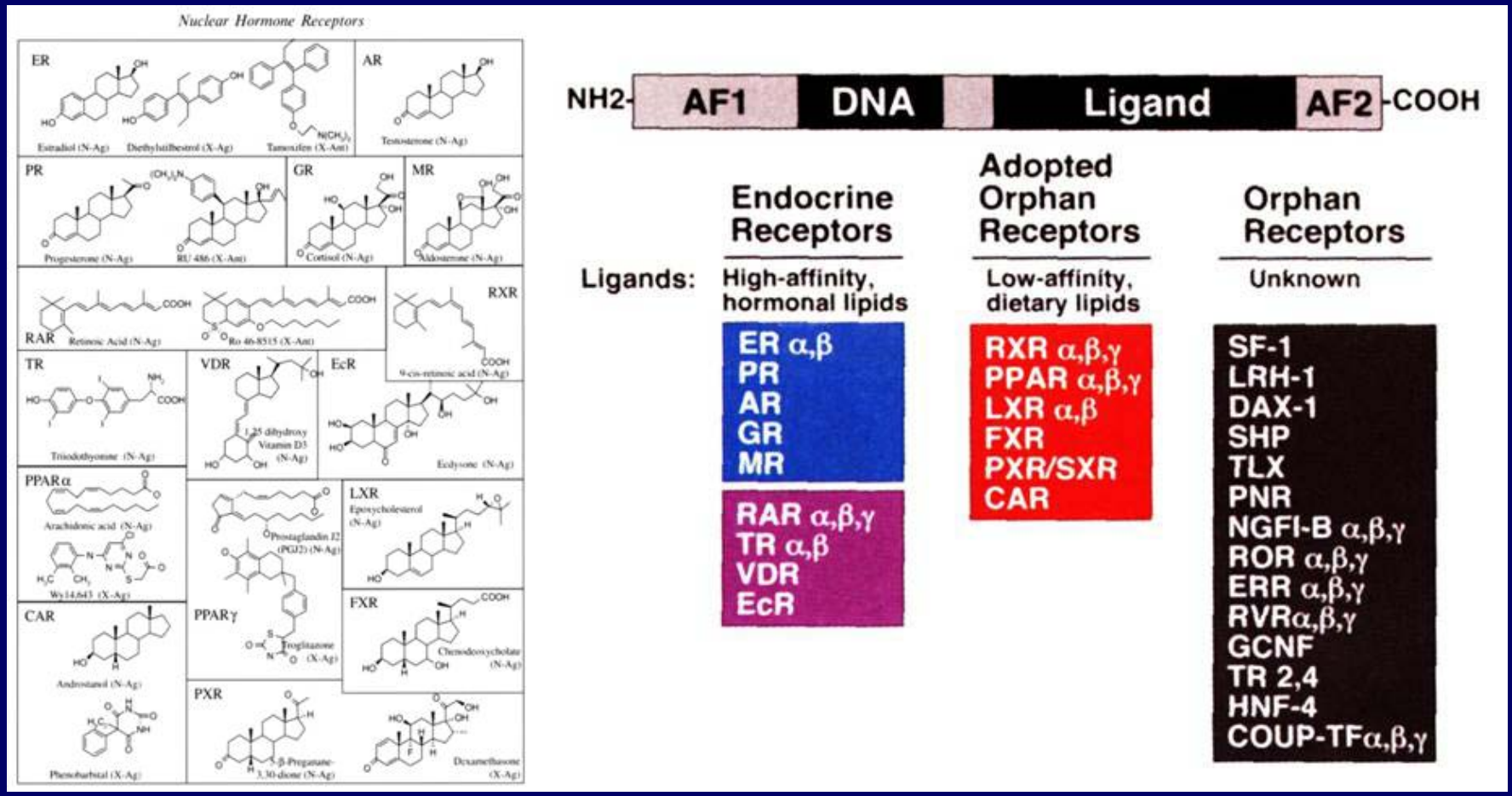
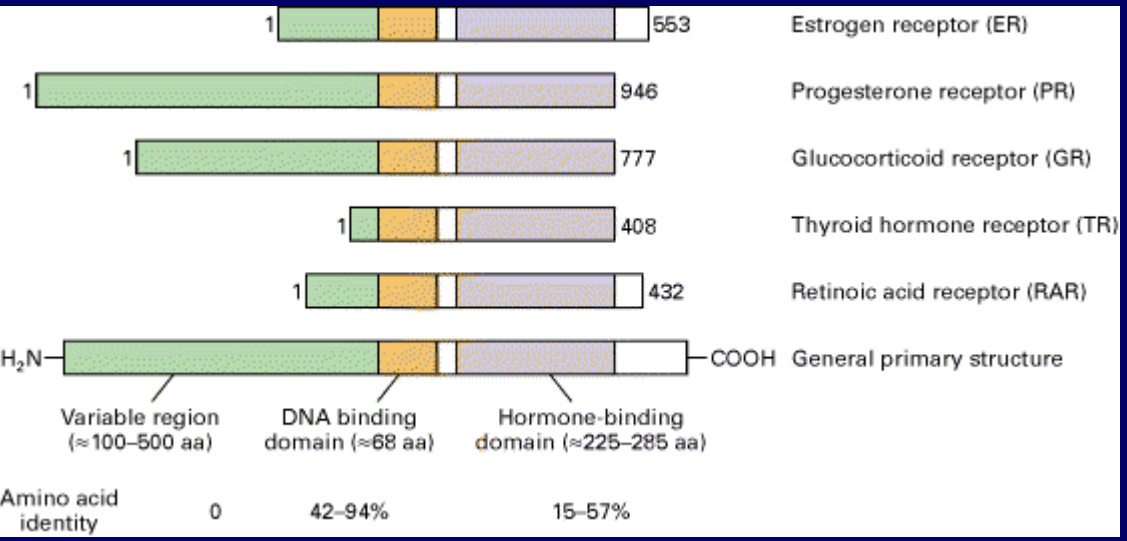
Modelové interakce jaderných receptorů a enzymových systémů

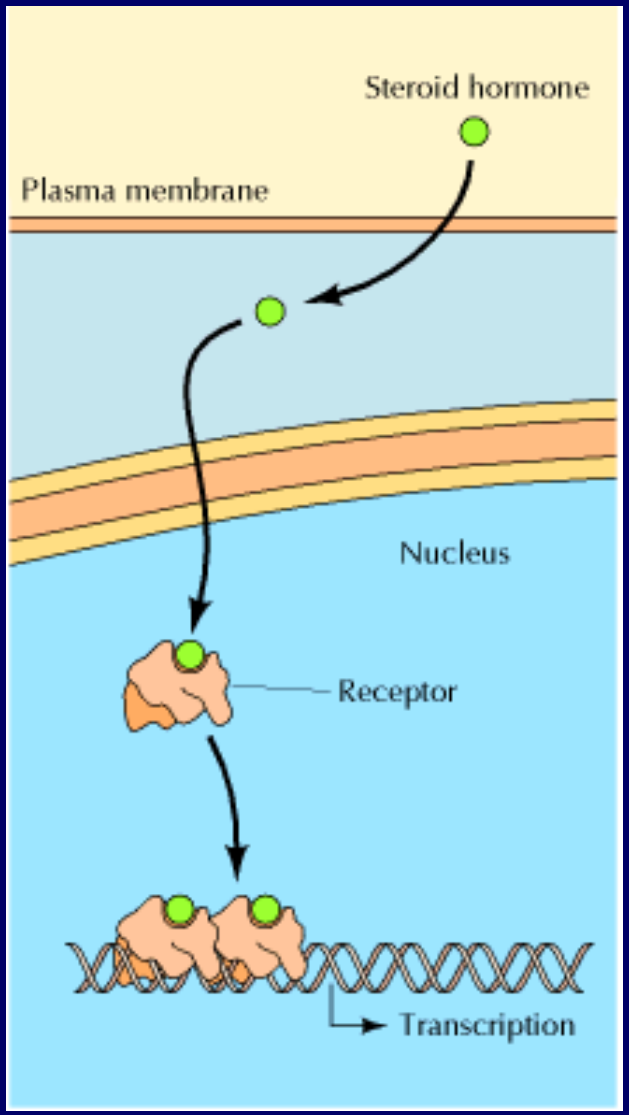
JADERNÉ RECEPTORY



http://www.ens-lyon.fr/LBMC/laudet/nurebase/nurebase.html



General design of transcription factors in nuclear-receptor superfamily. The centrally located DNA-binding domain exhibits considerable sequence homology among different receptors and has the C4 zinc-finger motif. The C-terminal hormone-binding domain exhibits somewhat less homology. The N-terminal regions in various receptors vary in length, have unique sequences, and may contain one or more activation domains. This general pattern has been found in the estrogen receptor (553 amino acids [aa]), progesterone receptor (946 aa), glucocorticoid receptor (777 aa), thyroid hormone receptor (408 aa), and retinoic acid receptor (432 aa). [See R. M. Evans, 1988, *Science* 240:889.]



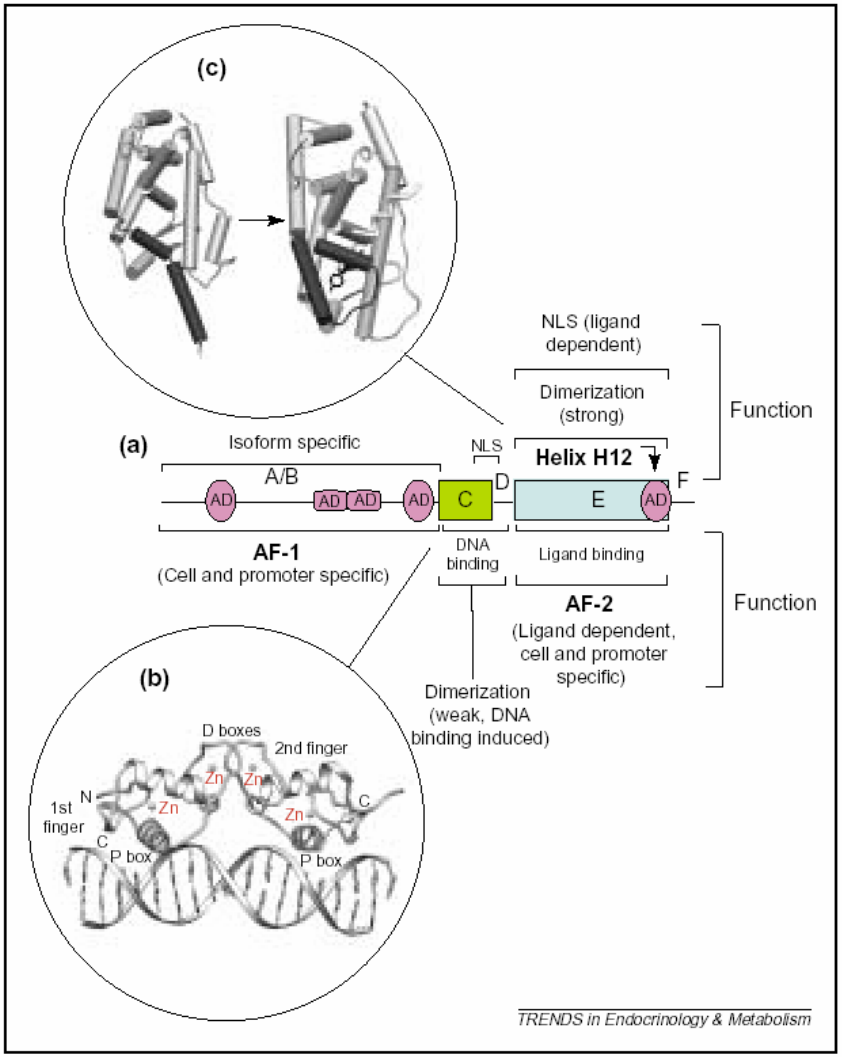
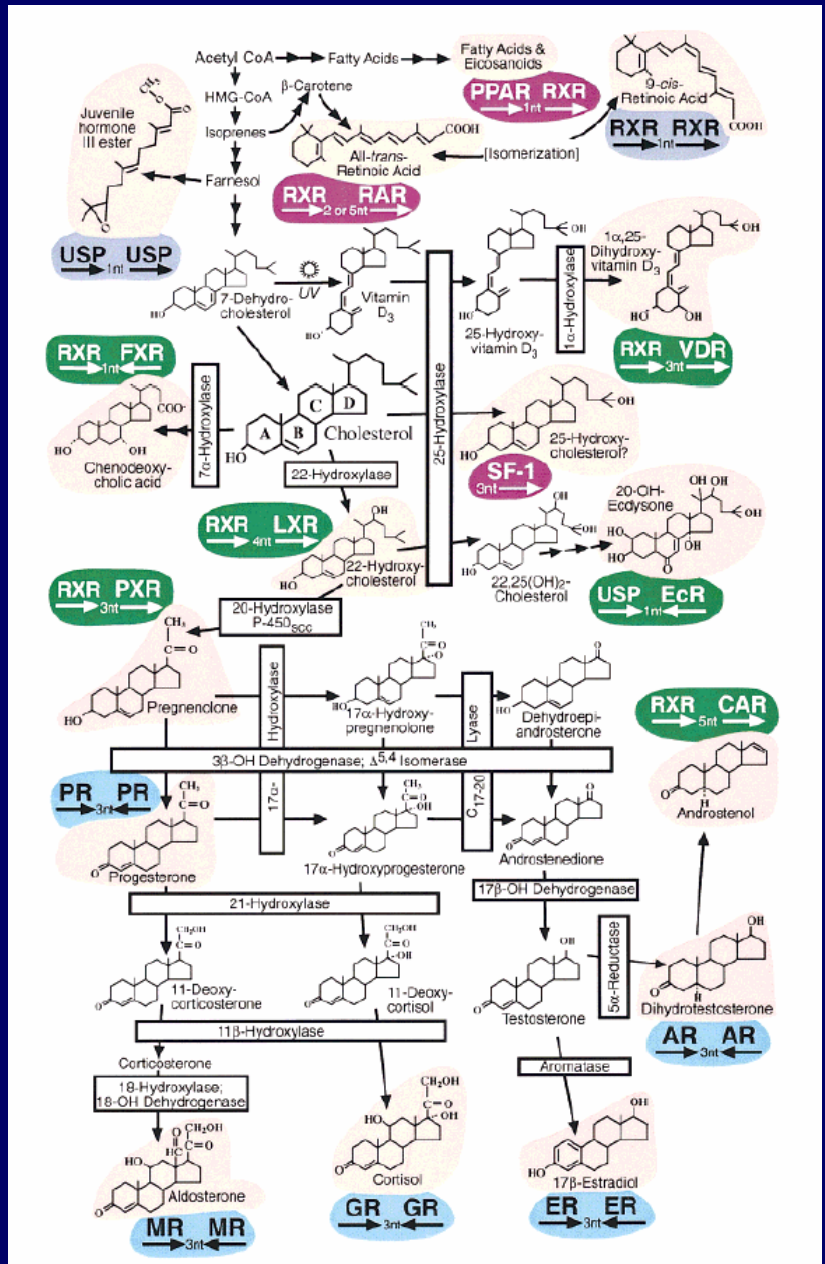


Fig. 1. (a) Schematic of the structural and functional organization of NRs. The evolutionary conserved regions C (DBD) and E (LBD) are indicated as boxes and a black line represents the divergent regions A/B, D and F. Two transcription AFs have been described in several NRs, a constitutively active (if taken out of the context of the receptor) AF-1 in region A/B and a ligand-inducible AF-2 in region E. Within these AFs, ADs have been defined. (b) Estrogen receptor DBD complex on a cognate DNA response element. (c) Agonist-induced changes of the LBD, allowing binding of coactivators (the bound coactivator-binding peptide is shown). Figures 1b,c are three-dimensional views derived from the corresponding crystal structures. Abbreviations: See Glossary.



