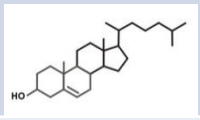
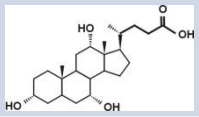
LIPIDS

sterol lipids

Marek Vecka

CLASSIFICATION OF LIPIDS

- molecular structure

Lipid class	Abbreviation	N of known structures
Fatty acyls	FA	5869
Glycerolipids	GL	7541
Glycerophospholipids	GP	8002
Sphingolipids	SP	4338
Sterol lipids  	ST	2715
Prenol lipids	PL	1259
Other – saccharolipids, polyketides	SL, PK	1293+6742

Fahy 2005, Fahy 2009

STEROL LIPIDS

STEROL LIPIDS = lipid molecules with backbone derived from cyclopenta[a]phenanthrene (?)

Division according to biochemical function

1. Sterols

cholesterol, phytosterols, marine sterols…

2. Bile acids and derivatives

C24, C26, C27, C28 bile acids, bile alcohols

3. Steroids

C18 steroids, C19 steroids, C21 steroids

4.Secosteroids

vitamins D

Other groups

conjugates, hopanoids, …

STEROL LIPIDS

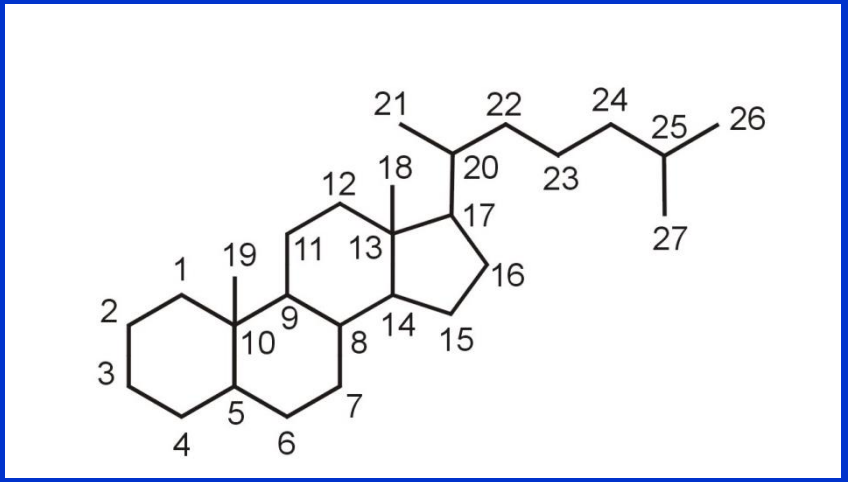
Structures

1. Numbering system for C27

four-ring system first

C´s on attached methyls

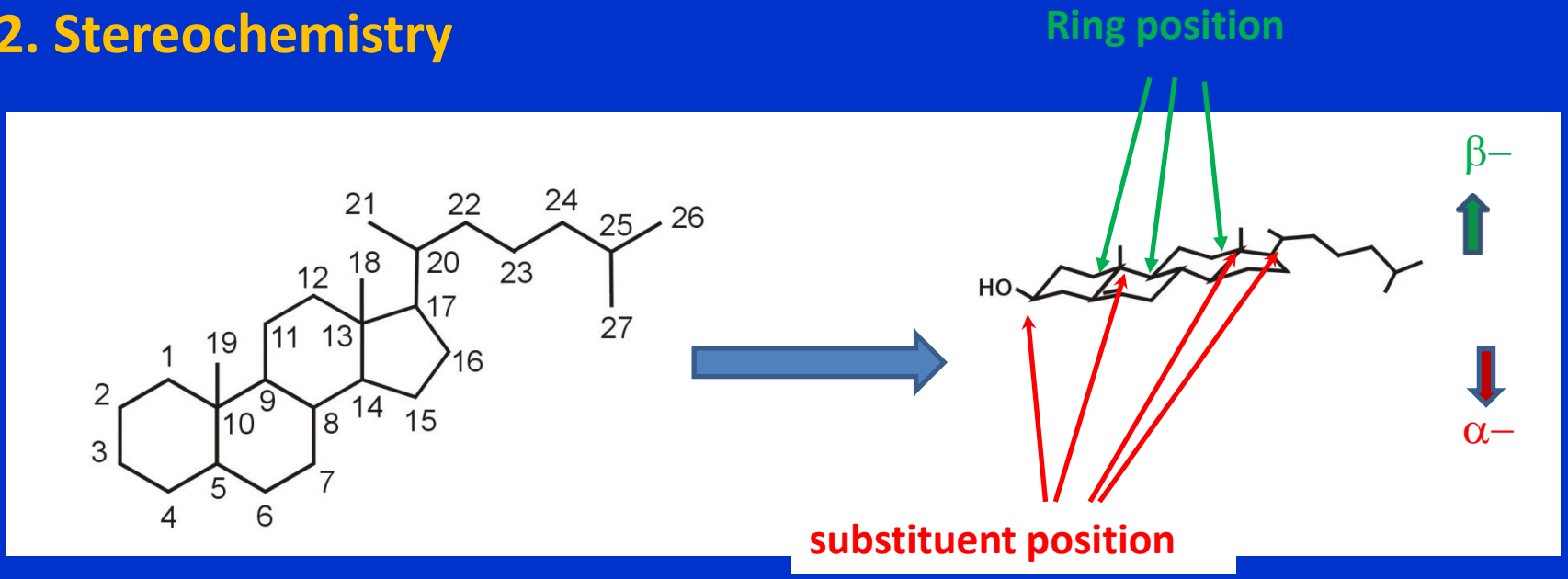
side chain



STEROL LIPIDS

Structures

2. Stereochemistry



Conventions:

1. Ring position: *cis*- (remaining 4th bonds of common C-C are *cis*-) (A-B *cis*-: bile acids)
   vs. *trans*- (remaining 4th bonds of common C-C are *trans*-) (all : cholesterol)
2. Substituents: **α-** (**below** cycle plane) vs. **β–** (**above** cycle plane)

STEROL LIPIDS

Structures

3. Important hydrocarbon structures

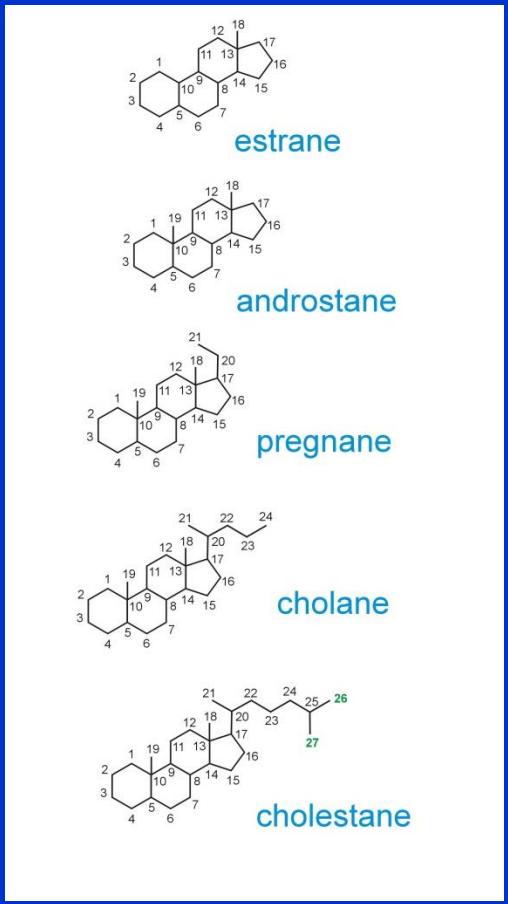
C18 structures: estra-
steroid hormones

C19 structures: androsta-
steroid hormones

C21 structures: pregna-
steroid hormones

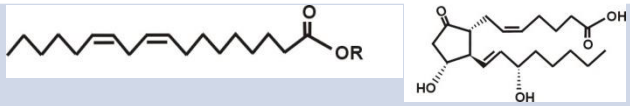
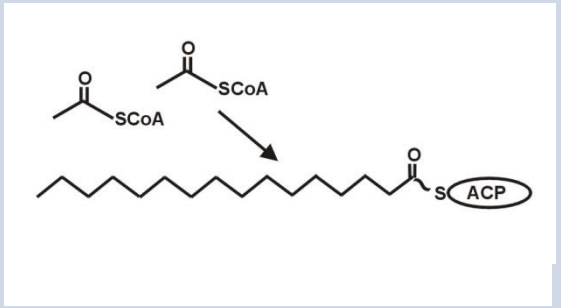
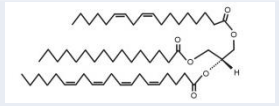
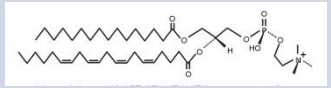
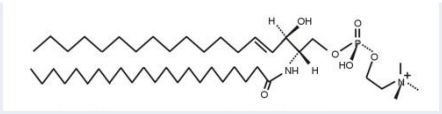
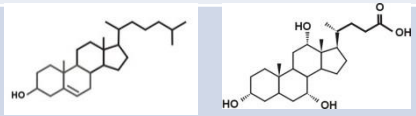
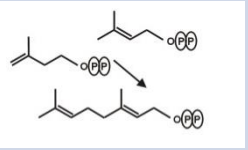
C24 structures: chola-
bile acids/alcohols

C27 structures: cholesta-
cholesterol, oxysterols



CLASSIFICATION OF LIPIDS

- biosynthetic route

Lipid class	Biosynthetic route
Fatty acyls 	condensation of thioesters 
Glycerolipids 	
Glycerophospholipids 	
Sphingolipids 	
Sterol lipids 	condensation of activated isoprene units 
Prenol lipids 	
Other – saccharolipids, polyketides	other types

STEROLS

Biosynthesis of sterols (cholesterol)

1. Biosynthesis of isopentenyldiphosphate
= activated isoprene unit

2. Condensation of isopentenyldiphosphate units
6 units are needed (C30)

3. Cyclization of squalene to lanosterol
oxygen needed

4. Further modification of lanosterol to cholesterol
C30 → C27 (three CH_3 have to be removed)
migration of double bond and reduction of the other

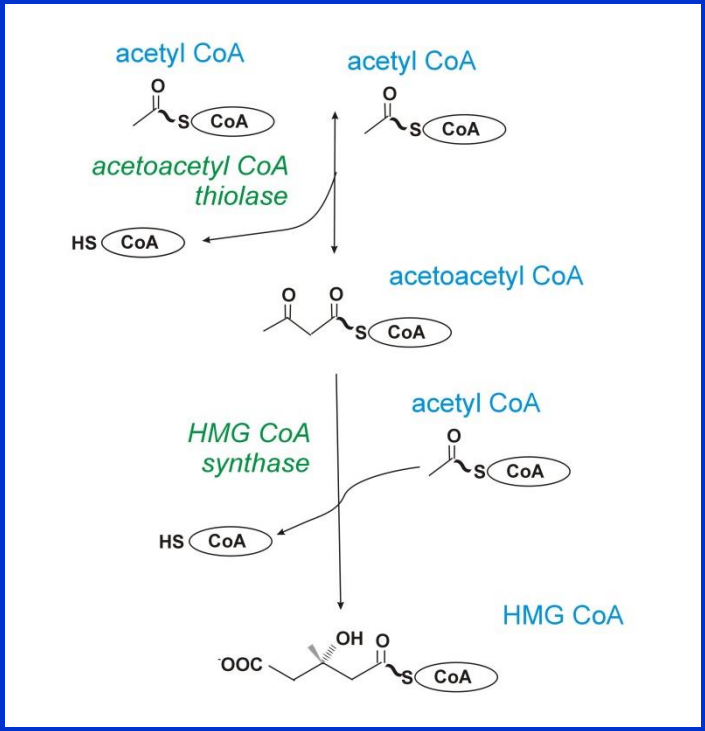
STEROLS

Biosynthesis of sterols (cholesterol)

