic adaptation.

Whereas estrogens exercise control of reproductive metabolism over a several-week period, the secretion of glucocorticoids is a means of adaptation to longer-term stress. This adaptation involves stimulation of gluconeogenesis and synthesis of a variety of proteins, including some that counteract the effects of inflammation.

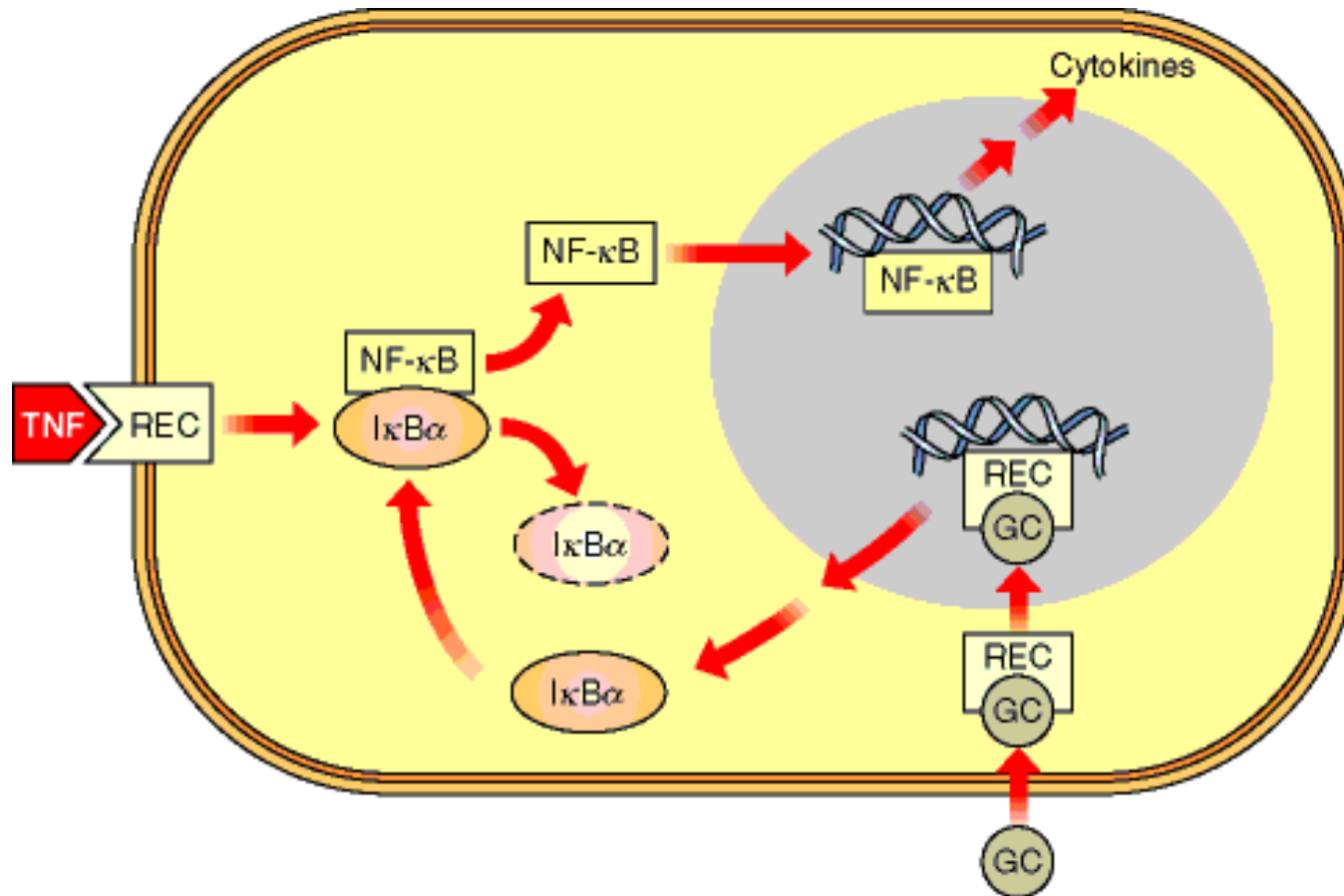
Hormone Class	Target Organ	Protein ^a
Glucocorticoids	Liver	Tyrosine aminotransferase Tryptophan oxygenase α -Fetoprotein (\downarrow) Metallothionein
	Liver, retina	Glutamine synthetase
	Kidney	Phosphoenolpyruvate carboxykinase
	Oviduct	Ovalbumin
	Pituitary	Pro-opiomelanocortin
Estrogens	Oviduct	Ovalbumin Lysozyme
	Liver	Vitellogenin apo-VLDL
Progesterone	Oviduct	Ovalbumin Avidin
	Uterus	Uteroglobin
Androgens	Prostate	Aldolase
	Kidney	β -Glucuronidase
	Oviduct	Albumin
1,25-Dihydroxyvitamin D ₃	Intestine	Calcium-binding protein
Thyroid hormones	Liver	Carbamoyl phosphate synthetase Malic enzyme
	Pituitary	Growth hormone Prolactin (\downarrow)
Ecdysone (in insects)	Epidermis	Dopa decarboxylase
	Fat body ^b	Vitellogenin

^aSynthesis of each indicated protein is increased by the hormone, except for the two identified by (\downarrow).

^bThe fat body is an organ in insects that plays some of the same roles as liver and adipose tissue.

STEROID HORMONES: MOLECULAR ACTION

- The glucocorticoids influence cells in a wide variety of target tissues. Glucocorticoids act to stimulate transcription of a protein called B, which inactivates the transcriptional factor called NF- κ B. NF- κ B helps control transcription of the cytokines, which stimulate the immune response.