Vazba na DNA:

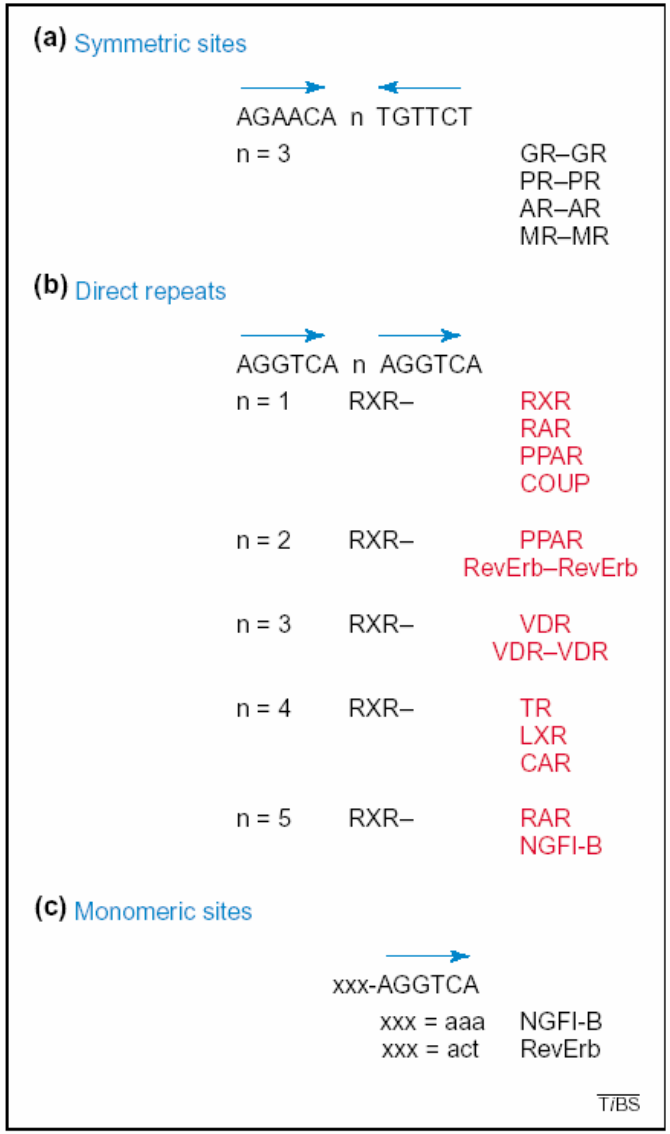
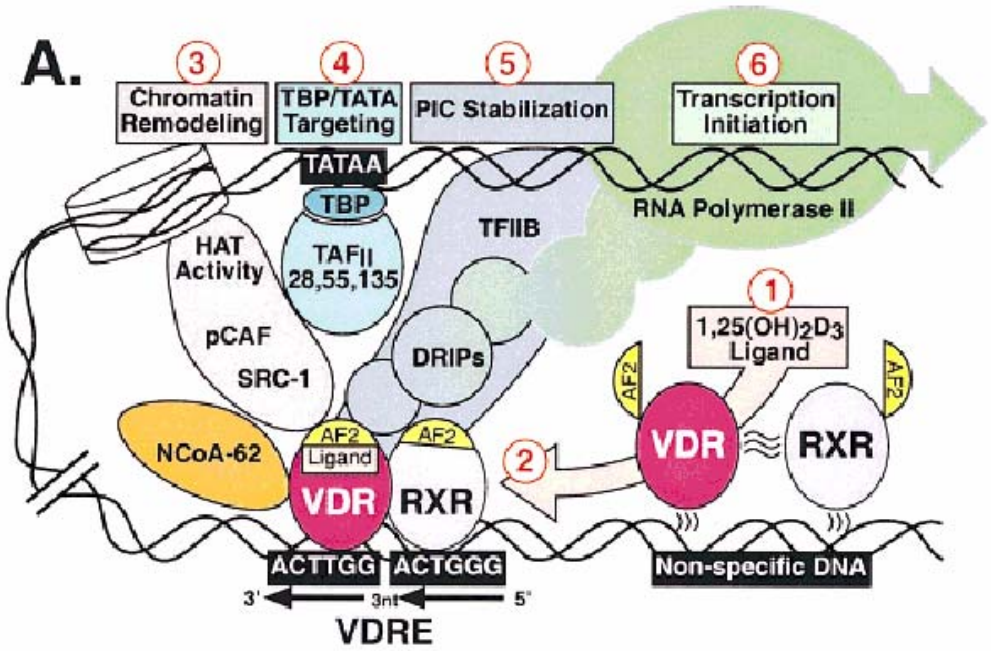
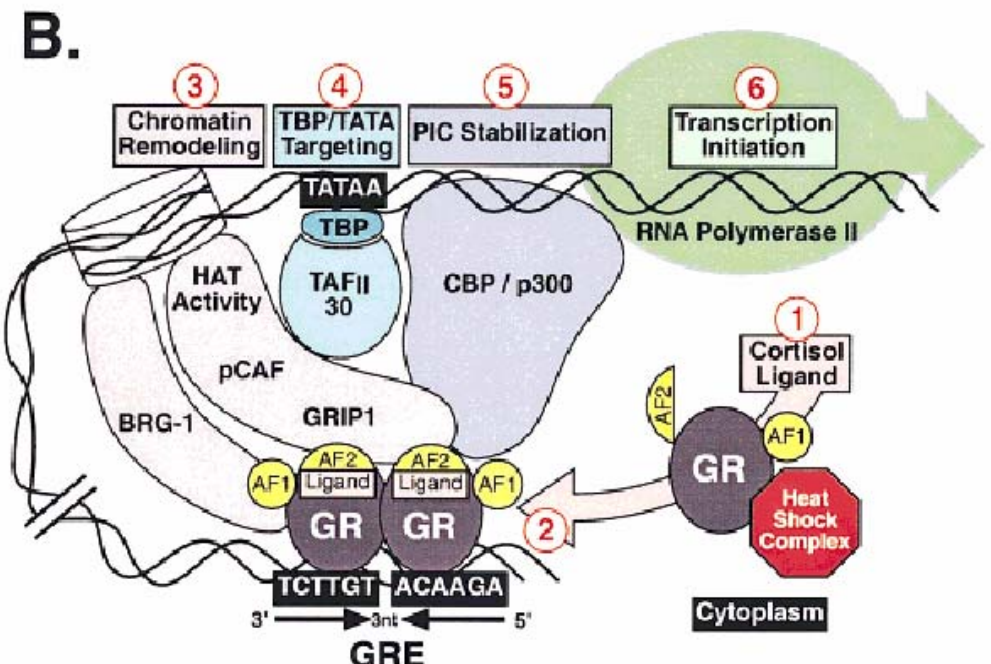


Fig. 2. The types of DNA-response elements used by nuclear receptors. (a) Symmetric repeats using the consensus half-site 5′–AGAACA–3′ are used by the glucocorticoid receptor (GR), progesterone receptor (PR), androgen receptor (AR) and mineralocorticoid receptor (MR), each of which is a homodimer. The estrogen receptor (ER) binds similar symmetric sites but with consensus 5′–AGGTCA–3′ half-sites. (b) A '1–5 rule' specifies the use of direct-repeats with variable spacings by RXR and its many partners (depicted in red). Some receptors, such as the vitamin D receptor (VDR) or RevErb, can form homodimers as an alternative to heterodimers. The size of the inter-half-site spacing (n) can vary from one to five base-pairs. (c) Sites containing just one copy of 5′–AGGTCA–3′ flanked with specific 5′ sequences (xxx) are used by the nerve growth factor induced B (NGFI-B) receptor, RevErb and some other orphan receptors.

We can divide the receptors into subgroups on the basis of their pattern of dimerization. One group consists of the steroid receptors, all of which appear to function as homodimers. This group includes receptors for estradiol (ER), progesterone (PR), androgens (ARs), glucocorticoids (GRs) and mineralocorticoids (MRs). A second major group contains receptors that form heterodimers with retinoid X receptor (RXR) – the receptor for 9-*cis* retinoic acid. Members of this group include the receptors for all-*trans* retinoic acid (RAR),vitamin D3 (VDR) and thyroid hormone (TR), as well as liver X receptor (LXR), peroxisome proliferator activated receptor (PPAR) and others. A third group consists of receptors that can bind DNA as monomers, such as NGFI-B, RevErb, ROR and SF-1.

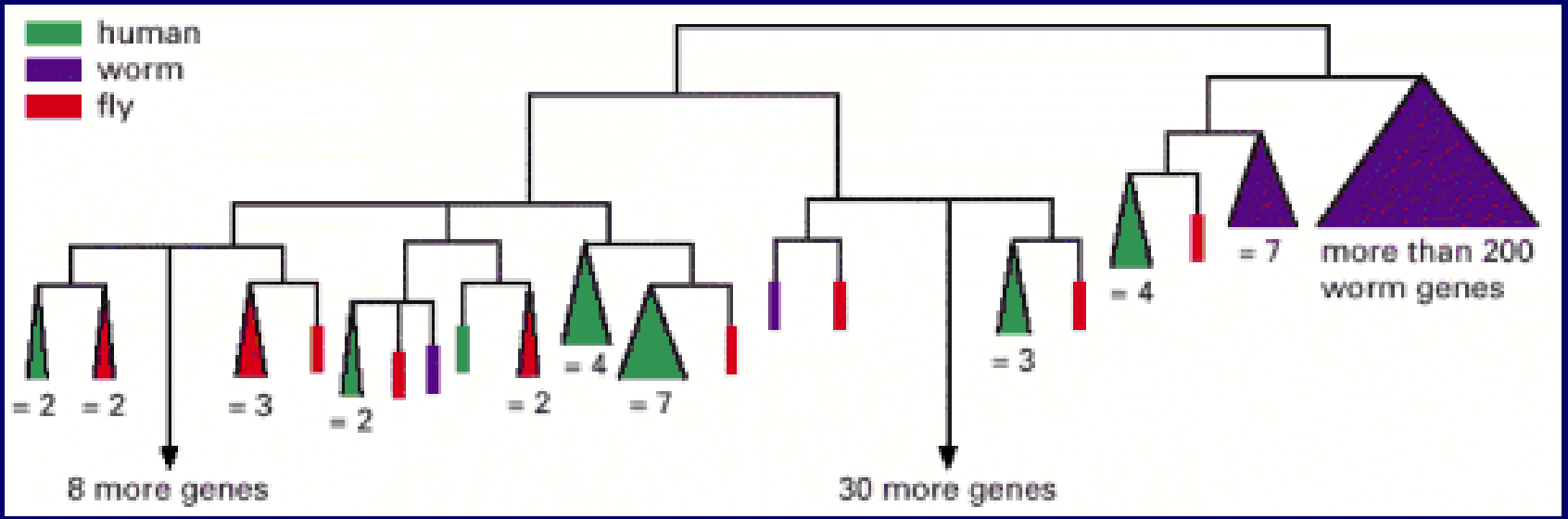




A: Unliganded heterodimerizing receptors, exemplified here by VDR, exist as weakly associated heterodime with RXR, presumably bound nonspecifically to DNA [Haussler et al. 1998]. Binding of the 1,25(OH)2D3 ligand to VDR (1) promotes high-affinit heterodimerization with RXR accompanied by binding of the heterodimer to its direct repeat VDRE (2).

B: Unliganded GR, like other receptors in group (d) (see Fig. 2), exists as a complex with heat shock proteins in the cytoplasm. Upon binding its cortisol ligand (1), GR dissociates from the cytoplasmic complex, translocates to th nucleus and forms a homodimer on its palindromic GRE (2). Triggered by a ligand-mediated change in GR conformation, the AF1 and AF2 domai then synergize to promote a series of events (3–6) involving the recruitment coregulatory complexes similar to thos described for the VDR-RXR heterodimer, but with some distinctive features.

Evoluce jaderných receptorů

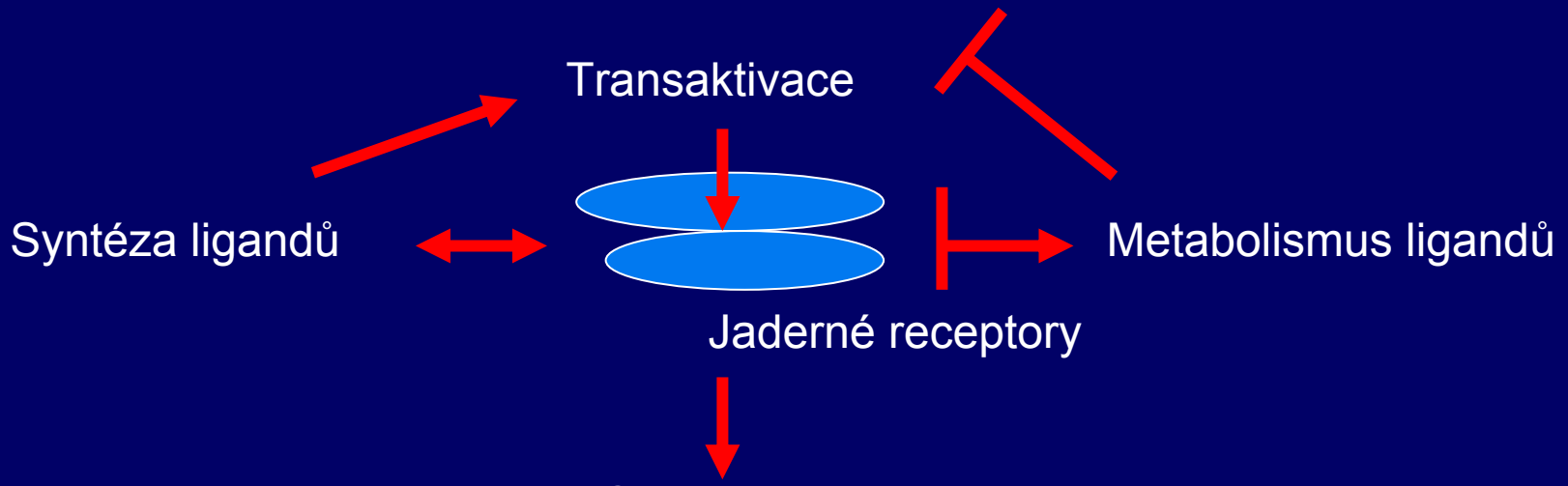


Many family members have been identified by DNA sequencing only, and their ligand is not yet known; these proteins are therefore referred to as *orphan nuclear receptors.* The importance of such nuclear receptors in some animals is indicated by the fact that 1–2% of the genes in the nematode *C. elegans* code for them, although there are fewer than 50 in humans.