1. Biosynthesis of isopentenyldiphosphate

= activated isoprene unit

<u>biosynthesis of HMG-CoA</u>
(hydroxymethylglutaryl CoA)
- takes place in cytosol



STEROLS

Biosynthesis of sterols (cholesterol)

1. Biosynthesis of isopentenyldiphosphate

= activated isoprene unit

<u>biosynthesis of mevalonate</u>

via ***HMG-CoA reductase***

irreversible reaction

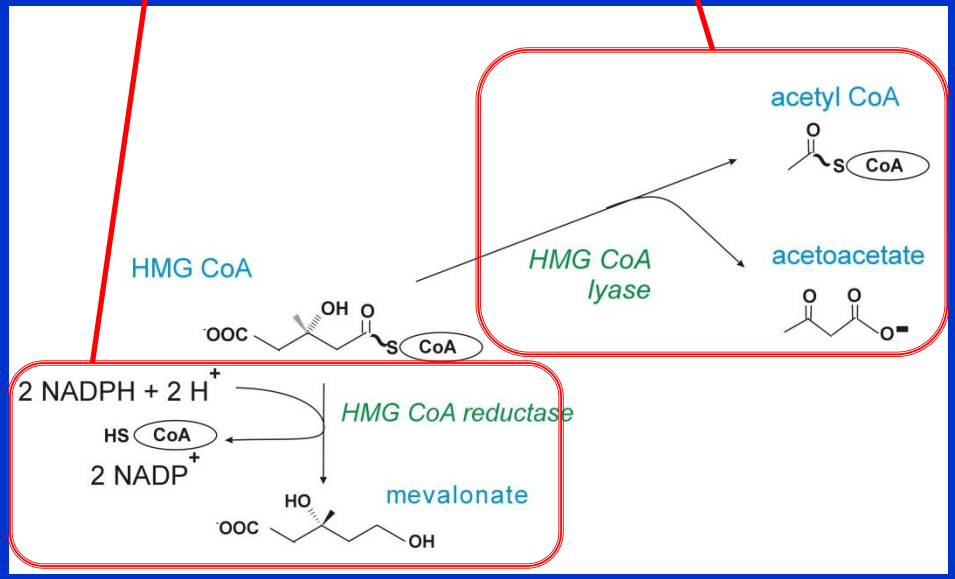
rate limiting step of synthesis

- takes place in ER

Inhibitors = **statins**

cholesterol biosynthesis in hepatocyte ER

ketogenesis in hepatocyte mitochondria



STEROLS

Biosynthesis of sterols (cholesterol)

Regulation of HMG-CoA reductase

1. directly by phosphorylation (inactive)/dephosphorylation (active)

AMP/ATP ratio responsive AMP activated protein kinase

glucagon, noradrenaline (↑cAMP)→ inhibition of CH biosynthesis

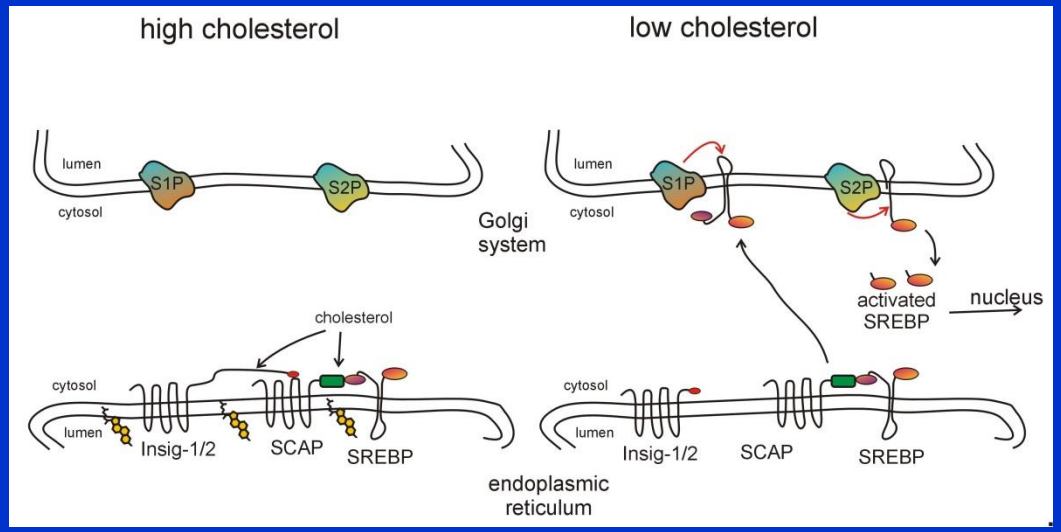
insulin (↓cAMP)→ stimulation of CH biosynthesis

2. transcriptionally via SREBP binding to SRE

cholesterol feedback

3. enzyme degradation

INSIG dependent



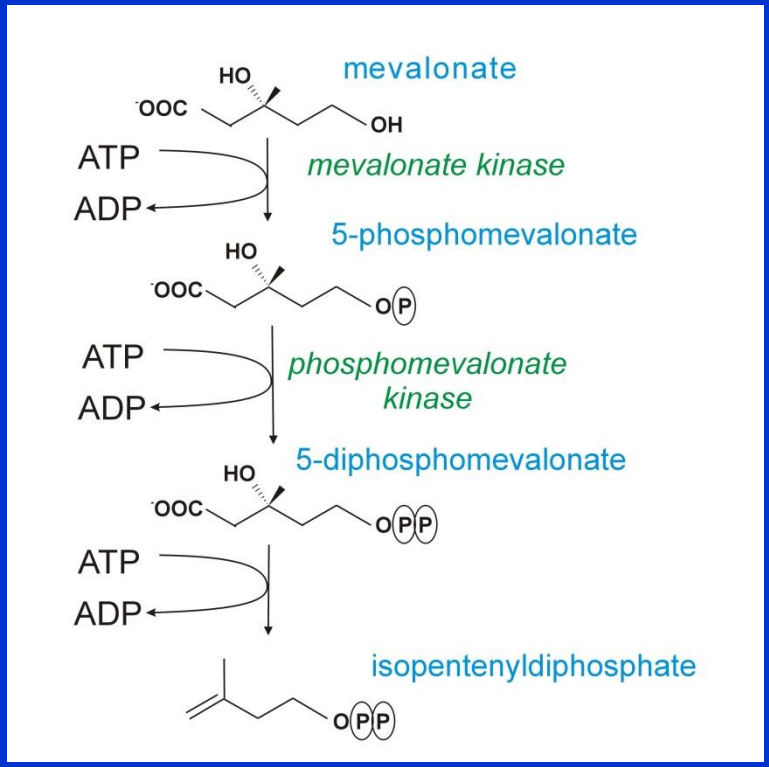
STEROLS

Biosynthesis of sterols (cholesterol)

1. Biosynthesis of isopentenyldiphosphate

= activated isoprene unit

activation of C6
decarboxylation (→C5 unit)
takes place in cytosol



STEROLS

Biosynthesis of sterols (cholesterol)

2. Condensation of isopentenyldiphosphate units

C5 units can isomerize (IPP ↔ DMAP)