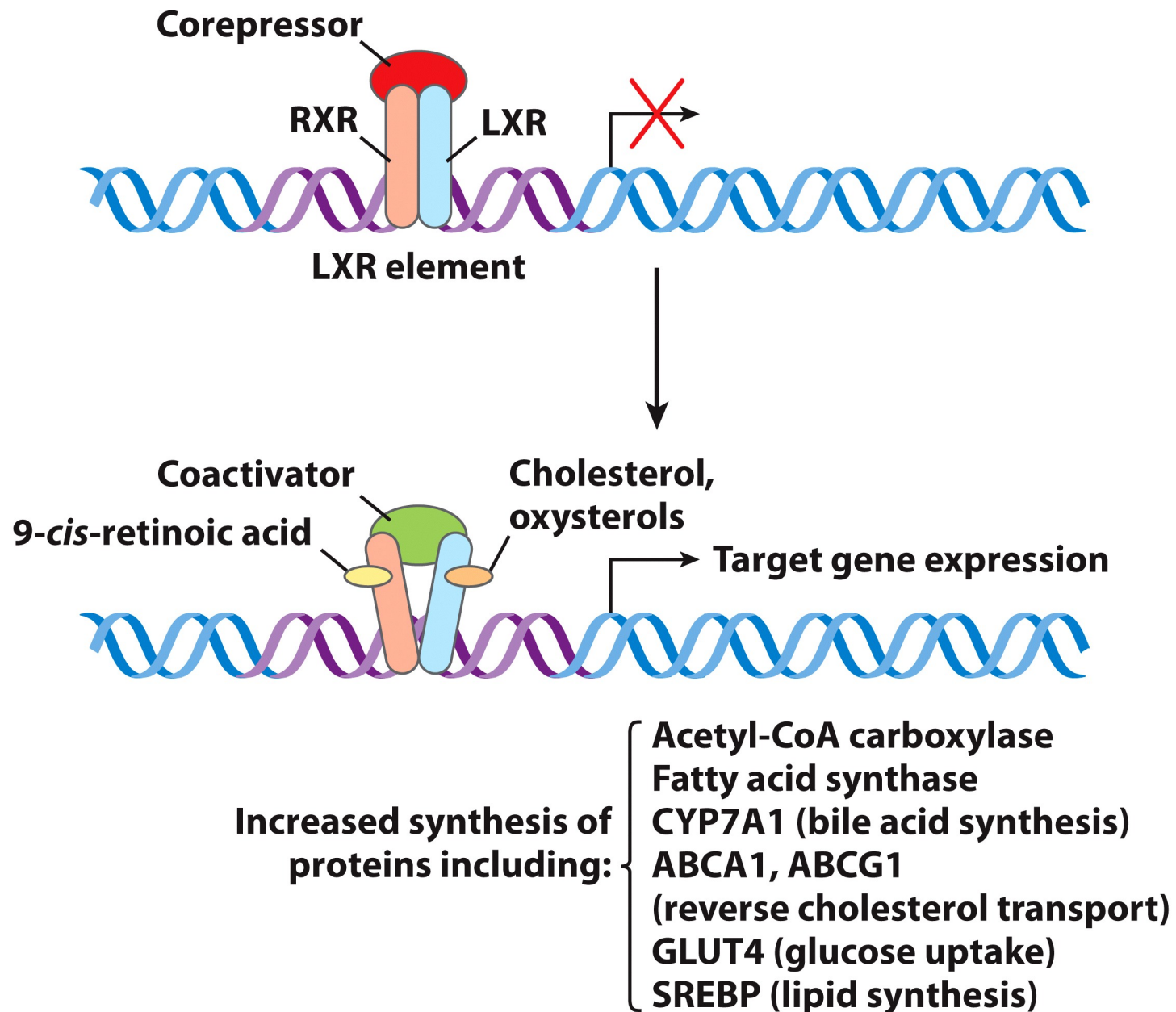


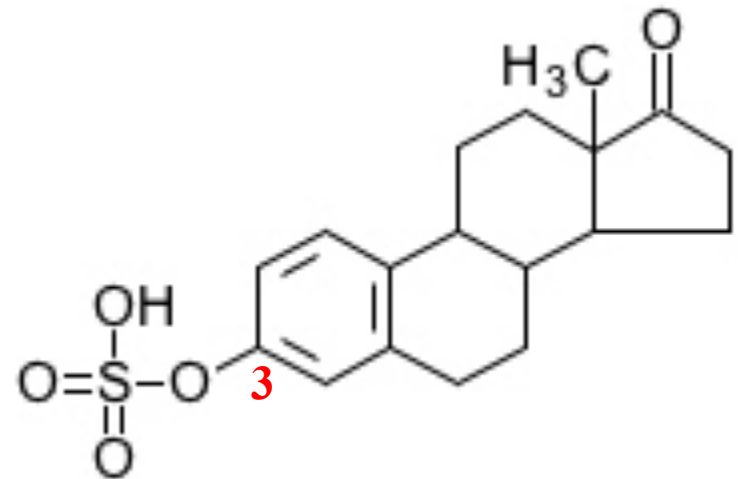
Figure 21-45

Lehninger Principles of Biochemistry, Sixth Edition

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HORMONE CATABOLISM AND EXCRETION

- Inactivation of steroids involves reductions and conjugation to glucuronides or sulfate to increase their water solubility.
- Most are catabolized by the liver and kidneys.
- 70% of the conjugated steroids are excreted in the urine, 20 % leave in feces and rest exit through the skin.



estron-3sulfate