Nízkomolekulární lipofilní sloučeniny jako ligandy = aktivita jaderných receptorů je do značné míry závislá na syntéze a degradaci ligandů a naopak

Toxické látky, farmaka

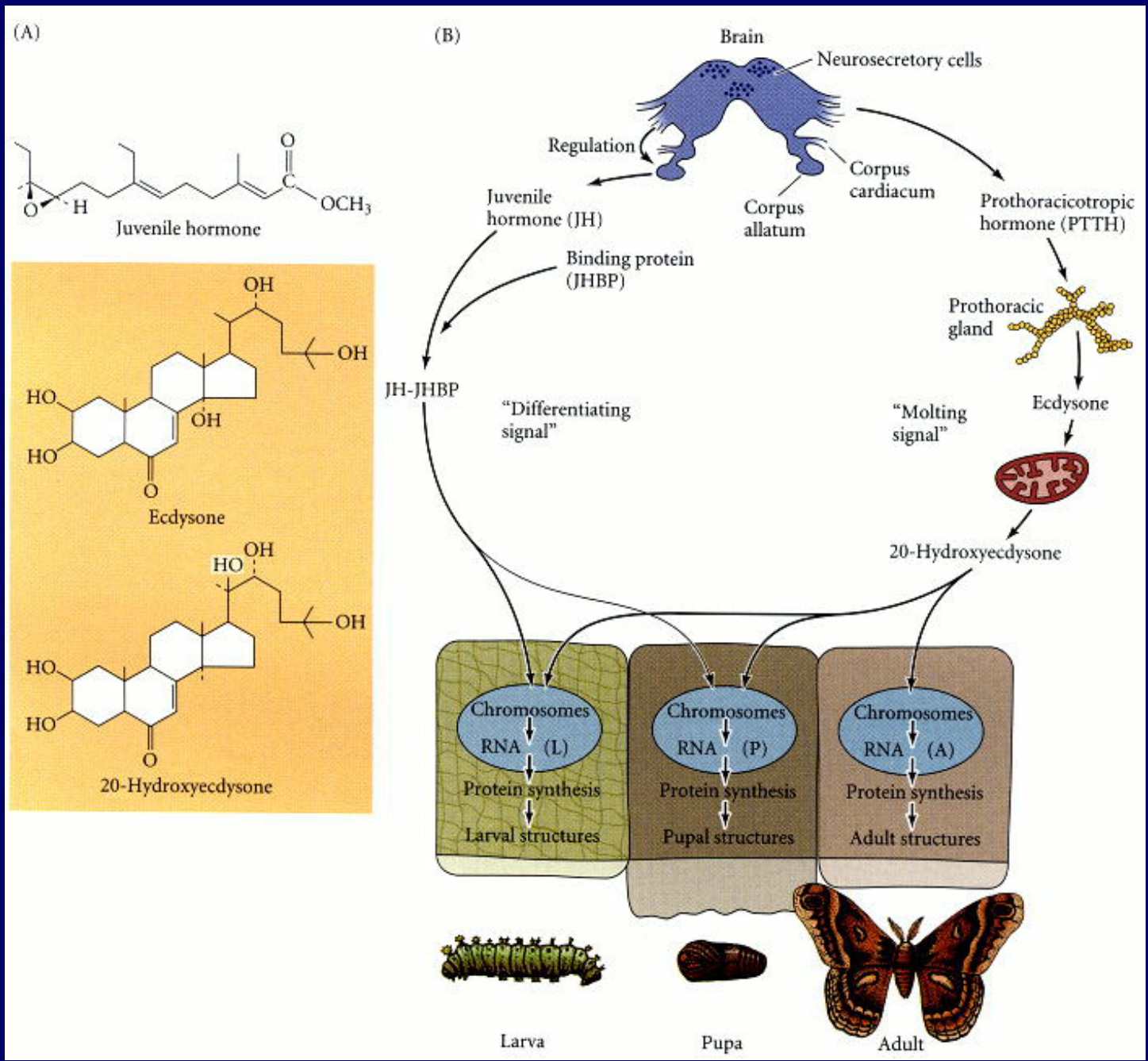
?????



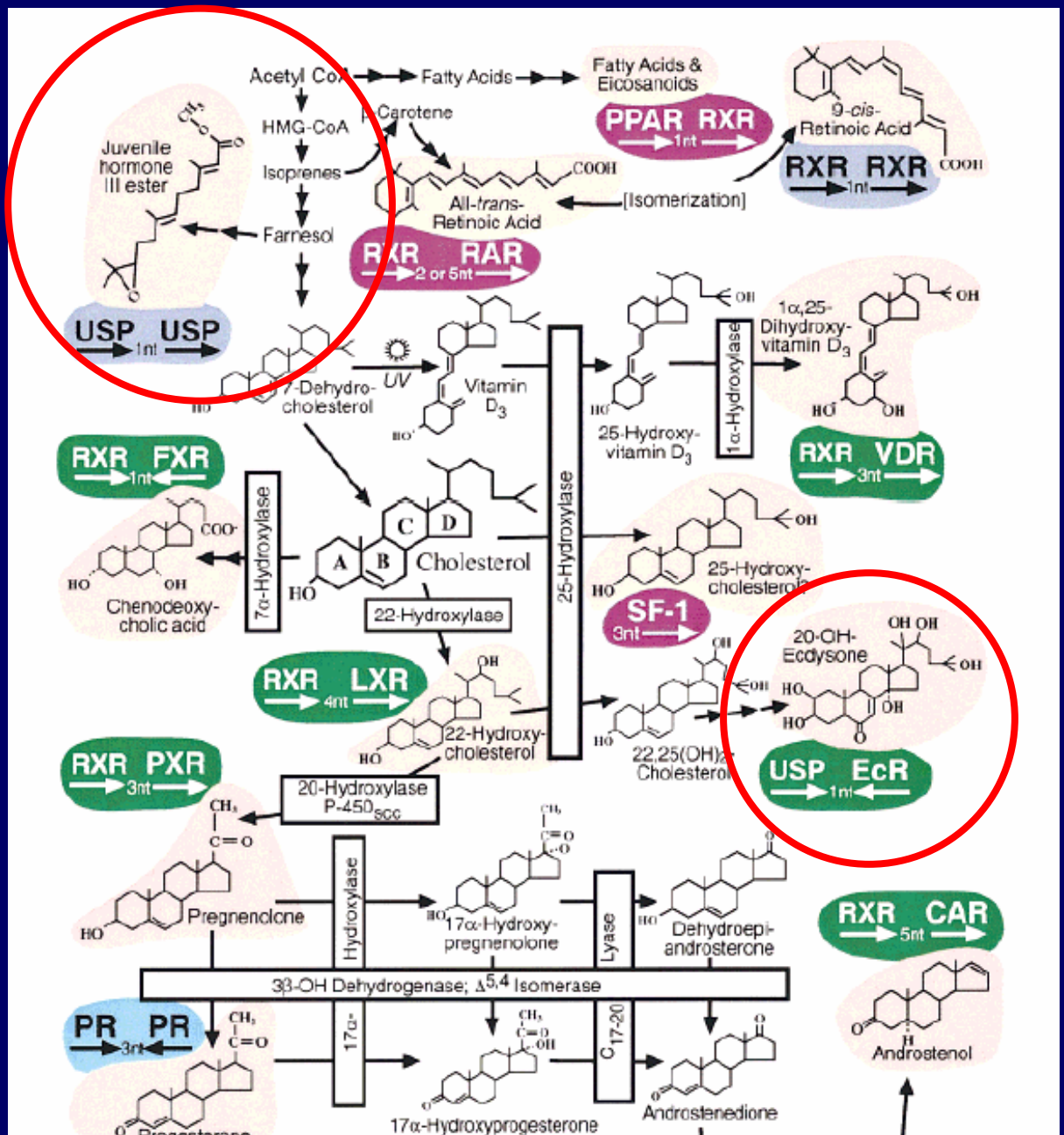
Úloha jaderných receptorů a enzymů katalyzujících degradaci nebo syntézu jejich ligandů:

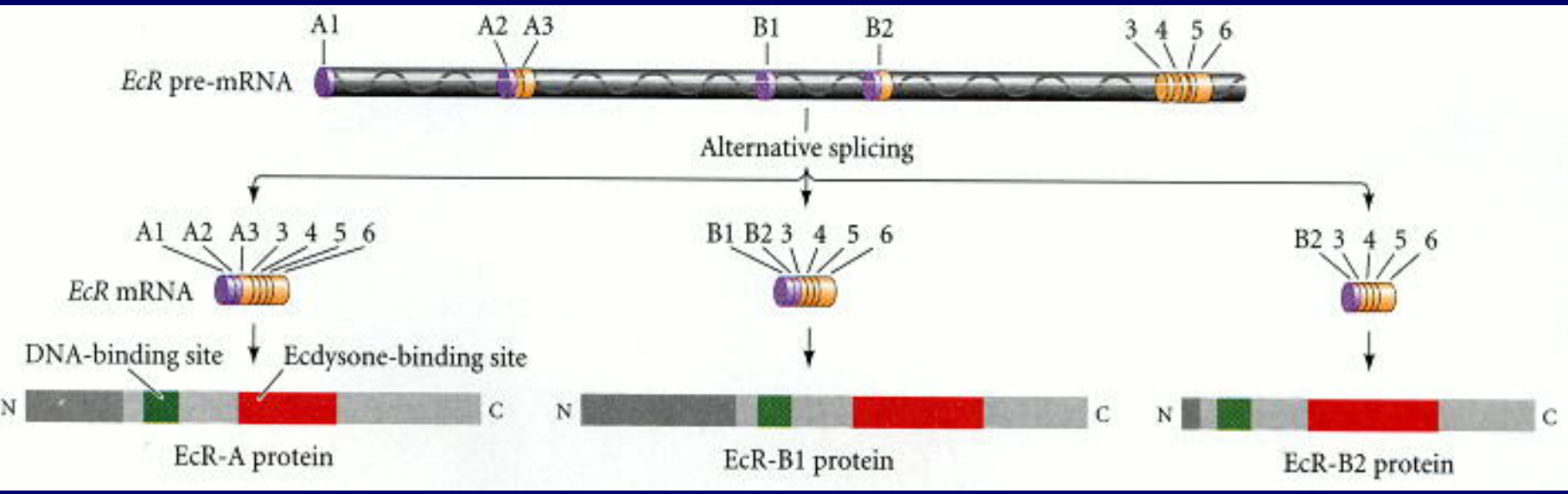
- endokrinní regulace - steroidní hormony, thyroidní hormony;
- regulace signálních drah – eikosanoidy, metabolismus kyseliny retinové, vitamínu D3;
- metabolismus lipidů;
- metabolismus xenobiotik;

Modelový příklad 1:
Metamorfóza hmyzu



Regulation of insec metamorphosis. (A Structures of juvenile hormone, ecdysone, and the active molting hormone 20-hydroxyecdysone. (B) General pathwa of insect metamorphosis. Ecdysone and juvenile hormone together cause molts to keep the status quo and forr another larval insta When there is a lower concentratio of juvenile hormon the ecdysone-induced molt produces a pupa. When ecdysone acts in the absence of juvenile hormon the imaginal discs differentiate, and th molt gives rise to the adult


Acetyl CoA
Fatty Acids
Fatty Acids & Eicosanoids
PPAR RXR 1nt
HMG-CoA
Isoprenes
β-Carotene
Juvenile hormone III ester
Farnesol
All-trans-Retinoic Acid
[Isomerization]
9-cis-Retinoic Acid
RXR RXR 1nt
RXR RAR 2 or 5nt
USP USP 1nt
7-Dehydro-cholesterol
UV
Vitamin D3
25-Hydroxy-vitamin D3
1α-Hydroxylase
1α,25-Dihydroxy-vitamin D3
RXR VDR 3nt
RXR FXR 1nt
7α-Hydroxylase
Chenodeoxy-cholic acid
Cholesterol
22-Hydroxylase
25-Hydroxylase
25-Hydroxy-cholesterol
SF-1 3nt
RXR LXR 4nt
22-Hydroxy-cholesterol
22,25(OH)2-Cholesterol
20-OH-Ecdysone
USP EcR 1nt
RXR PXR 3nt
20-Hydroxylase P-450scc
Pregnenolone
Hydroxylase
17α-Hydroxy-pregnenolone
Lyase
Dehydroepi-androsterone
RXR CAR 5nt
Androstenol
3β-OH Dehydrogenase; Δ5,4 Isomerase
PR PR 3nt
17α-
C17-20
17α-Hydroxyprogesterone
Androstenedione



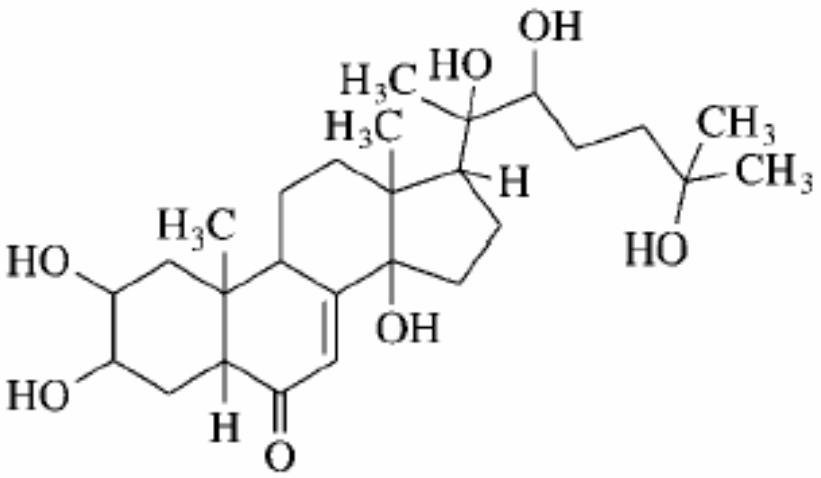
Formation of the ecdysone receptors. Alternative mRNA splicing of the ecdysone receptor (*EcR*) transcript creates three types of *EcR* mRNAs. These generate proteins having the same DNA-binding site (blue) and hydroxyecdysone-binding site (red), but with very different amino termini.