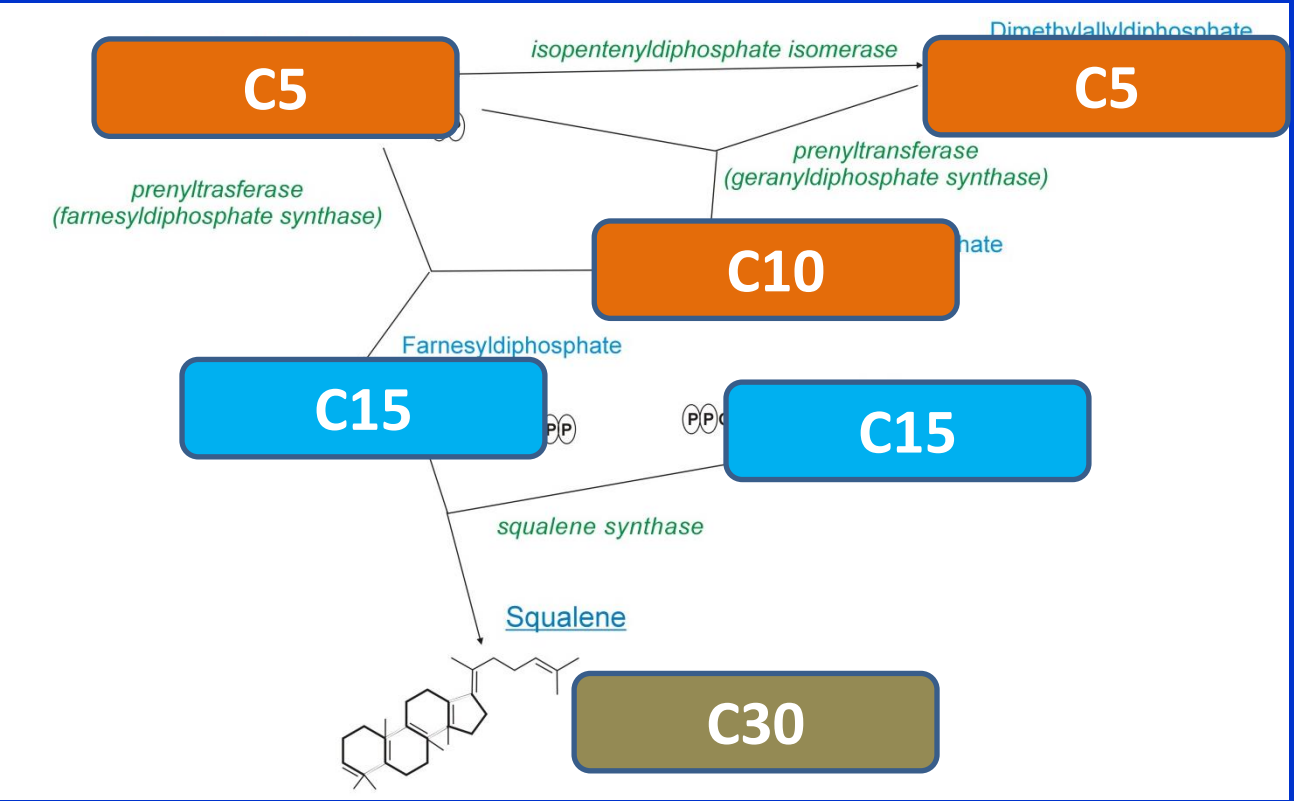
a) IPP + DMAP = GPP

b) GPP + IPP = FPP

c) 2 FPP = SQ

takes place in ER

peroxisomes



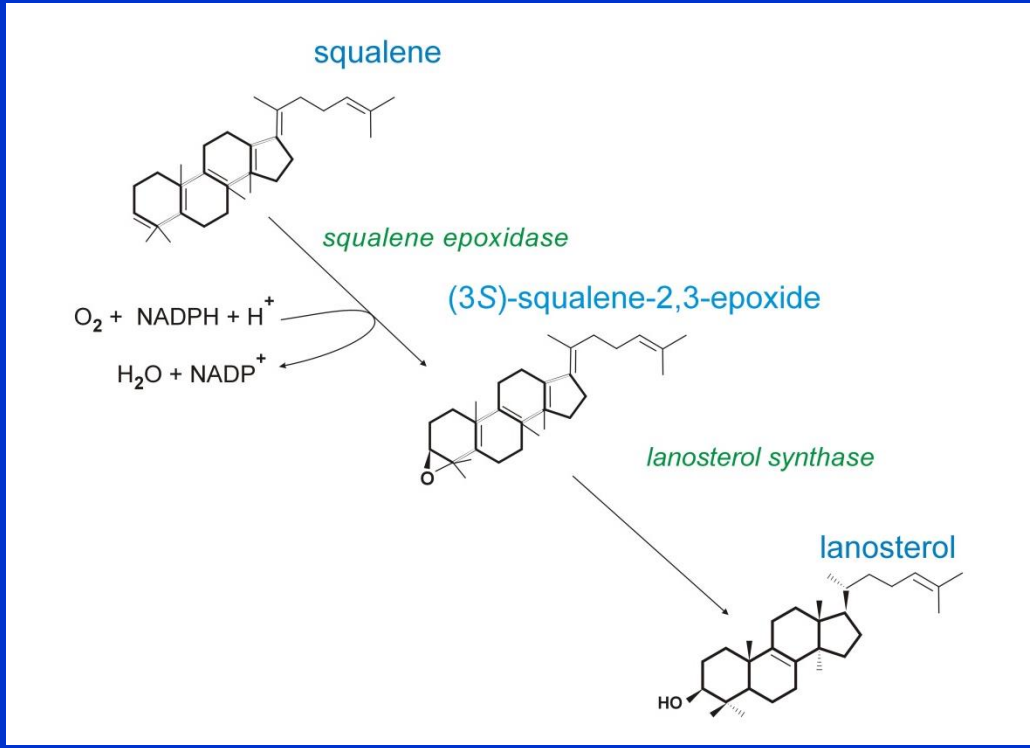
STEROLS

Biosynthesis of sterols (cholesterol)

3. Cyclization of squalene to lanosterol

oxygen is needed

procaryota do not synthesize sterols



STEROLS

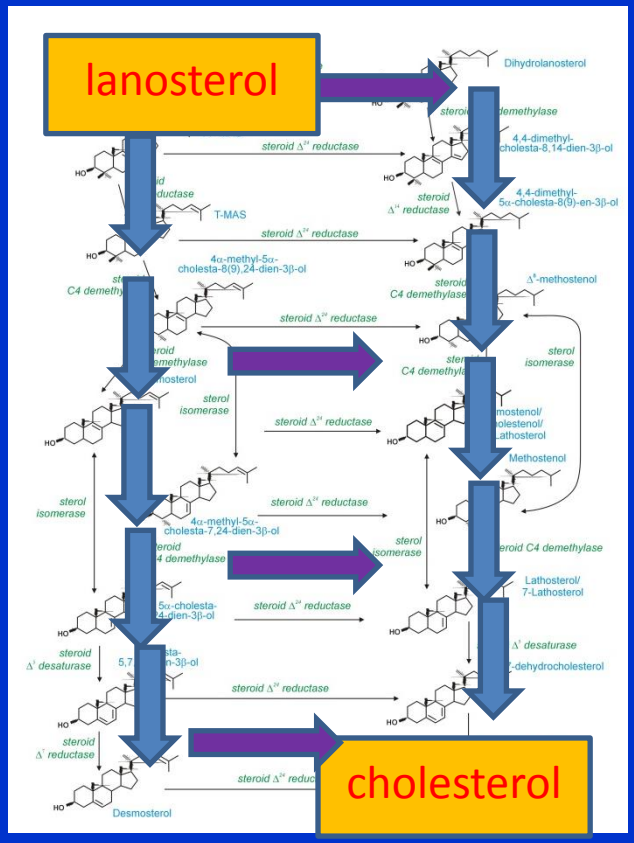
Biosynthesis of sterols (cholesterol)

4. Further modification of lanosterol to cholesterol

C30 → C27 (three CH_3 have to be removed)

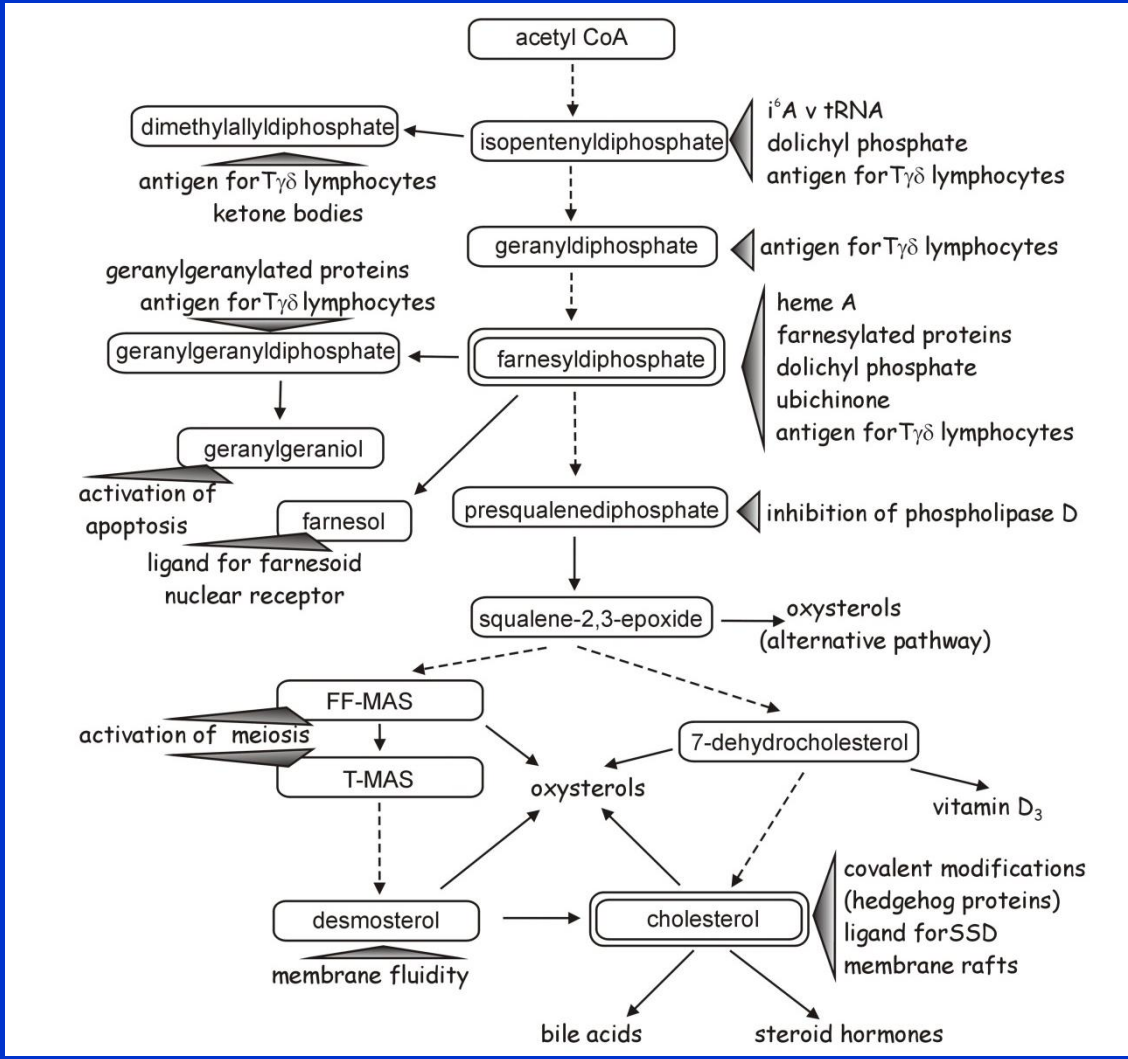
migration of double bond

reduction of double bond at C24



STEROLS

Function of cholesterol biosynthetic pathway



STEROLS

Inborn errors of biosynthesis of cholesterol

1. SLOS syndrome

= 3rd most common (US)
(after CF and PKU)

deficiency of d7-DHC dehydrogenase

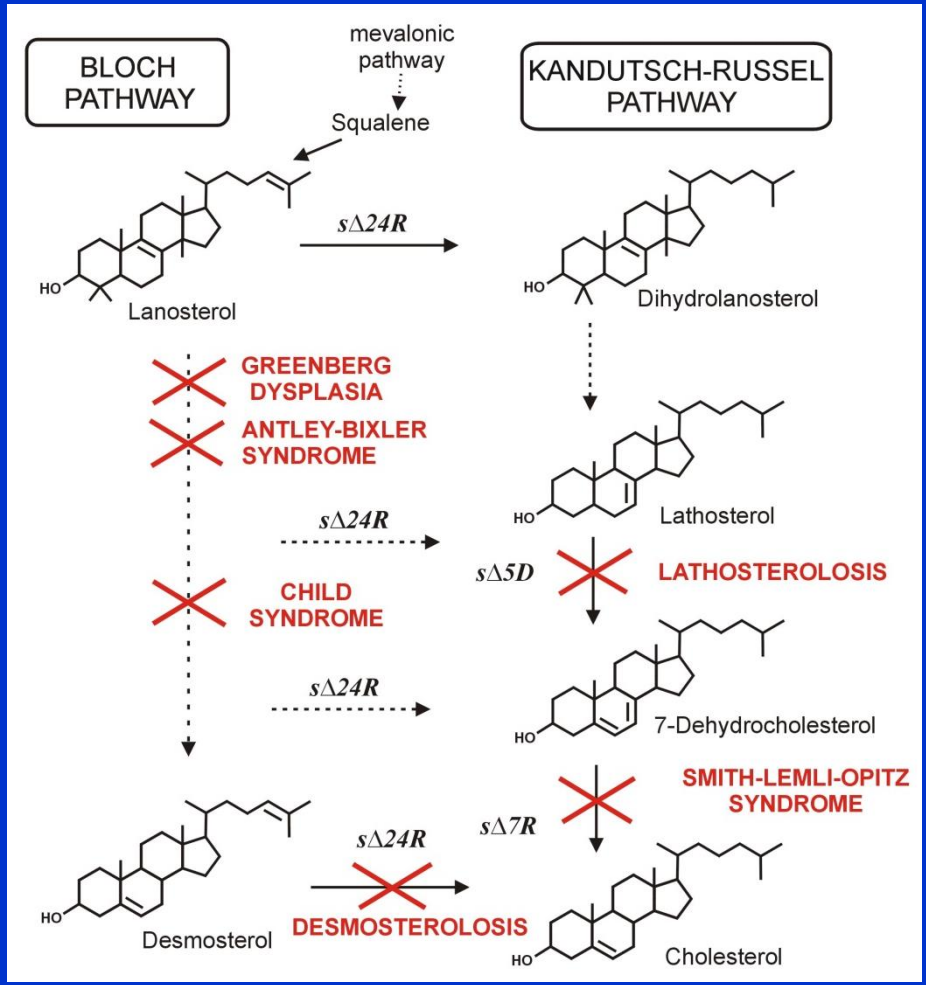
prevalence 1:20-60 000

multiple congenital anomalies

mental retardation

syndactyly

growth retardation



STEROLS

Fates of cholesterol

1. Membrane component

free (unesterified cholesterol) **fluidity modulation**

2. Substrate for further metabolization

→ bile acids (liver/skin/brain/peripheral nervous tissues)
CH elimination/lipid absorption/ signalling

→ steroid hormones (steroidogenic tissues) **hormones**

→ oxysterols (various tissues) **signalling / CH elimination**

3. Storing in droplets

as cholesteryl esters (CE) **CH storage**

4. Releasing into the circulation

→ via HDL (peripheral tissues/intestine) **excess CH**

→ via VLDL (liver) **CH source**

STEROLS

Phytosterols

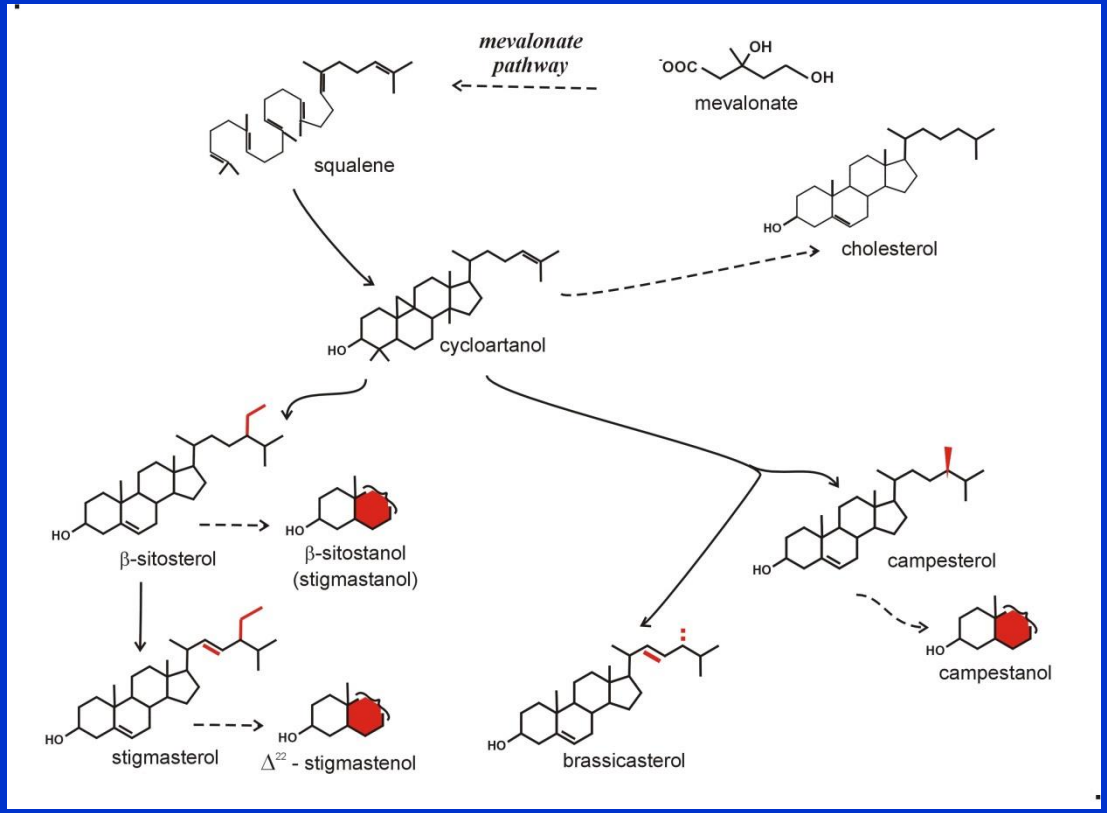
Phytoanalogs of cholesterol

membrane structure
phytohormones

Dietary content

100 – 400 mg/day

decreased CH absorption



STEROLS

Oxysterols

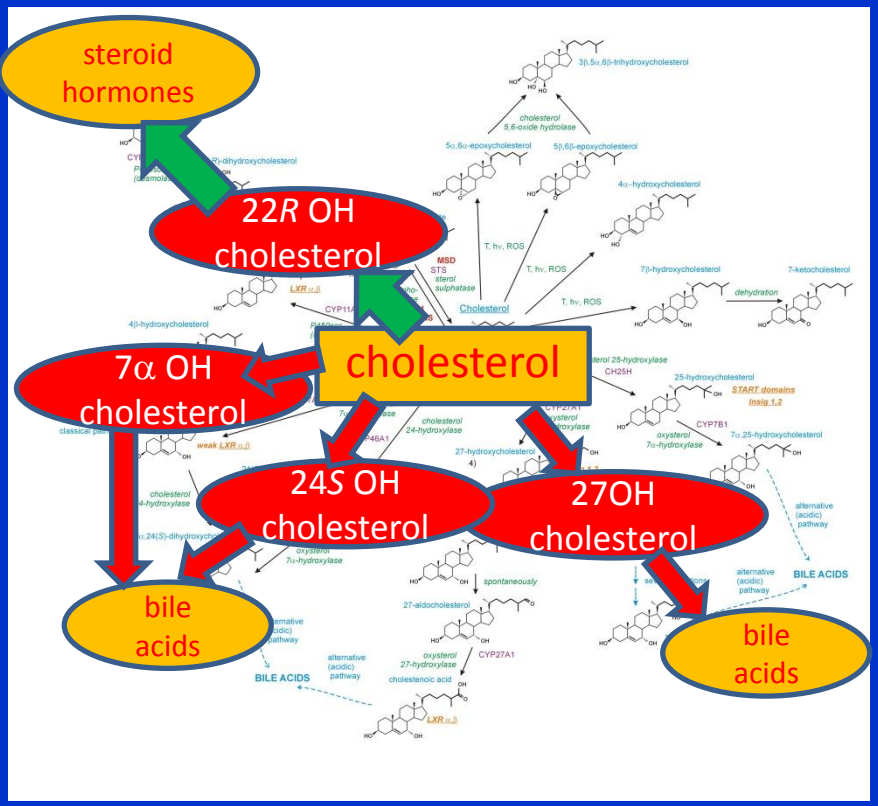
Oxygenated derivatives of cholesterol

Formation

1. enzymatically
   hydroxylases, monooxygenases
2. nonenzymatically
   ROS attack on sterol molecule

Effects of oxysterols

intermediates in biosynthesis
(steroids/bile acids)
ligands for nuclear receptors
(regulation of CH biosynthesis)
transport of CH (from brain)



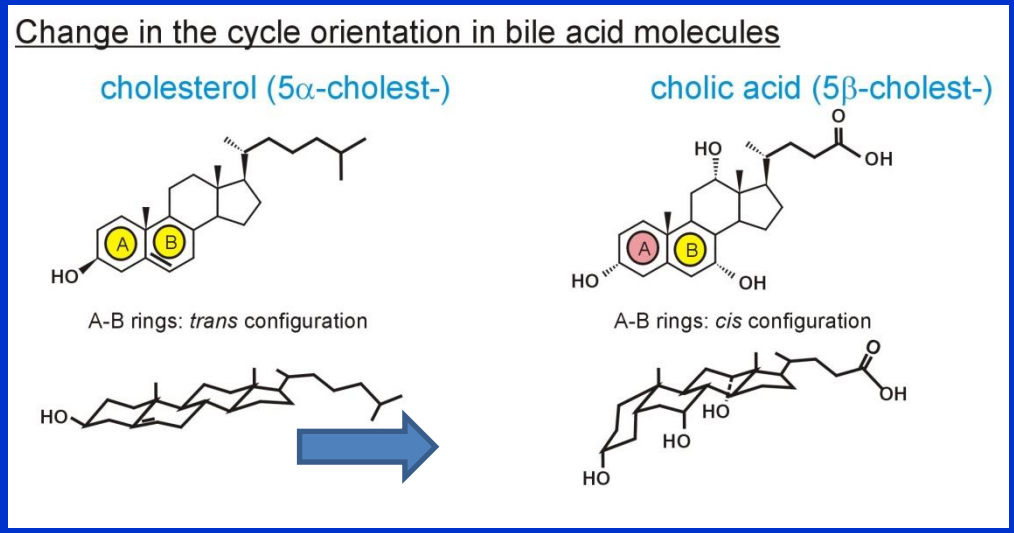
BILE ACIDS

Major excretion form of CH in humans

Biosynthesis of bile acids

in liver, 17 enzymes in total

1. hydroxylation
   CYP450/mixed function oxidase system (microsomal)
2. side chain cleavage
   mitochondria/cytosol/px
3. conjugation
   with glycine, taurine
   - lowering toxicity and more amphipatic (easily secreted in bile)



Secondary modifications

bacterial conversion

BILE ACIDS

Biosynthesis of bile acids

two pathways

1. classical pathway

cholyl/chenodeoxycholyl CoA are produced

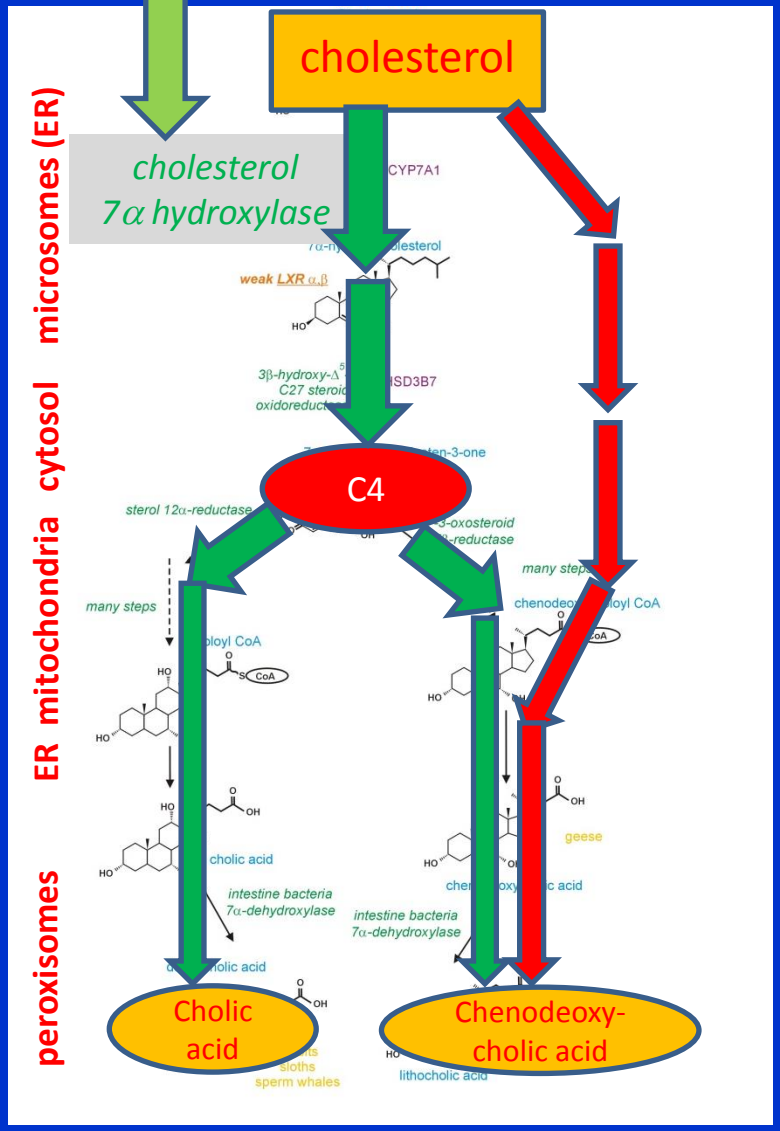
cholyl CoA:

major BA in bile (up to 30% of BAs)