Three isoforms of EcR have been identified in insects, each with a different, stage-specific role in regulation of molting and development. This allows for one steroid hormone to induce a variety of different tissue responses. In general, EcR A is predominant when cells are undergoing a maturation response (from juvenile to adult) and is predominant in imaginal discs, whereas EcR B1 predominates in juvenile cells during proliferation or regression. Little is known about the function of the EcR B2 isoform.

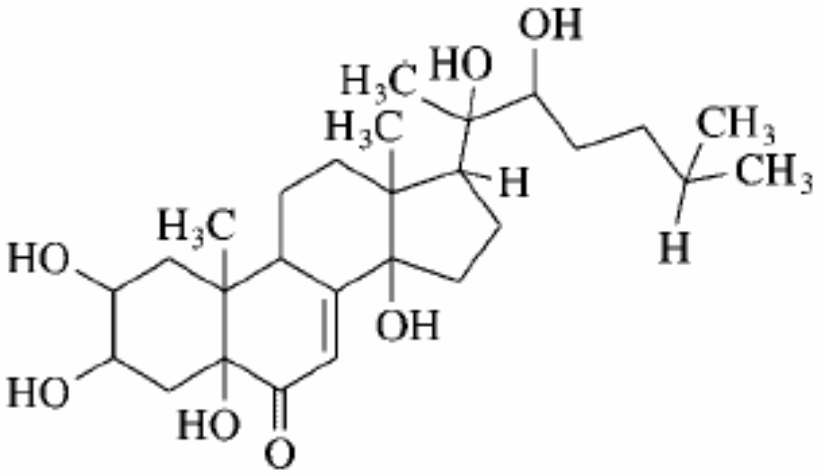
DNA and hormone binding are similar in the three isoforms of EcR. Little is known about the crustacean EcR isoforms and how they change during the molt cycle. However, the EcR that has been cloned from the crab, *Uca pugilator* (U31817, GenBank), shares 85–87% homology with that of *Drosophila* (M74078, GenBank). The differences are primarily in the region of the molecule involved with dimerization. Similar sequence similarities are found between the heterodimeric partner, USP.

There are several ecdysteroids which bind EcR, including 20-hydroxyecdysone, turkesterone, makisterone A, ponasterone A, and muristerone A. Some arthropods may use specific ecdysteroids as their principal molting hormone, but often several ecdysteroids are found within one group. The primary molting hormone for a range of organisms, including some insects and crustacea, is 20-OH ecdysone (20 HE). Among other examples, makisterone A is an important hormone for some crustacea and hemipteran insects.

20-OH Ecdysone
(20 HE)

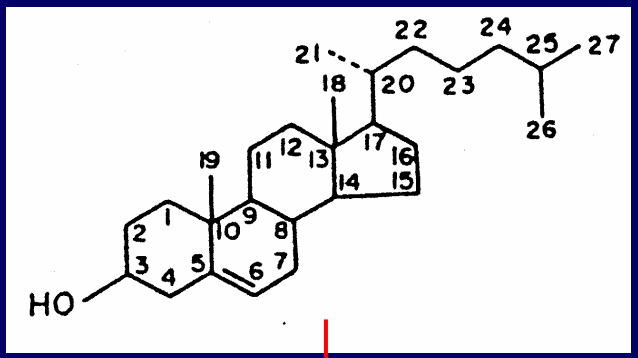


Muristerone A
(MurA)



Synthesis of molting hormones

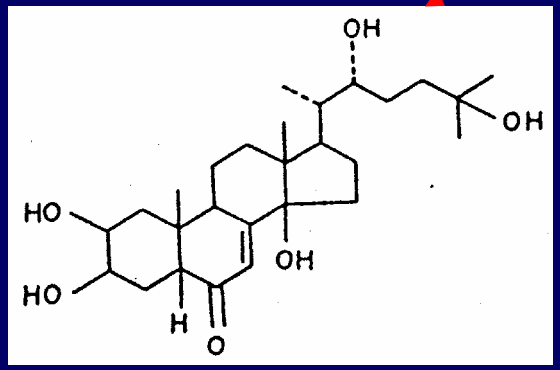
Cholesterol (from diet- a vitamin for insects)



Prothoracic gland

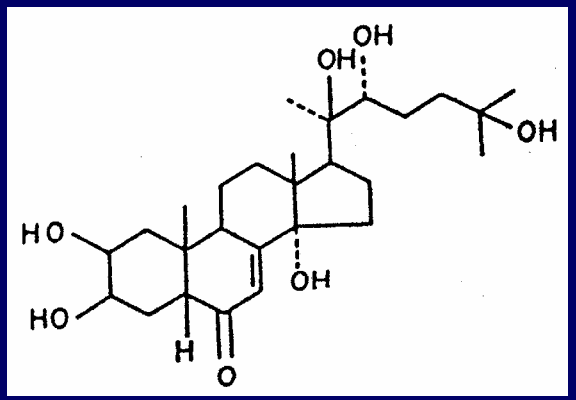
Metabolites (excretion)

Conjugates (storage)



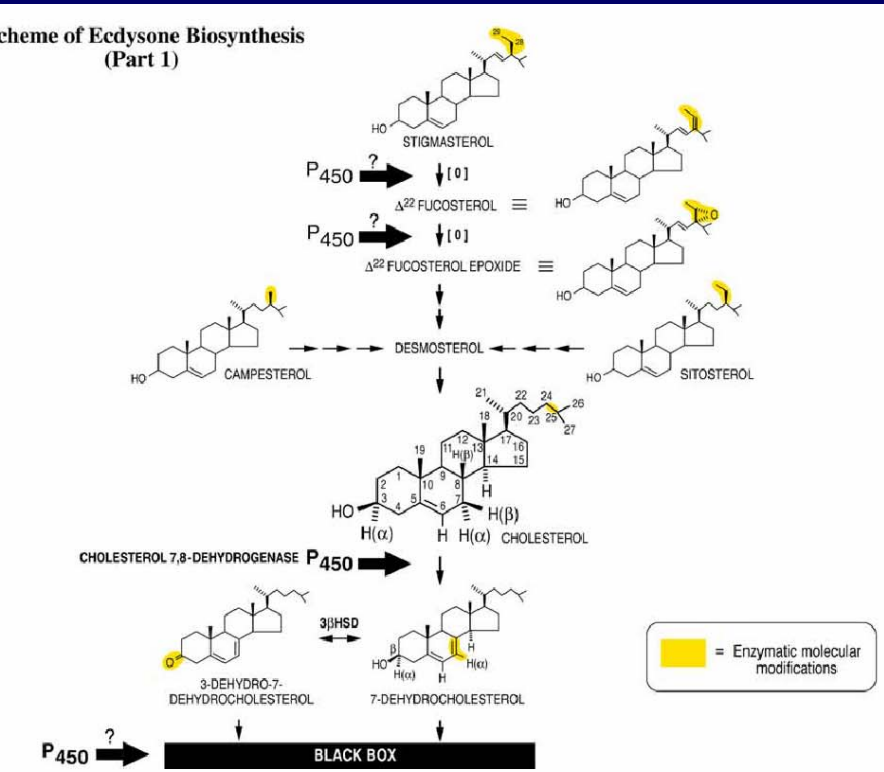
Ecdysone

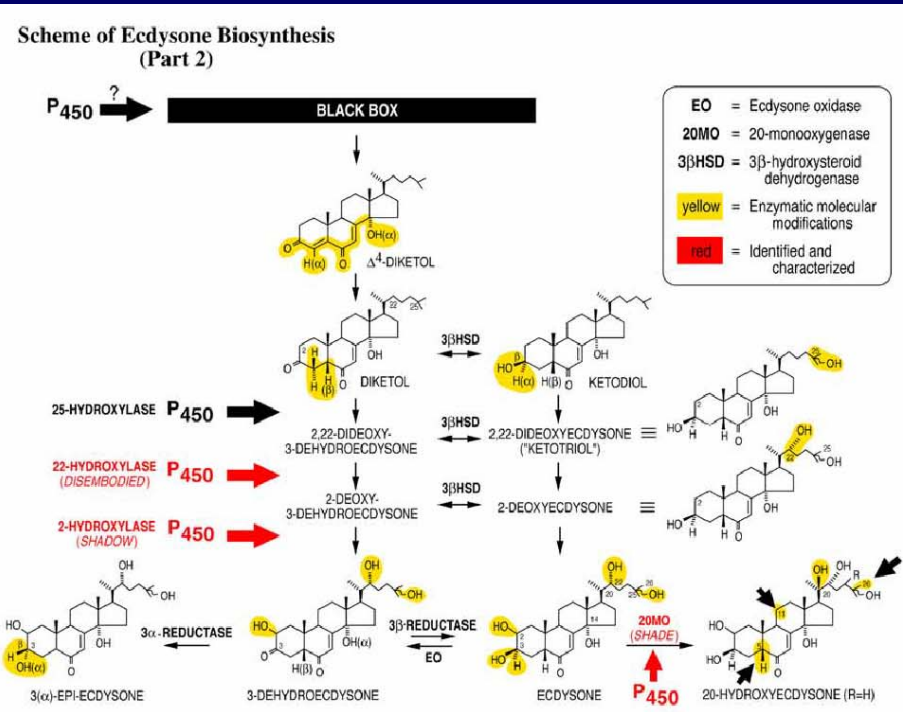
mono-oxygenase
(fat body, epidermis)



20-Hydroxyecdysone

Syntéza ekdysteroidů a úloha cytochromů P450:





5. (Parts 1 and 2). The biosynthesis of 20-hydroxyecdysone from plant sterols. Question marks denote possible involvement of P450 enzymes. Note specifically where the Halloween gene produ
red). 3-Dehydroecdysone is synthesized in the prothoracic glands of many insects (e.g. *Manduca sexta)* and converted to ecdysone in the hemolymph (left column of part 2). For *Drosophila*, ecdys
nthesized in the prothoracic gland cells of the ring gland (right column of part 2).

Modelový příklad 2: Metabolismus xenobiotik

Box 1 | **Representative list of XMEs**

Phase I enzymes

- Cytochrome P450s (CYPs).
- Hydroxylases.
- Reductases.
- Aldoketoreductases (AKRs).
- Flavin-containing monooxygenases (FMOs).
- Lipooxygenases (LOXs).
- Cyclooxygenases.
- Peroxidases.
- Epoxygenases.
- Oxidases.
- Monoamine oxidases (MAOs).
- Dioxygenases.
- NAD-dependent and NADP-dependent alcohol dehydrogenases (ADHs).
- NAD-dependent and NADP-dependent aldehyde dehydrogenases (ALDHs).
- NAD-dependent and NADP-dependent steroid dehydrogenases.
- Carboxylesterases.
- Glycosylases.
- Glucuronidases.
- Hydrolases.
- Esterases.
- Sulphatases.

Phase II enzymes

- Uridine diphosphate glucuronosyltransferases (UGTs).
- Glutathione S-transferases (GSTs).
- Sulphotransferases (SULTs).
- Epoxidases.
- Acyltransferases.
- Acetyltransferases.
- Methyltransferases.
- Transaminases.

This classification is not rigid. Some of these classes of enzymes can arguably be in either the phase I or phase II category.

http://drnelson.utmem.edu/CytochromeP450.htm

Table 3 | **XME receptors that regulate XMEs and/or XRTs**

XME receptor	Ligands	XMEs up- or downregulated	XRTs up- or downregulated
AHR	Dioxin, coplanar PAHs, coplanar PHAHs, benzoflavones	CYP1, CYP2A, CYP2C*, CYP2S1*, NQO1, ALDH3A1, GSTA1, UGT1A6/7	?
CAR	Phenobarbital, TCPOBOP, colupulone, androstanes	CYP2B, ALDH, esterase, FMO, methyltransferase, GST, SULT, UGT1A6	ABCC2
FXR	Bile acids	CYP7A1, CYP8B1	ABCB11
HNF-1α	Bile acids	UGT1A7, GSTA2, UGT1A1, UGT2B17	SLC21A6
HNF3α,β,γ	Epidermal growth factor, fushi tarazu factor-1α, LPS	CYP2C, CYP3A, CYP7A1	SLC21A10
HNF4α	Long-chain fatty acyl-coA thioesters, chenodeoxycholic acid	CYP2D6	Proteins involved in glucose transport and metabolism
LXRα,β	Oxysterols	CYP7A1	ABCA1, ABCD2, ABCG1, ABCG4, ABCG5, ABCG8
PPARα	Fibrates, fatty acids	CYP4A1, CYP4A3	ABCC3, ABCC4, proteins involved in glucose transport and metabolism
PPARδ	Fatty acids, carboprostacyclin	?	?
PPARγ	Fatty acids, eicosanoids, thiazolidinediones	CYP4B1	?
PXR (SXR)	Pregnenolone 16α-carbonitrile, rifampicin, LCA	CYP1, CYP2A, CYP2B, CYP2C, CYP3A, CYP4F, carboxylesterase, MAO, CAT, FMOs, GSTs, UGTs, SULTST2A	ABCB1, ABCC2
RARα,β,γ	Retinoic acids	CYP26A1	?
RXRα,β,γ	9-cis-retinoic acid	?	?
VDR	1α,25-dihydroxy-vit D_3	CYP24A1, CYP27B1	?

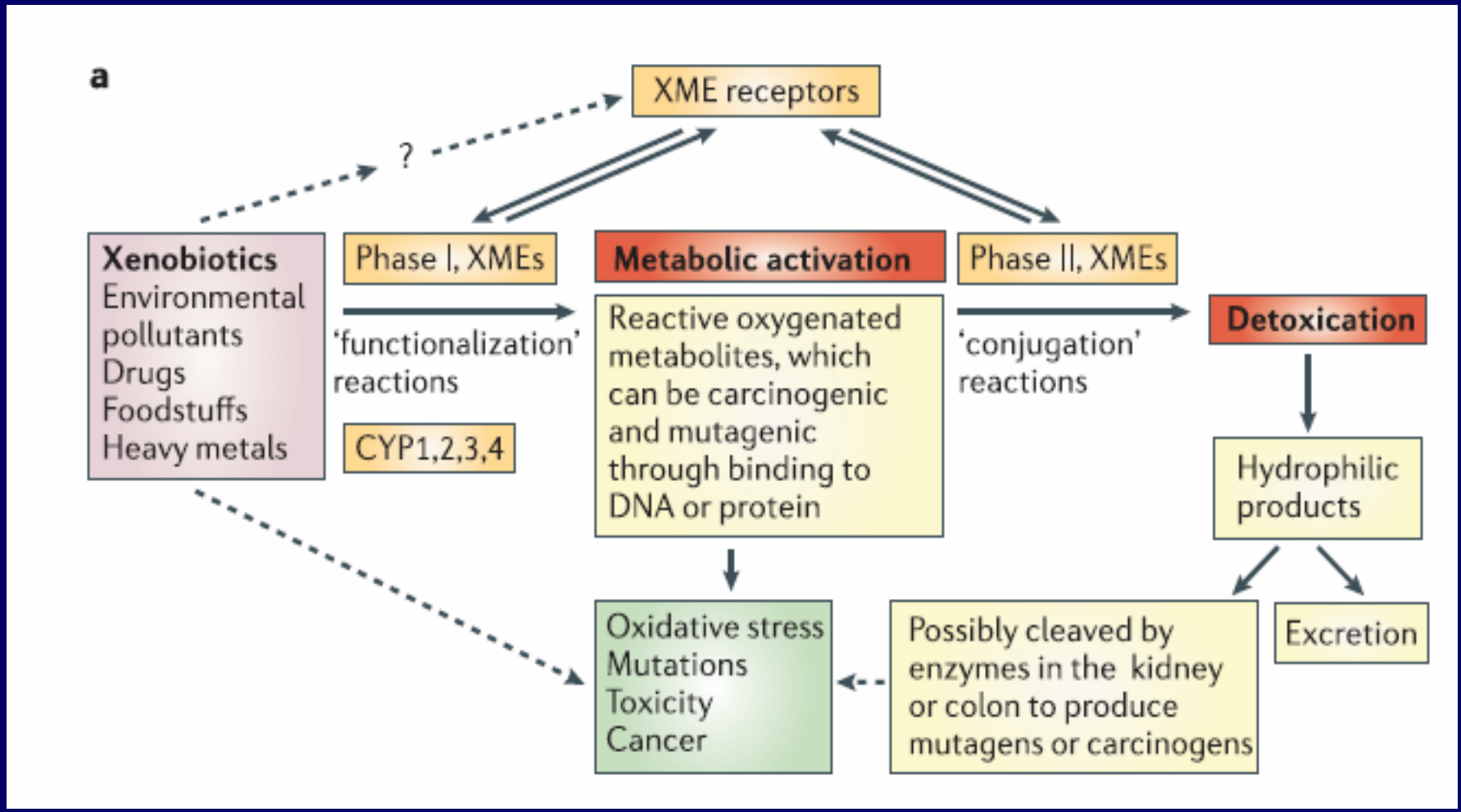
Further details of xenobiotic-metabolizing enzymes (XMEs) receptors that regulate XMEs and/or xenobiotic-related transporters (XRTs) can be found in several excellent reports[61,132–135]. *Only one (or very few) members of the CYP2A and CYP2C subfamilies are upregulated by the aryl hydrocarbon receptor (AHR). All the gene products in this table are given their official names according to the HUGO gene nomenclature homepage. '?' denotes that XMEs and XRTs are expected to be regulated by this XME receptor, but that none have been identified to date. CAR, constitutive androstane receptor; FXR, farnesoid X receptor; HNFs, hepatocyte nuclear factors; LCA, the toxic bile acid lithocholic acid; LPS, lipopolysaccharide; LXRs, liver X receptors; PAHs, polycyclic aromatic hydrocarbons; PHAHs, polyhalogenated aromatic hydrocarbons; PPARs, peroxisome proliferator-activated receptors; PXR, pregnane X receptor; RARs, retinoic acid receptors; RXRs, retinoid X receptors; TCPOBOP, 1,4-*bis*[2-(3,5-dichloropyridyloxy)]benzene; VDR, vitamin D_3 receptor.

Aktivace promutagenů:

Table 2 Precarcinogens metabolized by cytochromes *P*450

Enzyme	*Activation of carcinogens*
CYP1A1	Polycyclic aromatic hydrocarbons: benzo(*a*)pyrene, dimethylbenz[*a*]anthracene, PhIP[a]
CYP1A2	Activation of aryl and heterocyclic amines in industrial settings and food mutagens: *N*-nitrosodimethylamine, 4-aminobiphenyl, 2-acetyl-aminofluorene, *N*-nitrosodiethylamine, PhIP, IQ, aflatoxin B1
CYP1B1	Polycyclic aromatic hydrocarbons: benzo(*a*)pyrene, dimethylbenz[*a*]anthracene, benz[*a*]anthracene, 3-methylcholanthrene, DMBA, oestradiol
CYP2A6	Activation of tobacco-related *N*-nitrosamines: NNK, NNAL, NDEA, NNN, NATB, Aflatoxin B1, 1,3-butadiene, 2,6-dichlorobenzonitrile
CYP2B6	Aflatoxin B1 and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone
CYP2E1	Low-molecular-weight toxicants and cancer suspect agents: benzene, carbon tetrachloride,chloroform, styrene, vinyl chloride, vinyl bromide, *N*-nitrosodimethylamine, NNK
CYP3A4/5/7	Diverse carcinogens: aflatoxin B1, aflatoxin G1, benzo(*a*)pyrene, naphthalene, NNN, 1-nitropyrene, 6-amino-chrysene, oestradiol, senecionine, stergmato-cystine

[a]DMBA, 7,12,-dimethylbenz[a]anthracene; IQ, 2-amino-3-methylimidazo[4,5-f]quinoline; NATB, *N*-nitrosoanatabine; NDEA, *N*-nitrosodiethylamine; NNAL, 4-(methylnitrosoamino)-1-(3-pyridyl)-1-butanol; NNK, 4-(methylnitrosoamino)-1-(3-pyridyl)-1-butanone; NNN, *N*9-nitrosonornicotine; PhIP, 2-amino-1-methyl-6-phenylimidazo-[4,5-b]pyridine.


a
XME receptors
?
Xenobiotics
Environmental pollutants
Drugs
Foodstuffs
Heavy metals
Phase I, XMEs
'functionalization' reactions
CYP1,2,3,4
Metabolic activation
Reactive oxygenated metabolites, which can be carcinogenic and mutagenic through binding to DNA or protein
Phase II, XMEs
'conjugation' reactions
Detoxication
Hydrophilic products
Excretion
Possibly cleaved by enzymes in the kidney or colon to produce mutagens or carcinogens
Oxidative stress
Mutations
Toxicity
Cancer

Metabolismus léčiv:

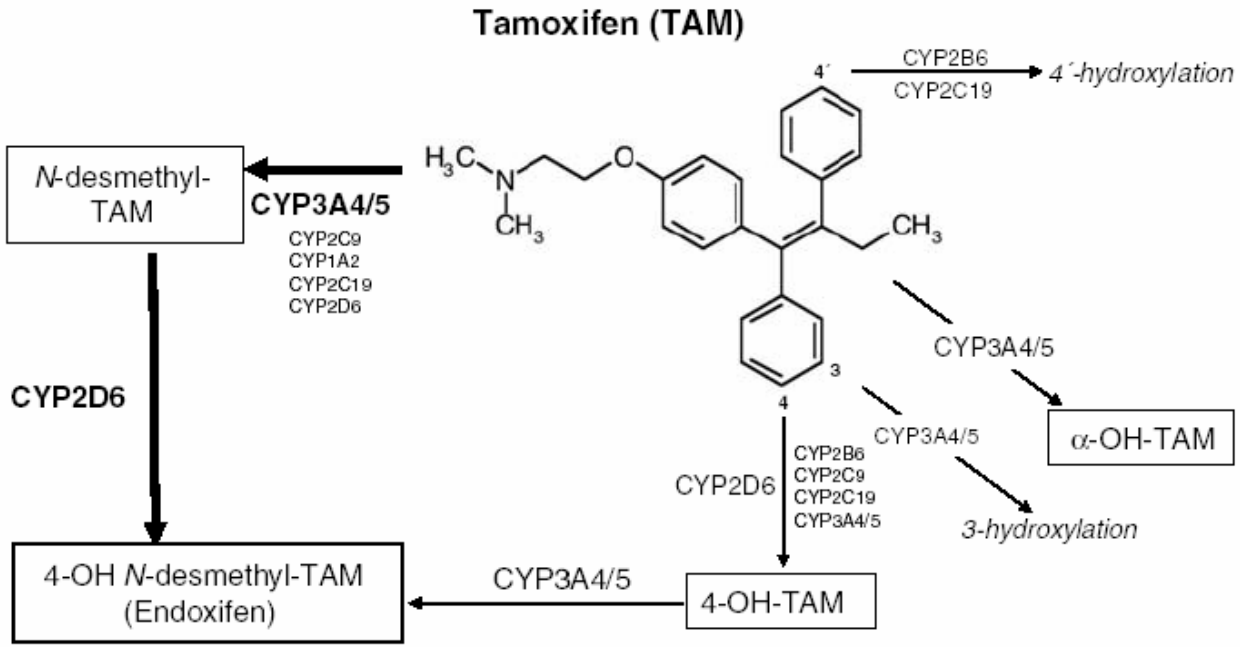


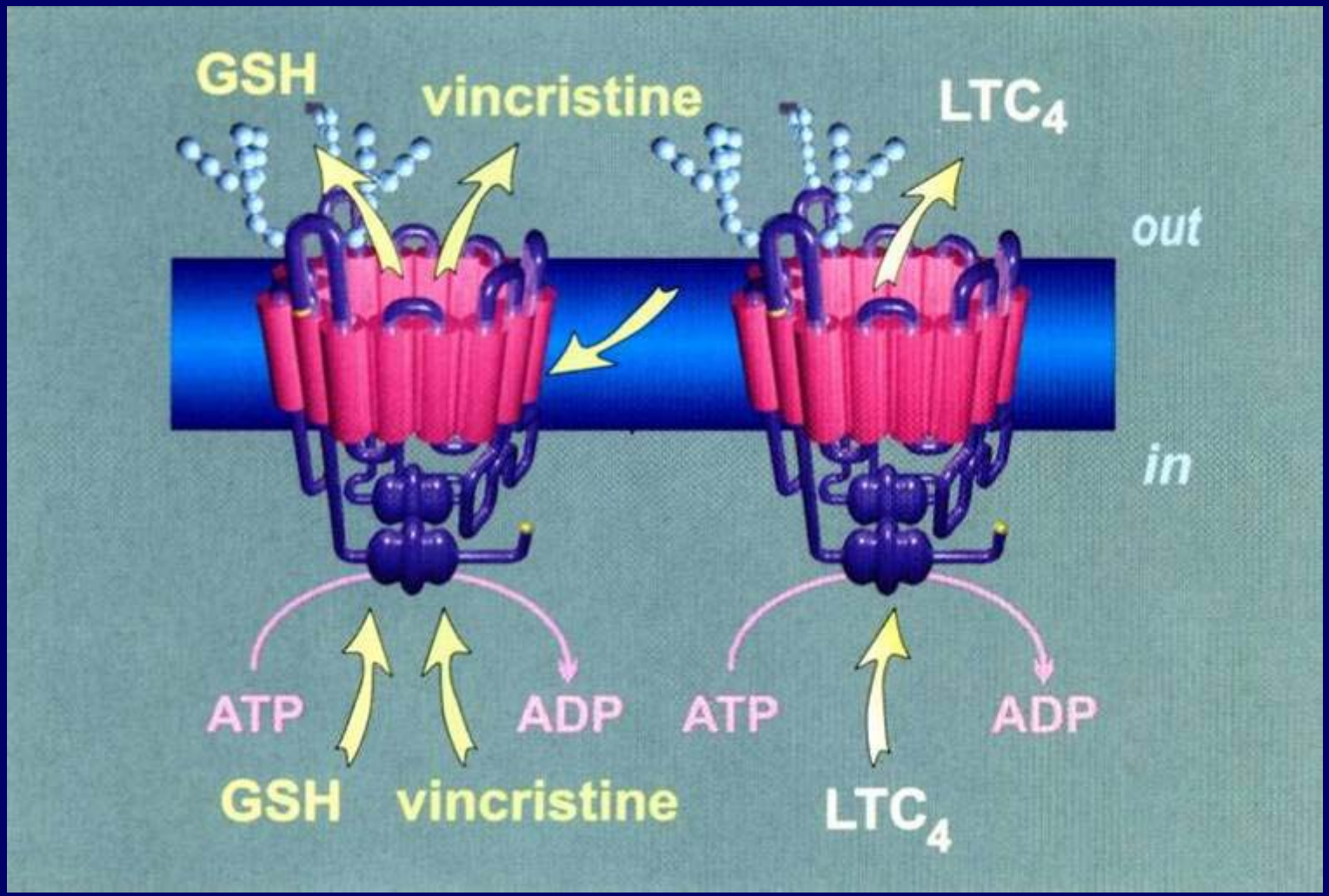
Figure 2 Chemical structure of tamoxifen and major biotransformation pathways. CYP3A4/5 are the more efficient enzymes responsible for the *N*-demethylation of tamoxifen (TAM), whereas the generations of endoxifen and 4-hydroxytamoxifen (4-OH-TAM) are predominantly catalysed by CYP2D6. Other CYP isoforms, including CYP2C19, CYP2C9, CYP2B6 and CYP1A2, have also been shown to participate in the metabolism of tamoxifen. The most abundant compounds in plasma are *N*-desmethyltamoxifen and endoxifen, and endoxifen has approximately 100 times greater affinity for the oestrogen receptor than tamoxifen and *N*-desmethyltamoxifen. *CYP2D6* polymorphisms have been shown to affect the plasma concentrations of endofixen.