2. acidic pathway

chenodeoxycholyl CoA is produced

major BA in bile (up to 50% of BAs)



BILE ACIDS

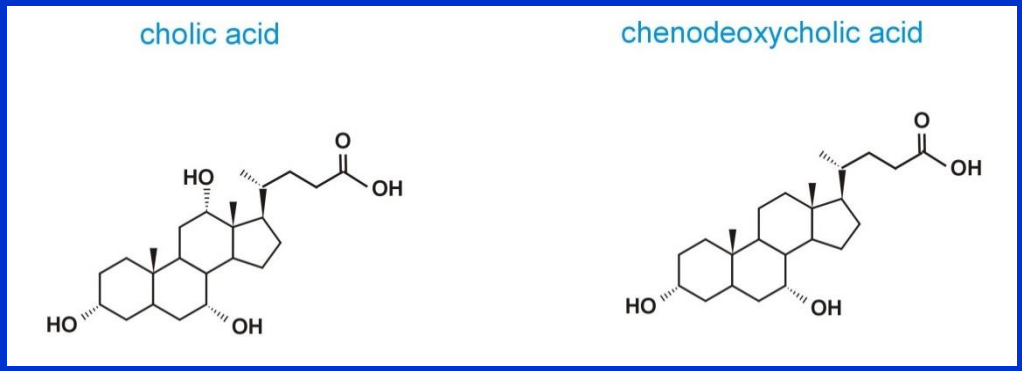
Major excretion form of CH in humans

Primary bile acids

formed in liver

$pK_a \approx 6$

→ at pH = 7.4 not fully ionized



Conjugation (bile "salts")

from the CoA derivatives

in peroxisomes

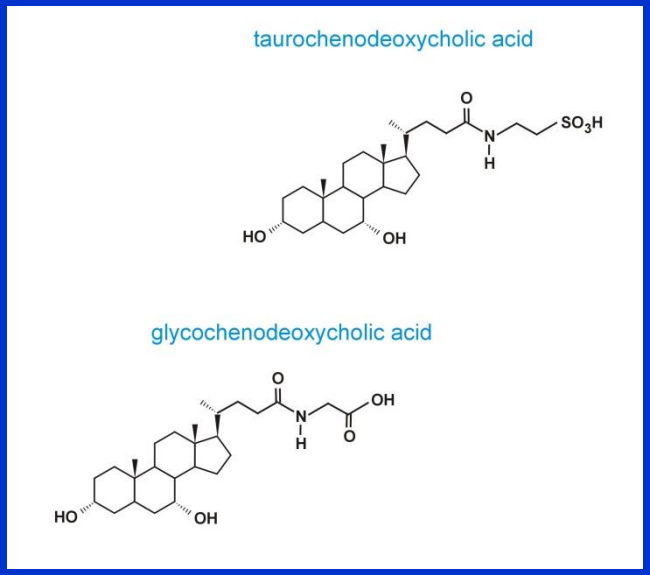
needed for secretion into bile

BA/AA N-acyl transferases

$pK_a << 6$

→ at pH = 7.4 fully ionized

→ more amphipatic

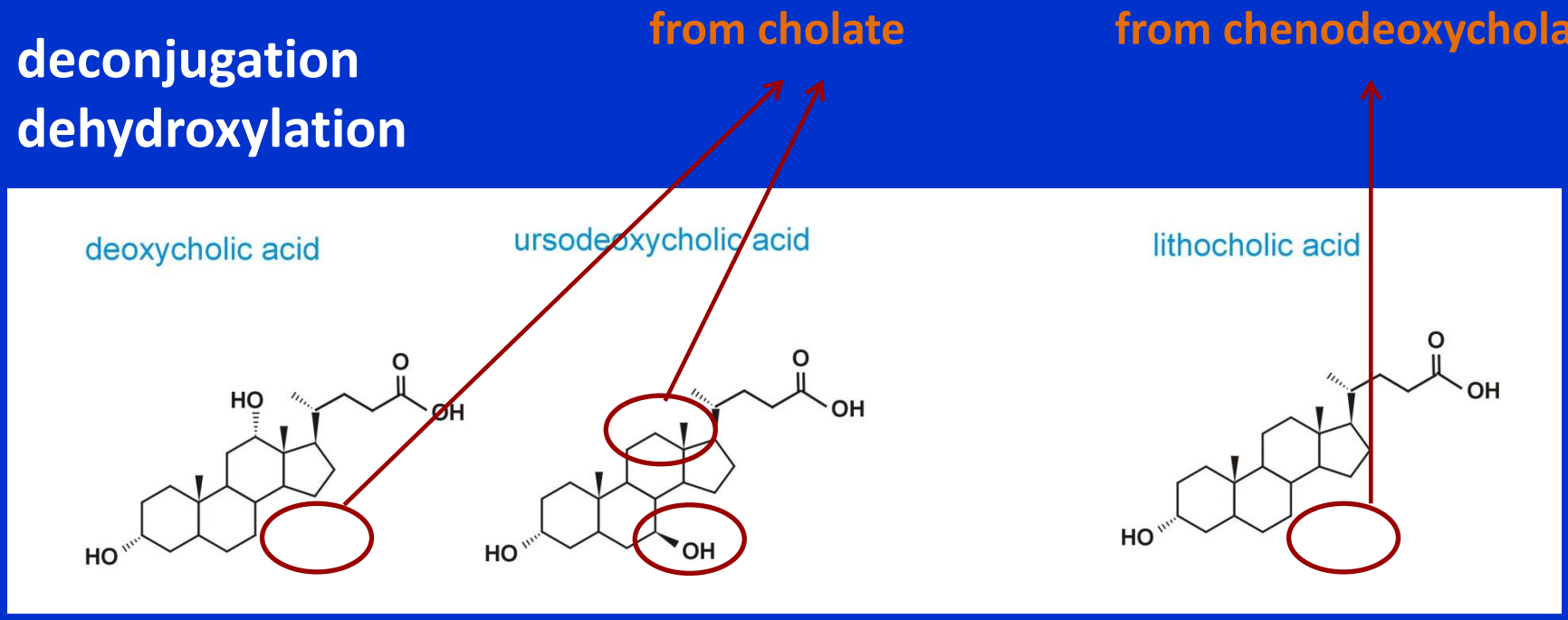


BILE ACIDS

Major excretion form of CH in humans

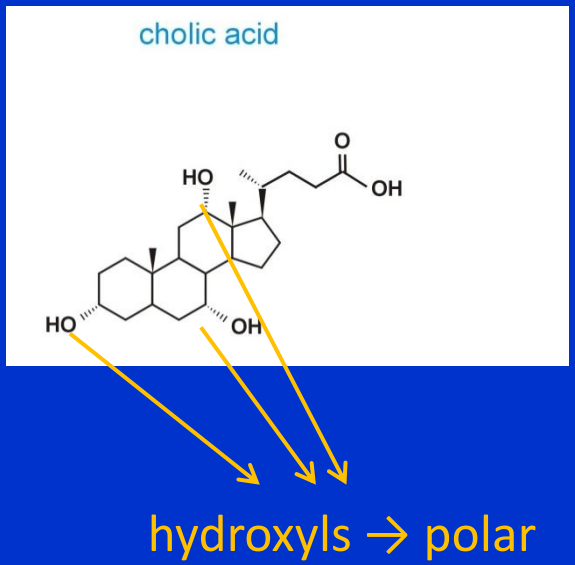
Secondary bile acids
in intestine – microbiome

deconjugation
dehydroxylation



BILE ACIDS

Major excretion form of CH in humans



Functions of bile acids

lipid digestion – emulsifiers

emulsification of FC, CE, TAG,
fat soluble vitamins

→ more accesible to pancreatic lipase

prevent CH precipitation in bile

excretion of cholesterol

(humans are not able to degrade CH)

ligands for nuclear receptors

control of BA metabolism

control of Glc and lipid homeostasis, liver regeneration

increase intestinal motility

BILE ACIDS

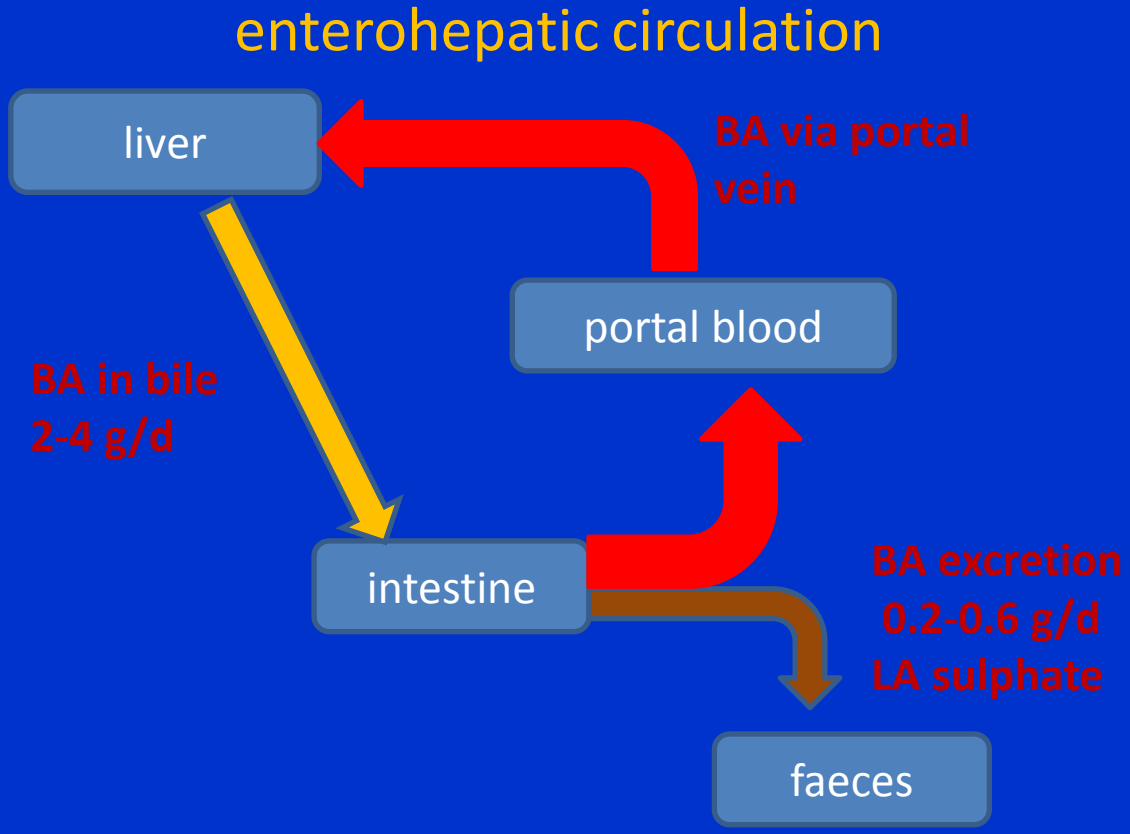
Major excretion form of CH in humans

Recycling of bile acids

up to 95% BA is recycled

Reabsorption
in illeum

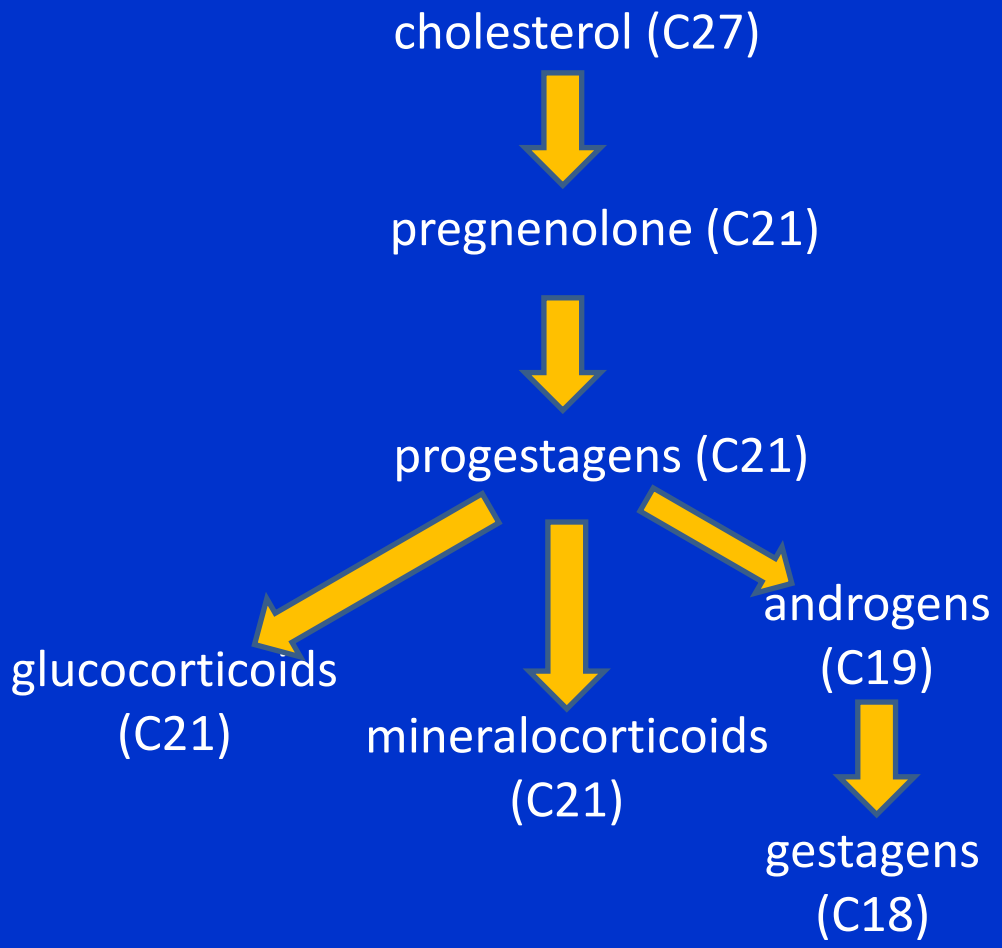
Recycling
2-10 times/day



STEROID HORMONES

CHOLESTEROL - precursor of steroid hormones

1. **Progestagens**
2. **Glucocorticoids**
3. **Mineralocorticoids**
4. **Androgens/gestagens**



STEROID HORMONES

Mode of action of steroid hormones

Endocrine action

Unbound form of hormone in the circulation → diffusion to the target cell → passing through membrane → binding with receptor → interaction with hormone responsive DNA sequence → → protein production

Main sites of production

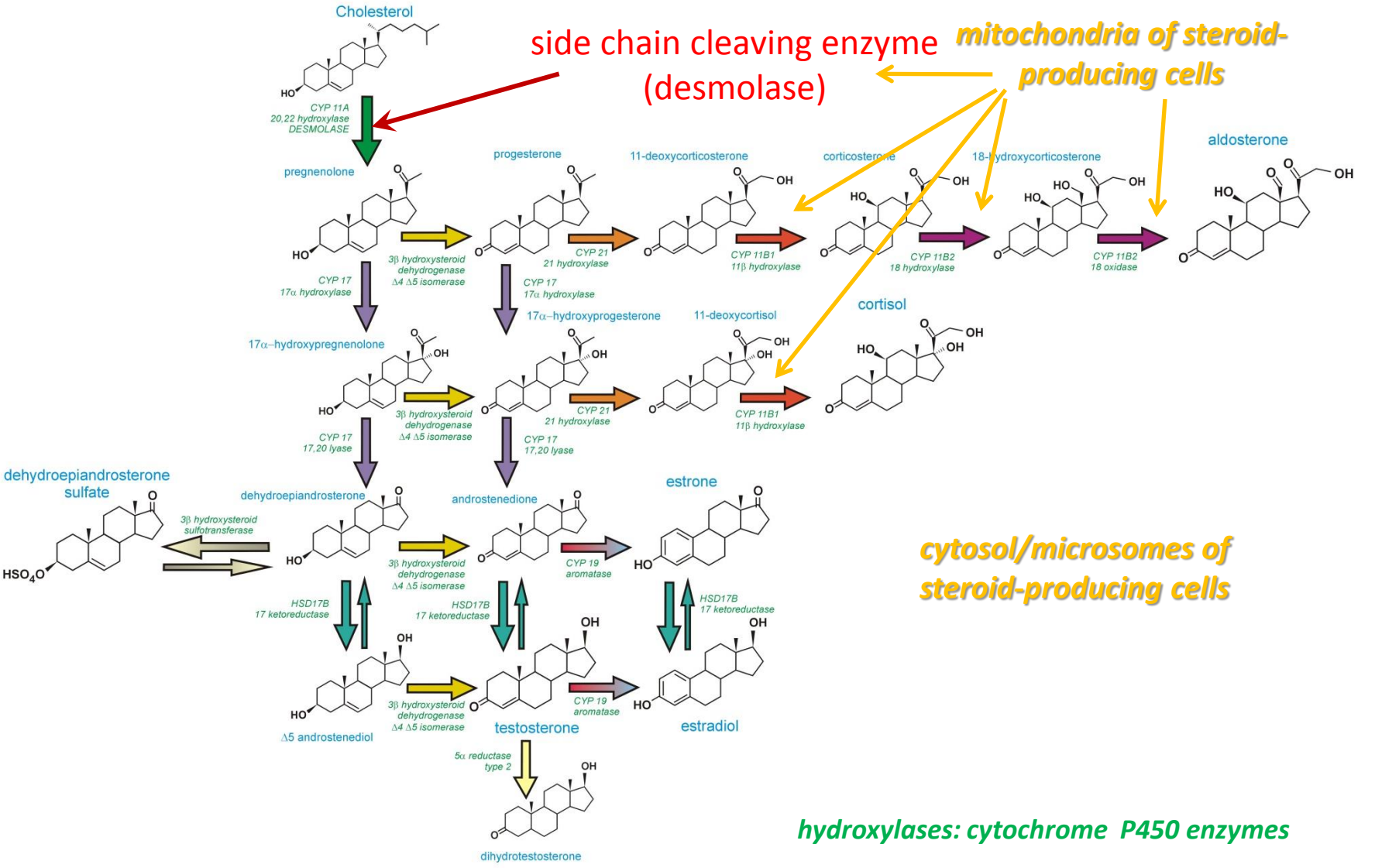
Progestagens (progesterone) corpus luteum, mammary gland
Androgens (testosterone) testes
Estrogens (estrone) ovary
Glucocorticoids (cortisol) *zona fasciculata* (adrenal cortex)
Mineralocorticoids (aldosterone) *zona glomerulosa* (adrenal cortex)

STEROID HORMONES

Functions of steroid hormones

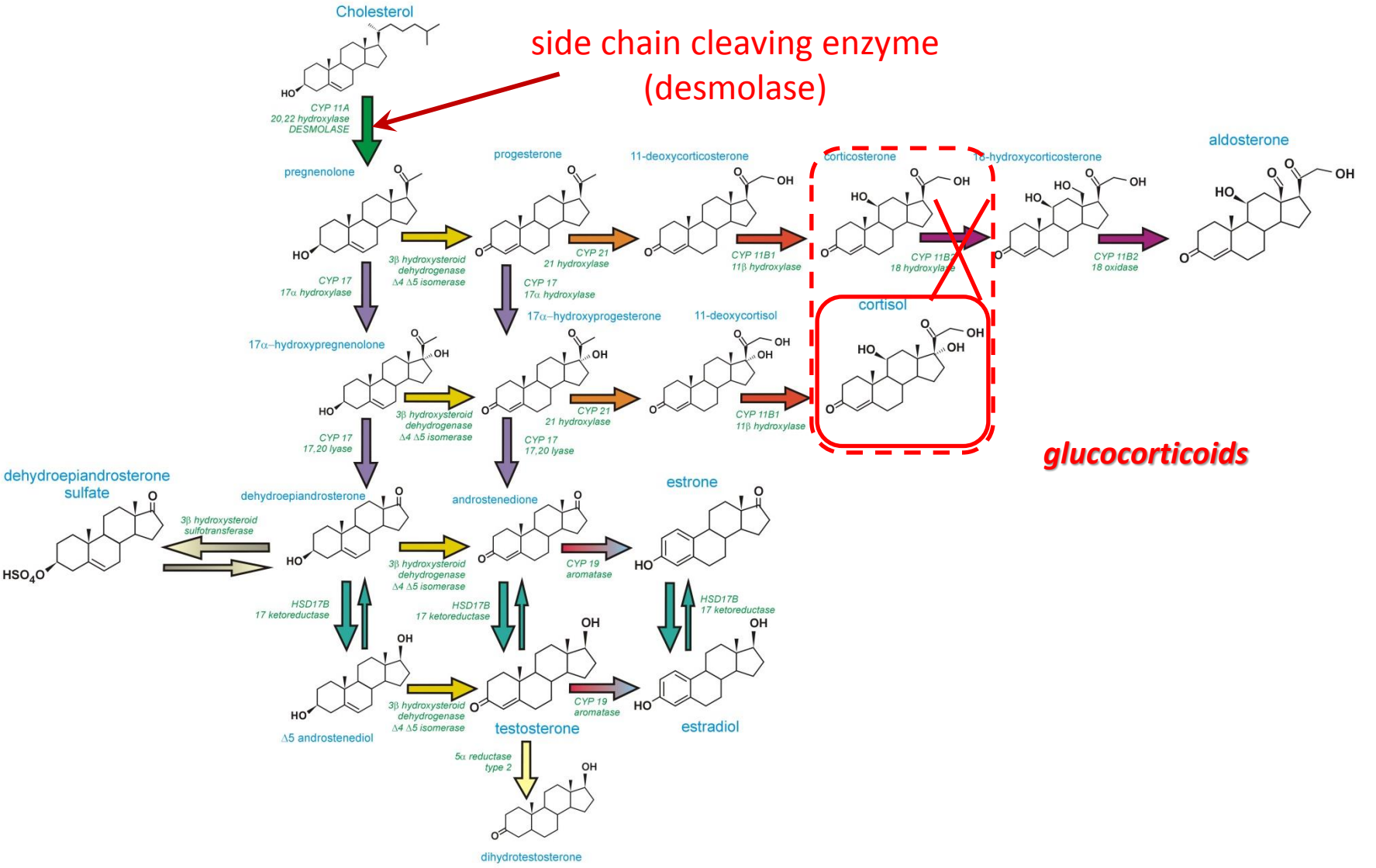
Progestagenes (progesterone)
– release of oocyte, facilitation of implantation
Androgenes (testosterone)
– development of secondary sexual characteristics in men
Estrogenes (estrone)
– development of secondary sexual characteristics in women, ovarial cycle
Glucocorticoids (cortisol)
– propagation of gluconeogenesis (synthesis of glycogen), inhibition of inflammation, stress adaptation, immune system
Mineralocorticoids (aldosterone)
– increased reabsorption of Na^+ and excretion of K^+ / H^+
→ increase in V and blood pressure