Jaderné receptory a další proteiny:

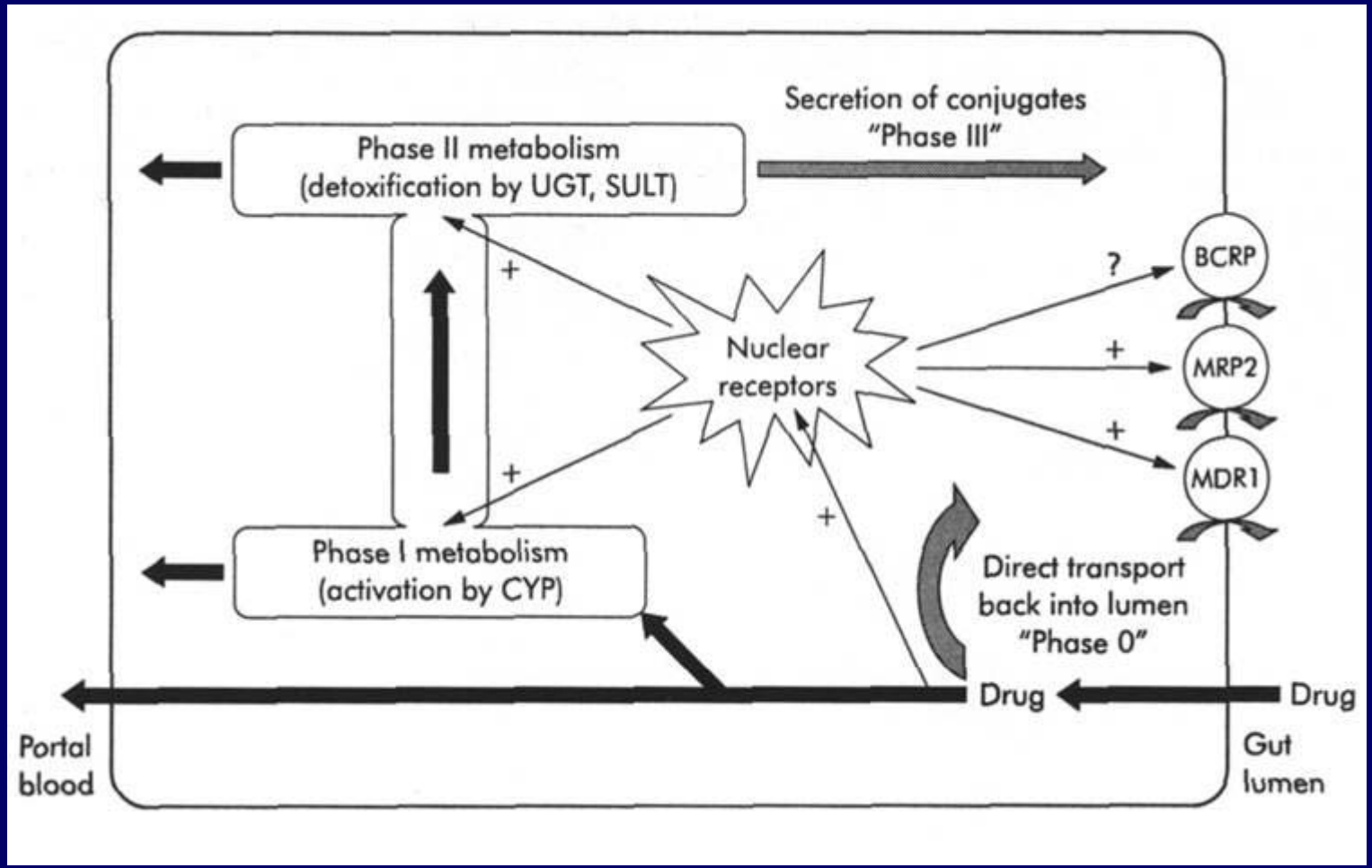
Nuclear receptor		Ligand	CYP enzyme	Cytosolic binding protein	ABC transporter
Retinoid X receptors*	RXRα,β,γ	9-*cis* Retinoic acid	–	–	–
Peroxisome proliferator-activated receptors	PPARα	Fatty acids Fibrates	↑ CYP4A1 ↑ CYP4A3	↑ L-FABP	↑ ABCD2, ABCD3 ↑ ABCB4
	PPARδ	Fatty acids Carboprostacyclin	(?)	(?)	(?)
	PPARγ	Fatty acids Eicosanoids Thiazolidinediones	↑ CYP4B1	↑ ALBP/aP2 ↑ H-FABP	(?)
Liver X receptors	LXRα,β	Oxysterols	↑ CYP7A1	OSBPs?	↑ ABCA1, ↑ ABCG1, ABCG4 ↑ ABCG5, ABCG8
Farnesoid X receptor	FXR	Bile acids	↓ CYP7A1 ↓ CYP8B1	↑ IBABP	↑ ABCB11
Xenobiotic receptors	SXR/PXR	Xenobiotics Steroids	↑ CYP3A ↑ CYP2C	(?)	↑ ABCB1, ABCC2
	CAR	Xenobiotics Phenobarbital	↑ CYP2B ↑ CYP2C	(?)	↑ ABCC3
Ecdysone receptor	EcR	20(OH)-ecdysone	↑ 26-(OH)ase	Hexamerins	↑ E23
Retinoic acid receptors	RARα,β,γ	Retinoic acids	↑ CYP26A1	↑ CRABPII ↑ CRBPI	(?)
Vitamin D receptor	VDR	1,25(OH)$_2$-vitamin D$_3$	↑ CYP24 ↓ CYP27B1	(?)	(?)

ABC TRANSPORTÉRY: MULTIDRUG RESISTANCE (MDR) SYSTEM

Transport
ipidů,
xenobiotik
aj. látek
přes buněčné
membrány



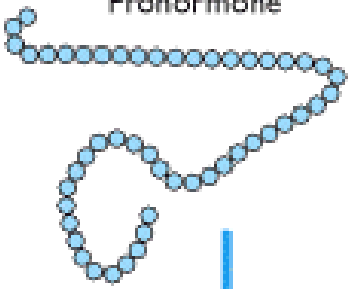
3. FÁZE BIOTRANSFORMACE (ABC TRANSPORTÉRY)



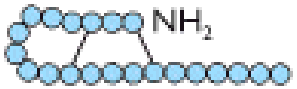
Modelový příklad 3:
Steroidní hormony

Protein and Peptide Hormones

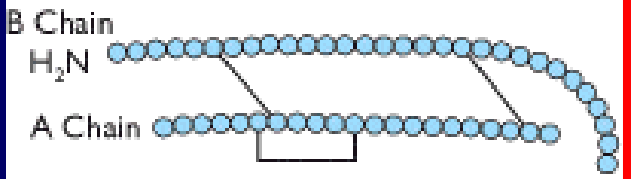
Prohormone



Endothelin

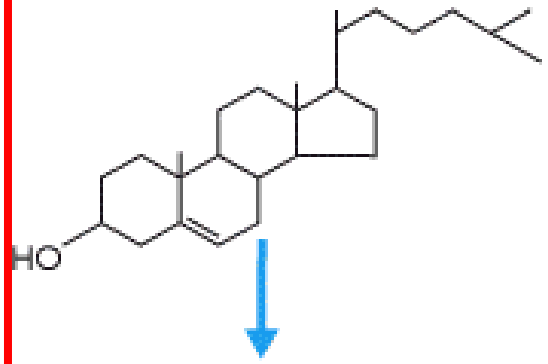


Insulin

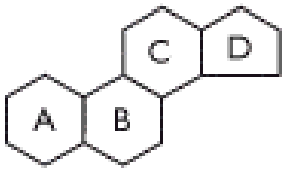


Steroid Hormones

Cholesterol

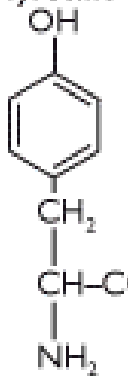


Steroid Nucleus

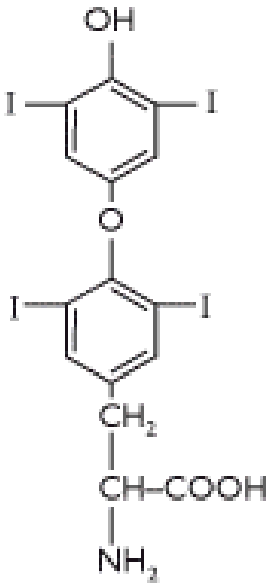


Tyrosine Derivatives

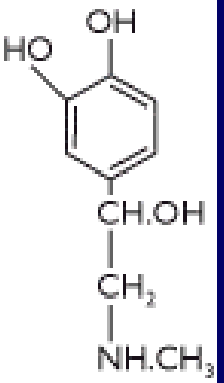
Tyrosine



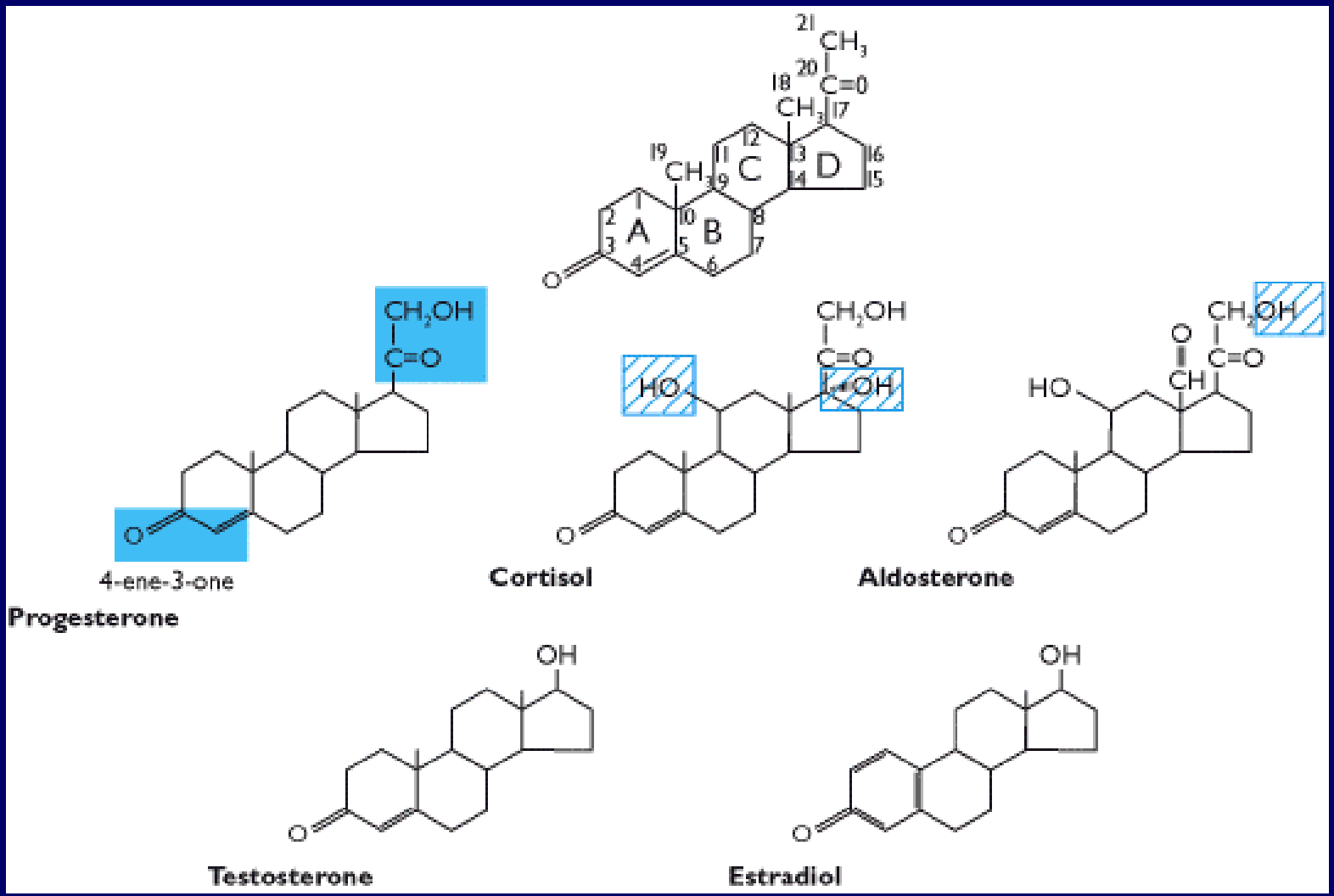
Thyroxine

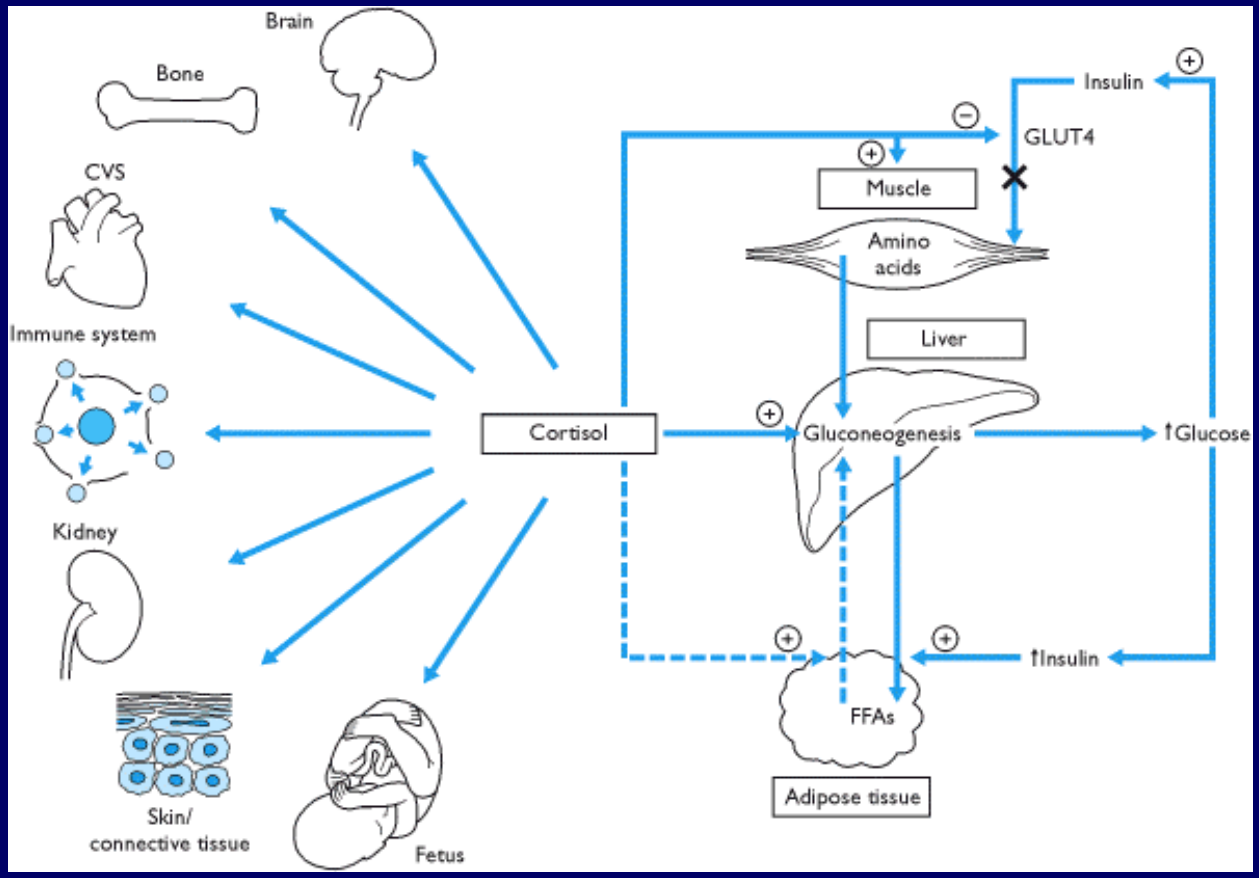


Epinephrine



Pět hlavních skupin steroidních hormonů:



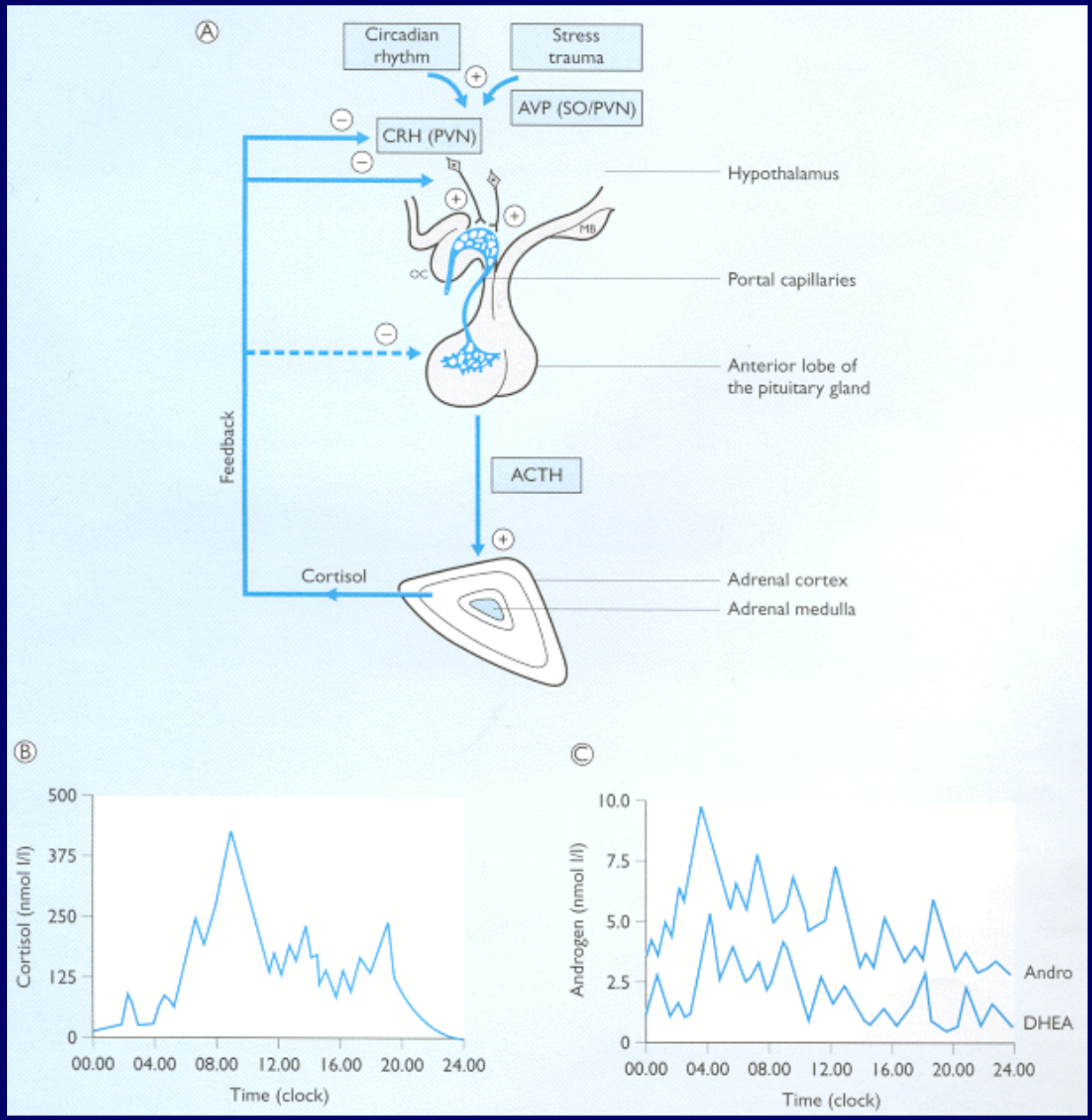


• Cortisol stimulates the release of amino acids from muscle. These are taken up by the liver and converted to glucose.

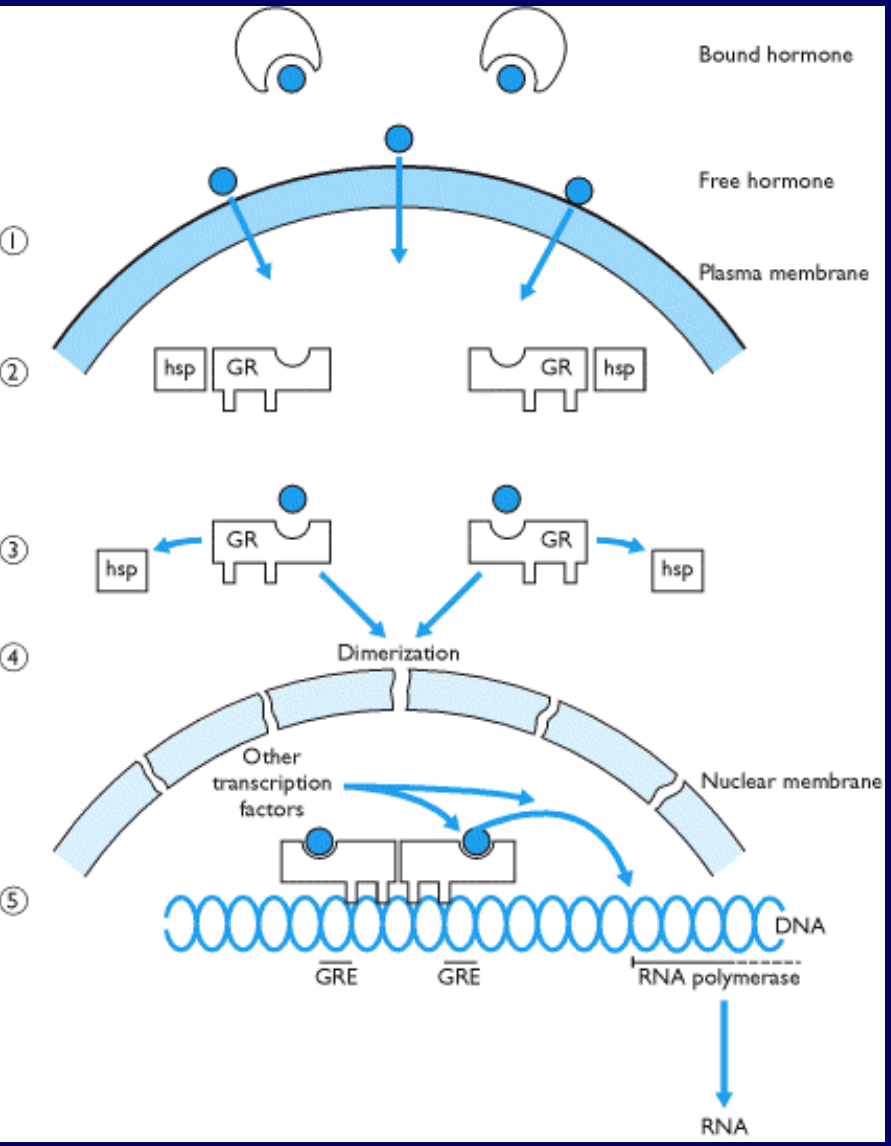
•The increased circulating concentration of glucose stimulates insulin release. Cortisol inhibits the insulin-stimulated uptake of glucose in muscle via the GLUT4 transporter.

•Cortisol has mild lipolytic effects. These are overpowered by the lipogenic action of insulin secreted in response to the diabetogenic action of cortisol.

•Cortisol also has varied actions on a wide range of other tissues

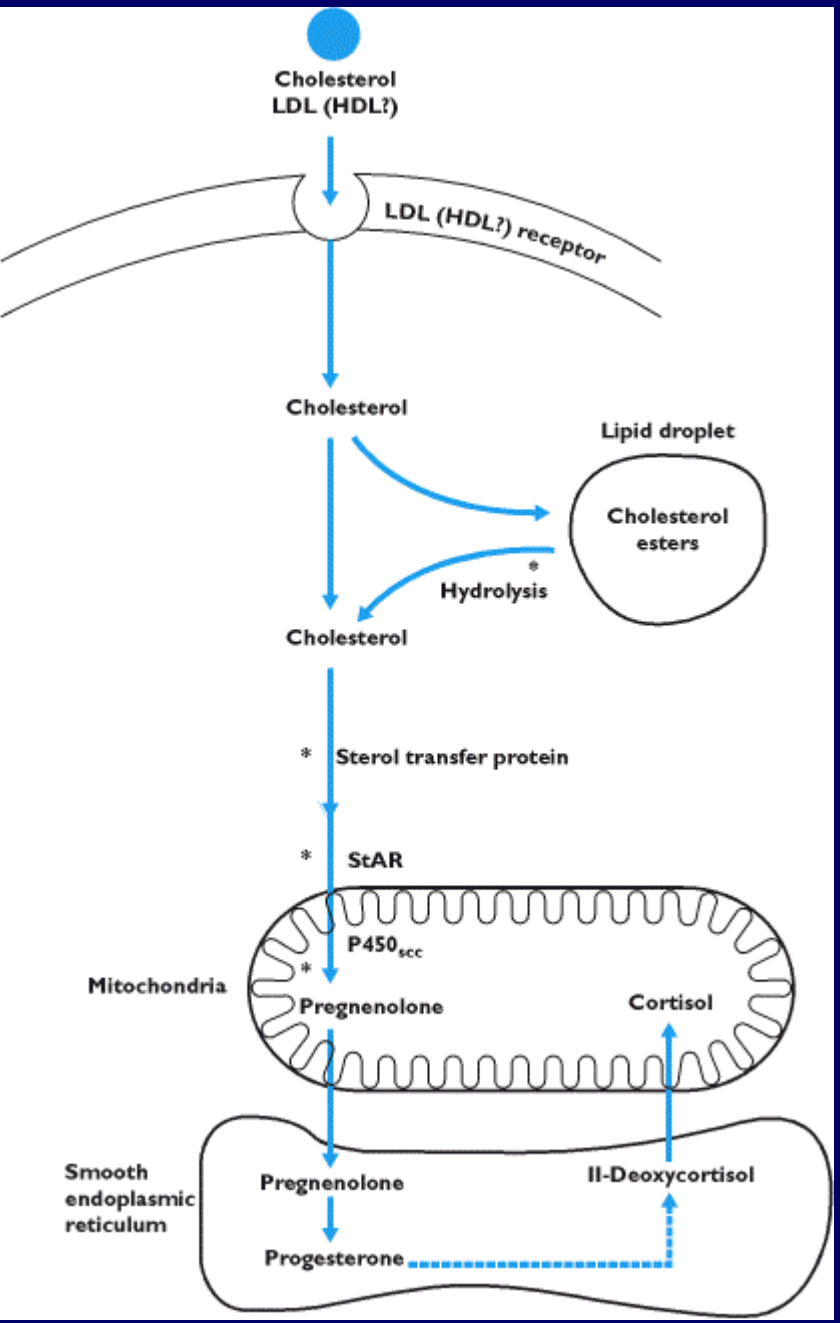

Ⓐ
Circadian rhythm
Stress trauma
AVP (SO/PVN)
CRH (PVN)
Hypothalamus
MB
OC
Portal capillaries
Anterior lobe of the pituitary gland
Feedback
ACTH
Cortisol
Adrenal cortex
Adrenal medulla
Ⓑ
Cortisol (nmol l/l)
500
375
250
125
0
00.00 04.00 08.00 12.00 16.00 20.00 24.00
Time (clock)
Ⓒ
Androgen (nmol l/l)
10.0
7.5
5.0
2.5
0
Andro
DHEA
00.00 04.00 08.00 12.00 16.00 20.00 24.00
Time (clock)

The glucocorticoid receptor and activation by cortisol



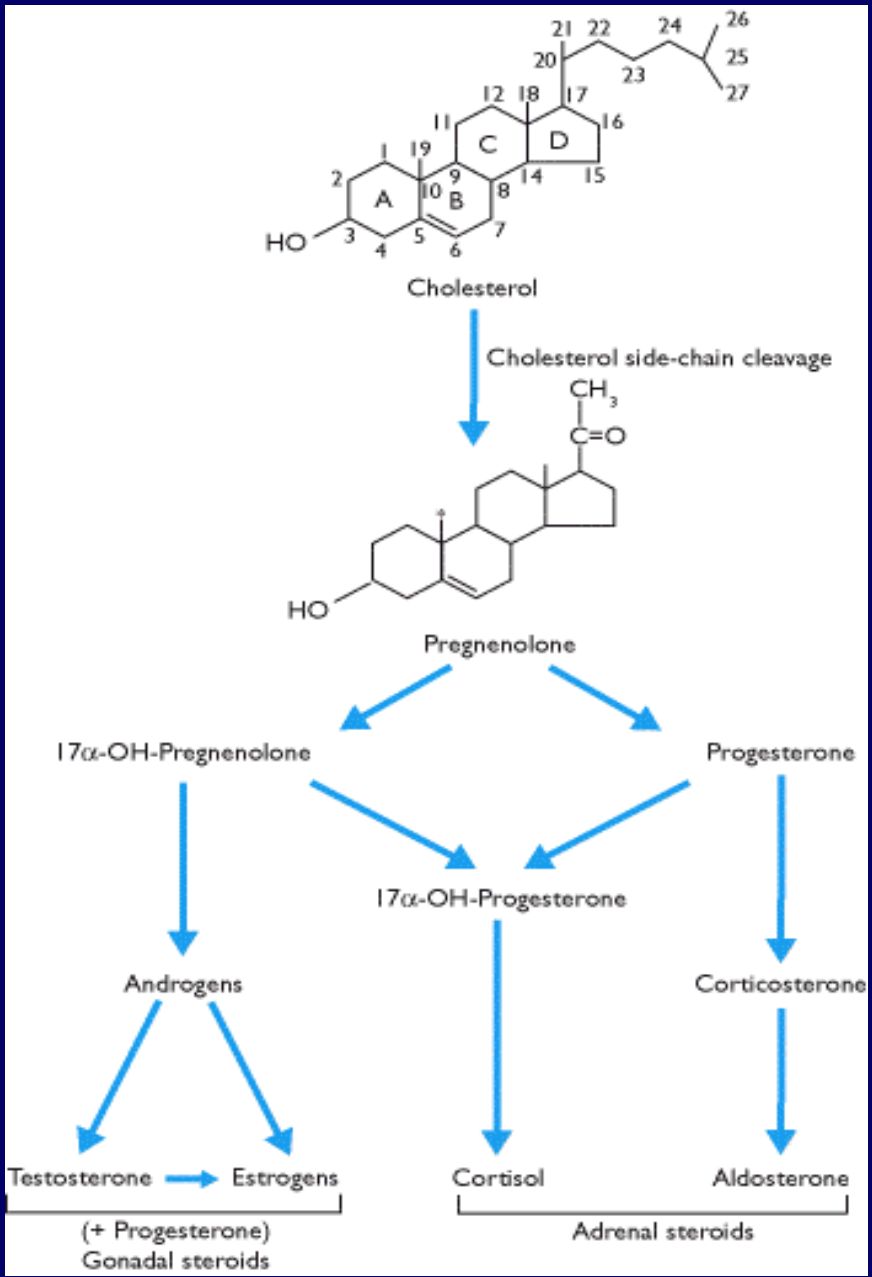
1) Unbound, lipophilic cortisol readily crosses cell membranes and in target tissues will combine with the glucorticoid receptor (GR).
2) Like the androgen and progesterone receptors, unliganded GRs are located in the cytoplasm attached to heat shock proteins (hsp-90, hsp-70 and hsp-56).
3) When hormones bind to these receptors hsps are released and the hormone receptor complexes translocate to the nucleus.
4) These complexes form homo- or heterodimers and the zinc fingers of their DNA-binding domains slot into the glucocorticoid response elements (GREs) in the DNA helix.
5) Together with other transcription factors, such as NF-κB or c-jun and c-fos, they initiate RNA synthesis (activation of RNA polymerase) downstream of their binding.