STEROID HORMONES



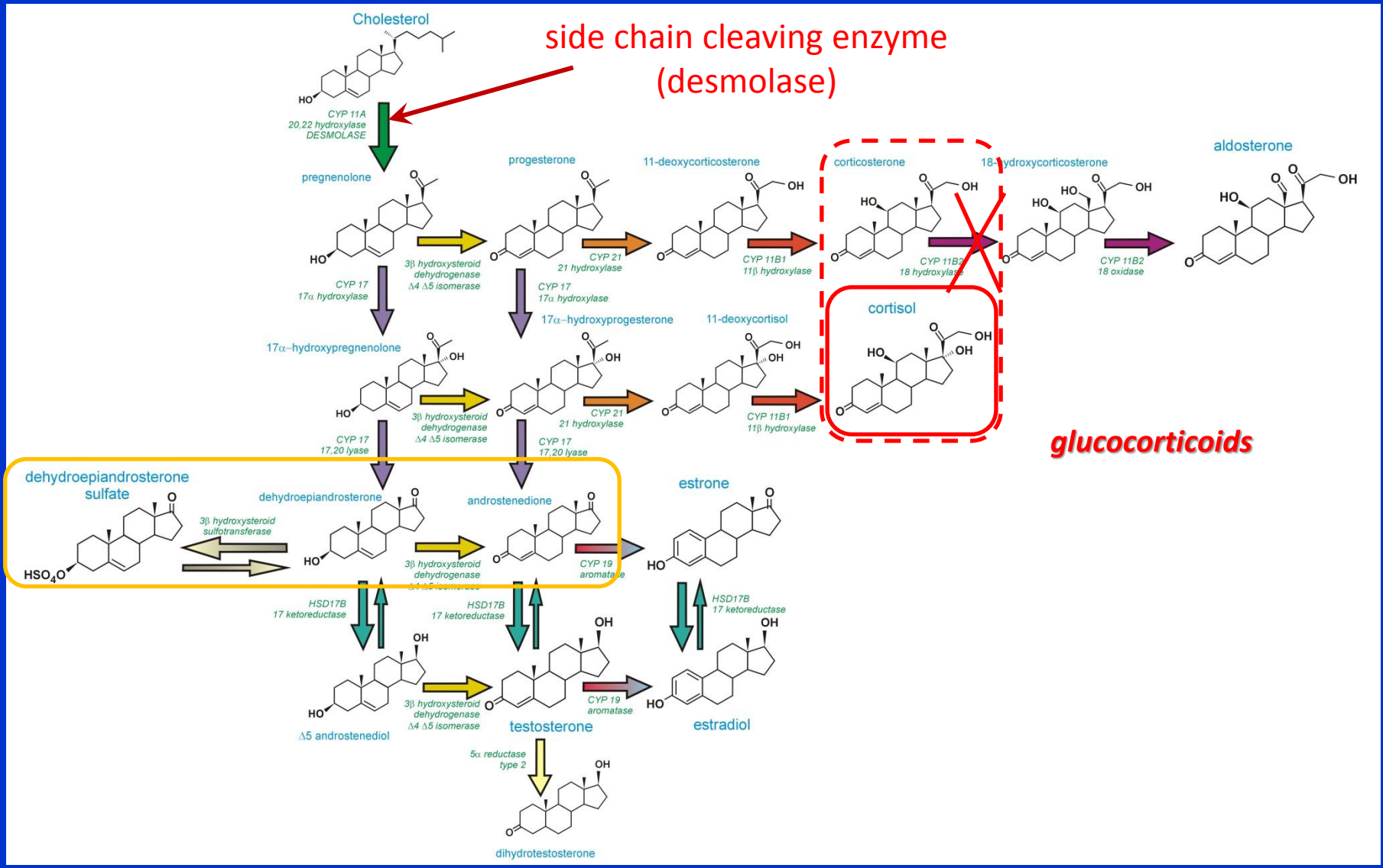
Adrenal steroid hormones

zona fasciculata



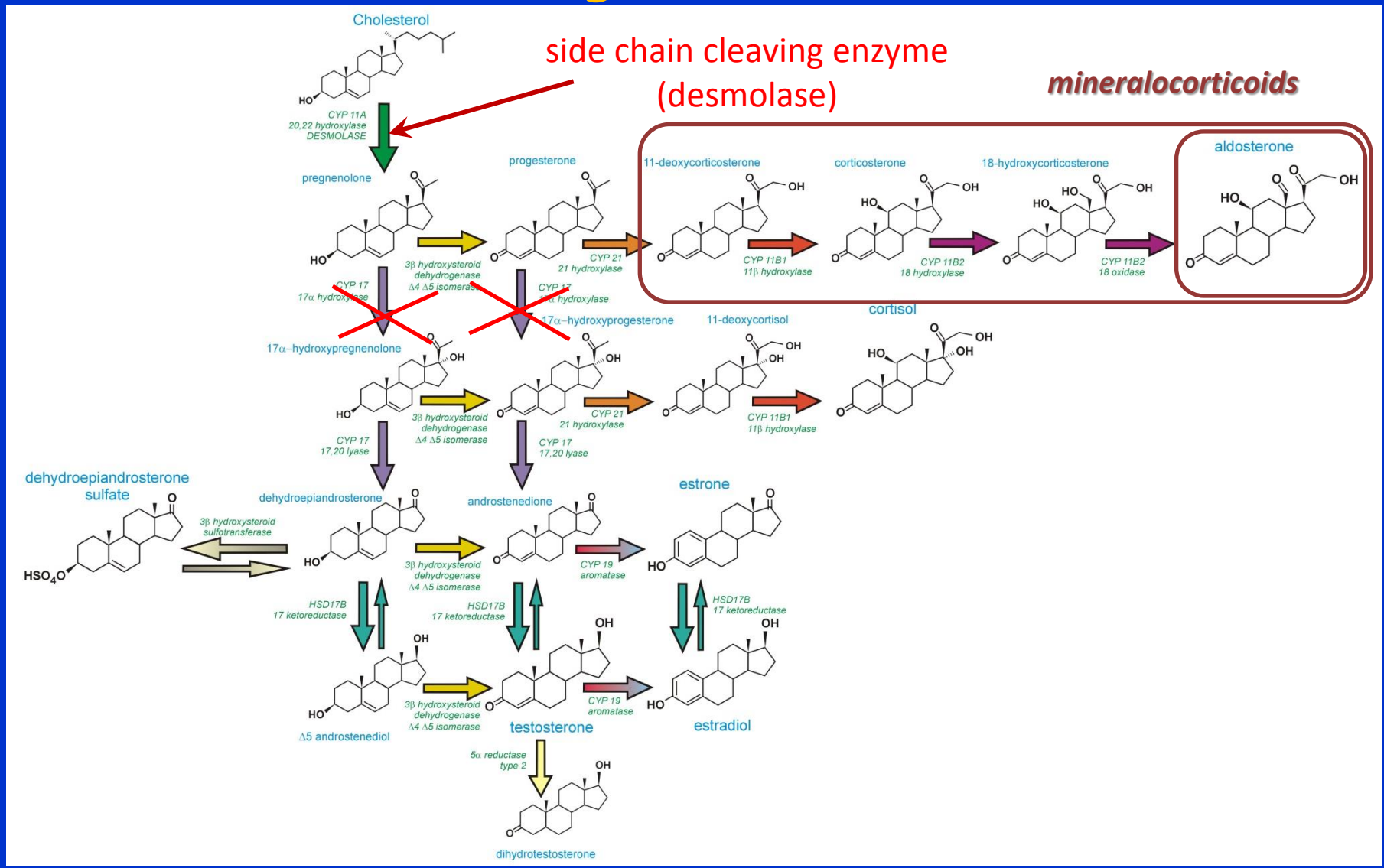
Adrenal steroid hormones

zona reticularis



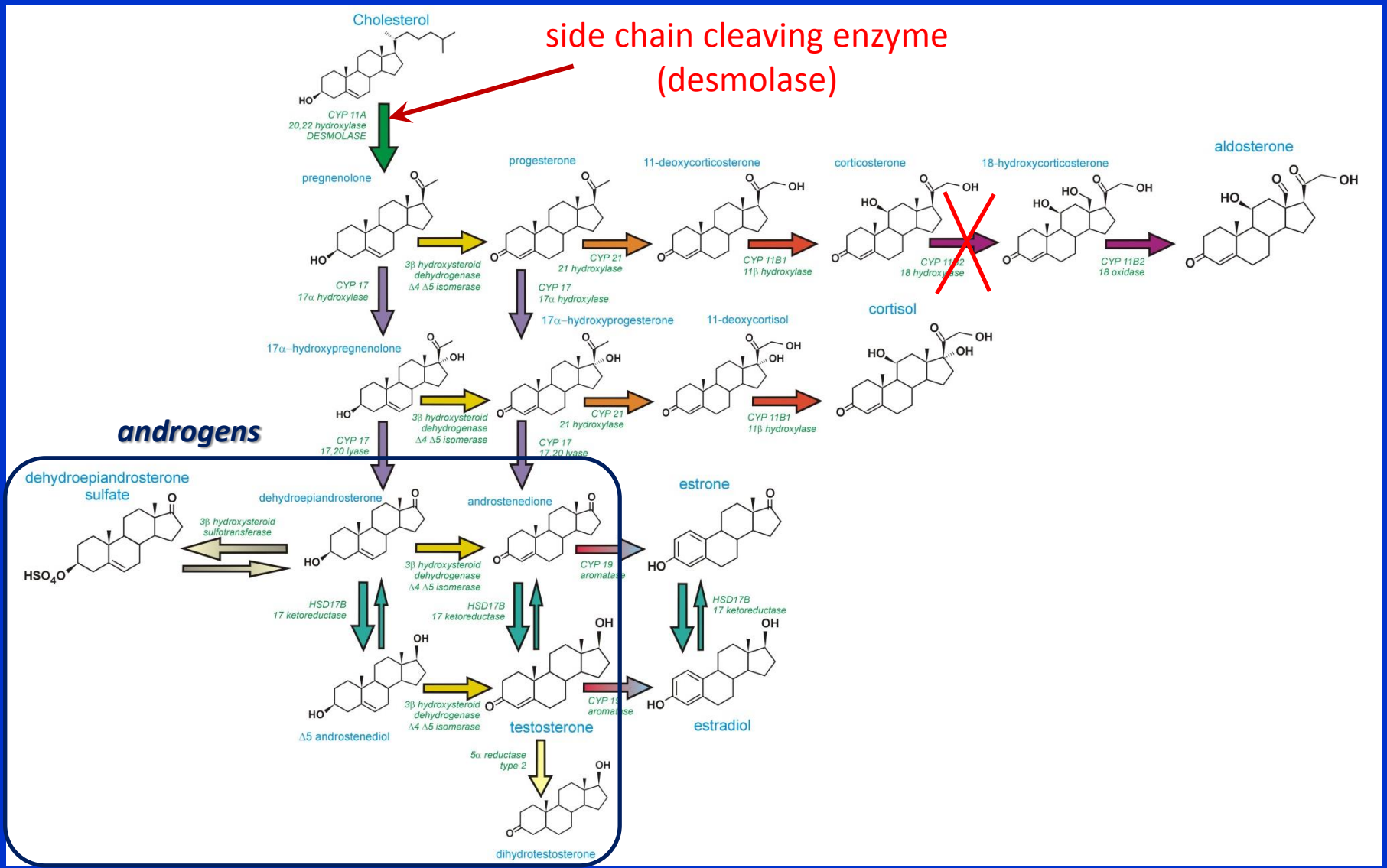
Adrenal steroid hormones

zona glomerulosa



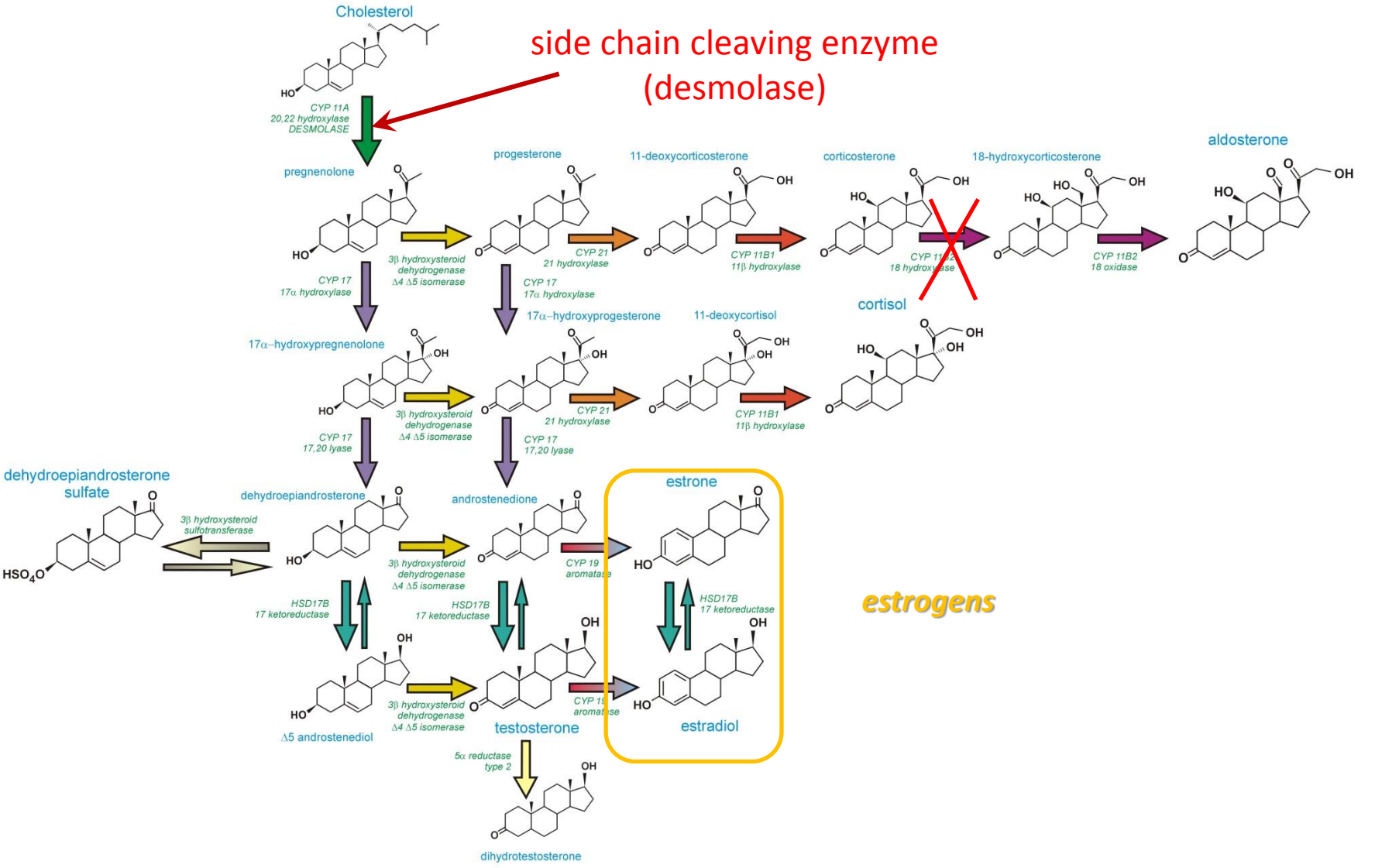
Gonadal steroid hormones

testes



Gonadal steroid hormones

ovary



VITAMINS D

Secosteroids = one/more cycles are broken

Vitamin D_3 (cholecalciferol)

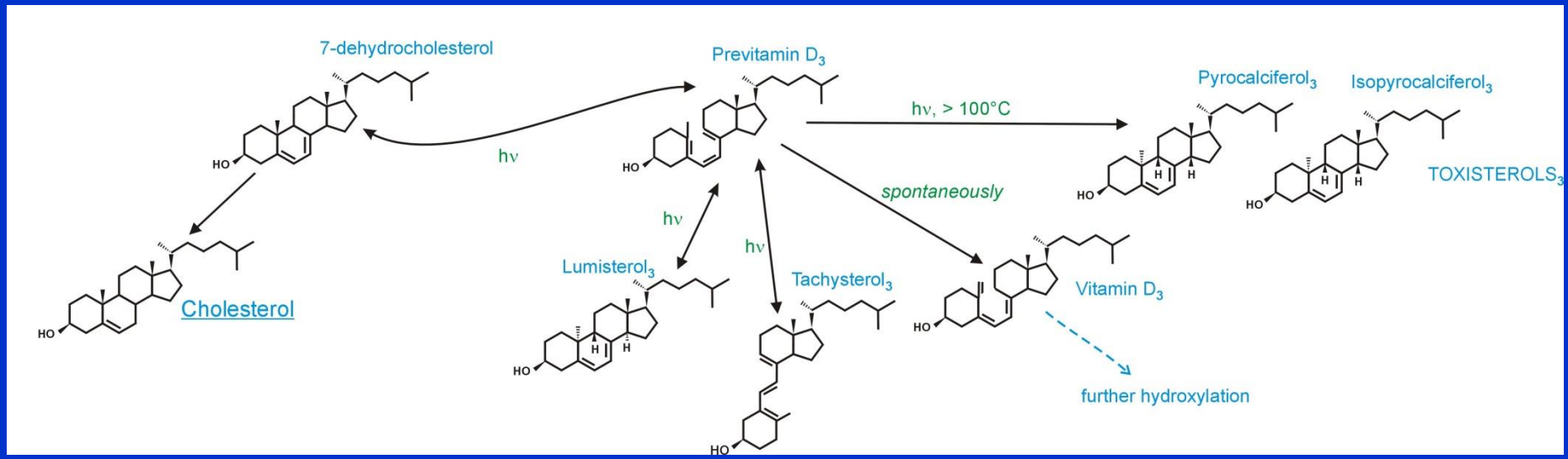
control of Ca^{2+} and phosphate metabolism

effects on immune system

biosynthesis from 7-dehydrocholesterol (skin)

inactive prohormone → further hydroxylations

25-OH vitD_3 in liver; 25,1α-$(OH)_2$ vitD_3 (**active**) in kidney

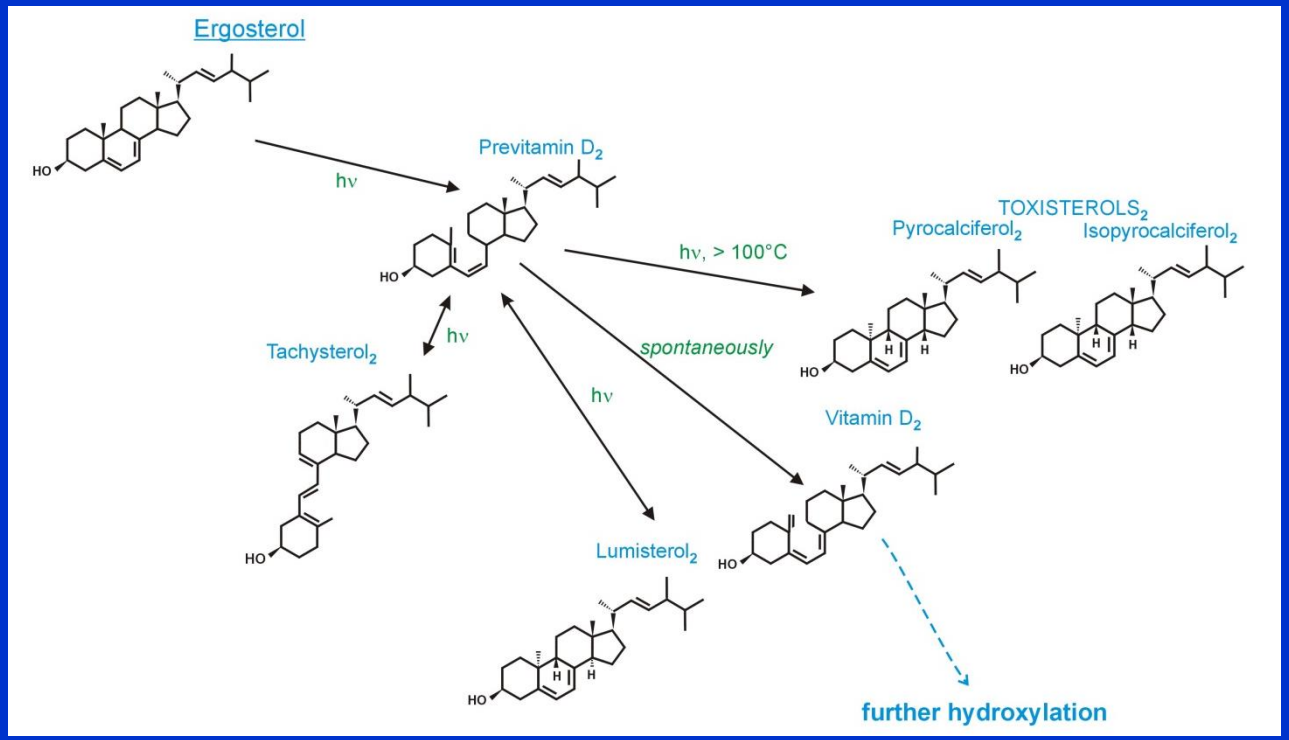


VITAMINS D

Secosteroids = one/more cycles are broken

Vitamin D_2 (ergocalciferol)

commercial analogue of vit D_3 (irradiation of ergosterol)
effects and metabolization similar to vit D_3



Further reading

Textbooks, monographs

Biochemistry of Lipids, Lipoproteins and Membranes (5th Ed); Vance DE, Vance Je (Eds.), Elsevier, Amsterodam (The Netherlands) 2008

Lehninger Principles of Biochemistry (6th Ed); Nelson DL, Cox MM (Eds.), Susan Winslow, New York (U.S.A.) 2013

Harper´s Illustrated Biochemistry (28th Ed); Murray RK, Bender DA, Botham KM, Kennely PJ, Rodwell VW, Weil PA (Eds.), McGraw-Hill, New York (U.S.A.) 2009

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