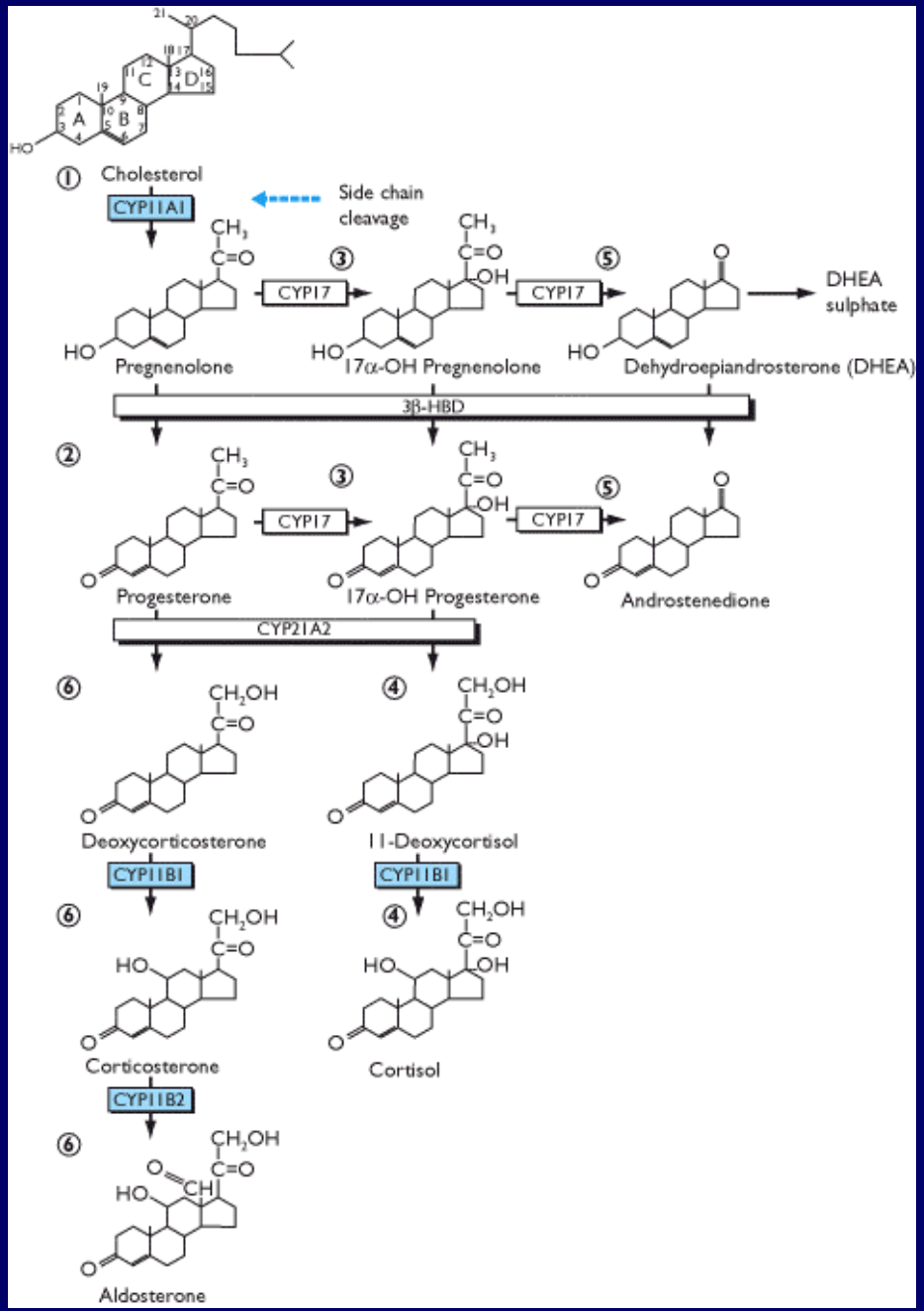
Diagrammatic outline of the synthesis of cortisol from cholesterol in the adrenal corte

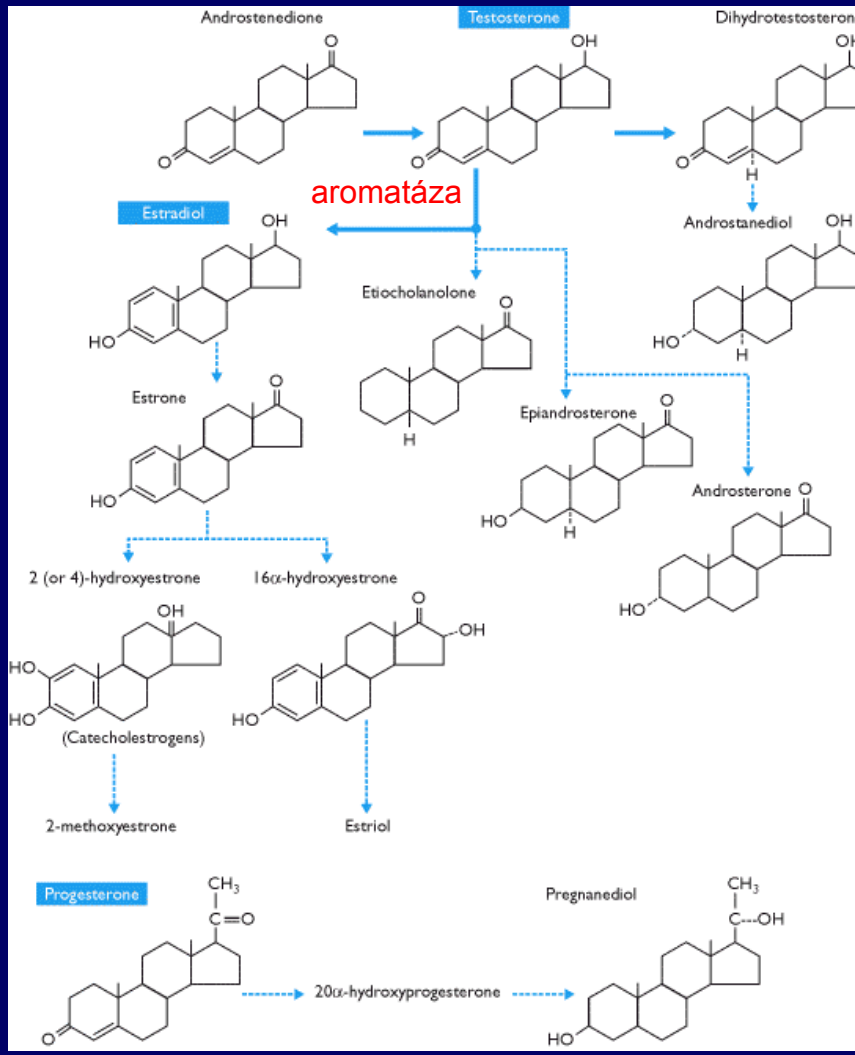


Cholesterol is either obtained from the diet or synthesized from acetate by a CoA reductase enzyme. Approximately 300 mg cholesterol is absorbed from the diet each day and about 600 mg synthesized from acetate. Cholesterol is insoluble in aqueous solutions and its transport from the main site of synthesis, the liver, requires apoproteins to form a lipoprotein complex. In the adrenal cortex, about 80% of cholesterol required for steroid synthesis is captured by receptors which bind low-density lipoproteins (LDL) although recent evidence has shown that high-density lipoprotein (HDL) cholesterol may also be taken up by adrenal cells. The remaining 20% is synthesized from acetate within the adrenal cells by the normal biochemical route.

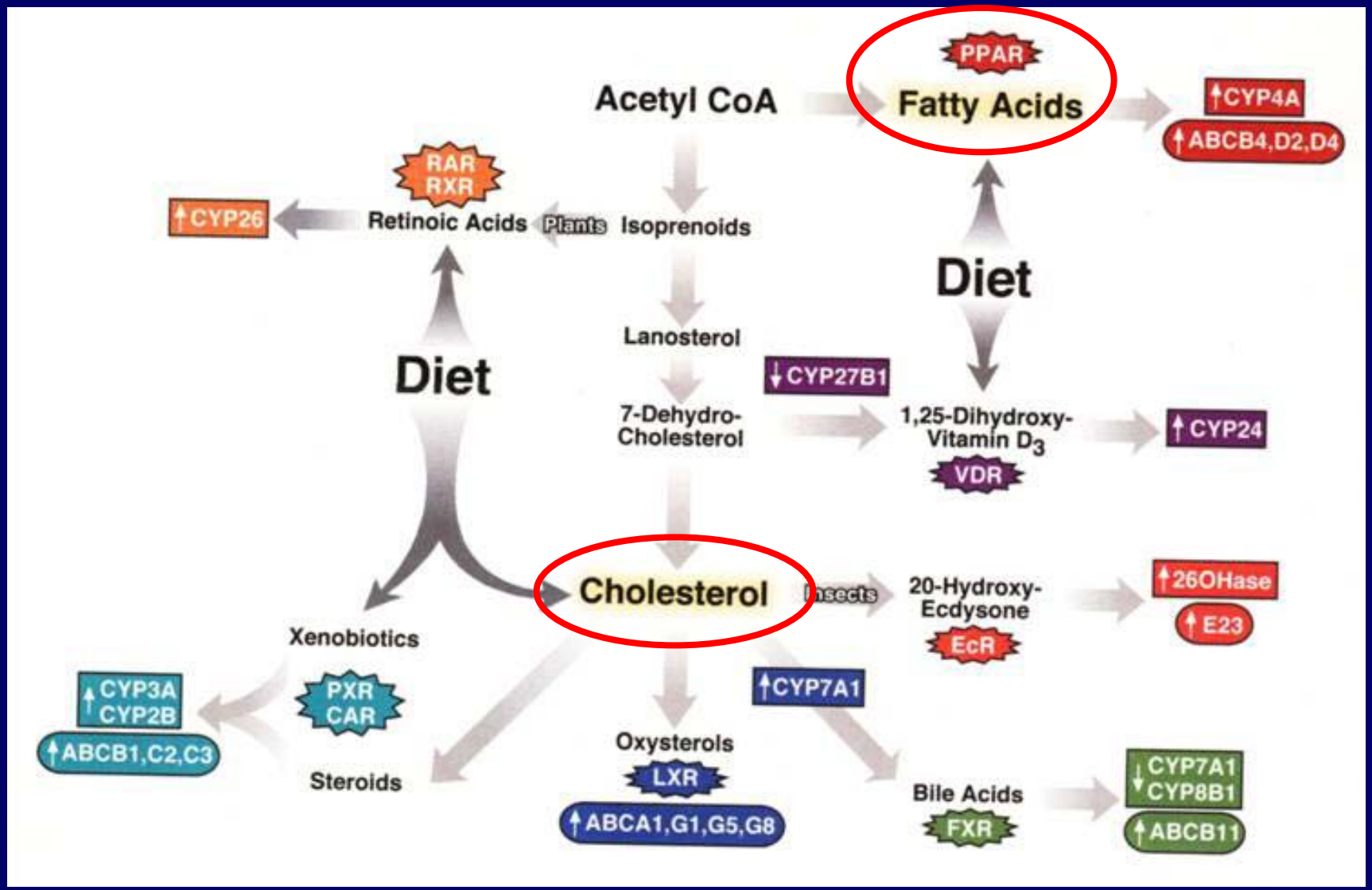
Biosyntéza steroidních hormonů:



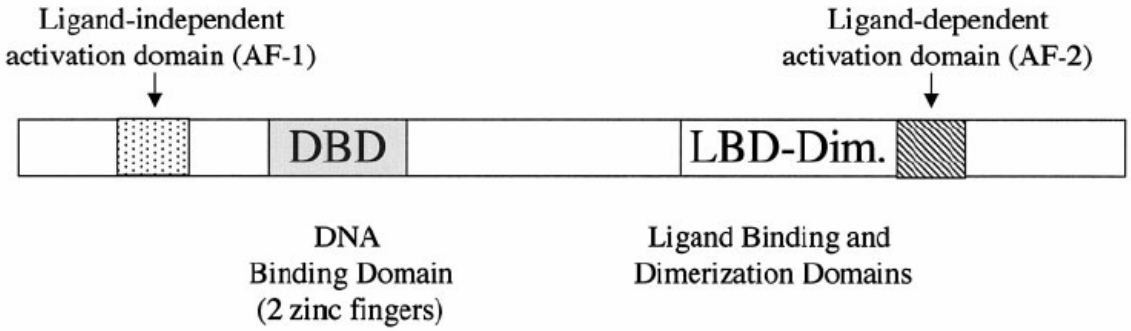

Cholesterol
CYP11A1
Side chain cleavage
Pregnenolone
CYP17
17α-OH Pregnenolone
CYP17
Dehydroepiandrosterone (DHEA)
DHEA sulphate
3β-HBD
Progesterone
CYP17
17α-OH Progesterone
CYP17
Androstenedione
CYP21A2
Deoxycorticosterone
11-Deoxycortisol
CYP11B1
CYP11B1
Corticosterone
Cortisol
CYP11B2
Aldosterone

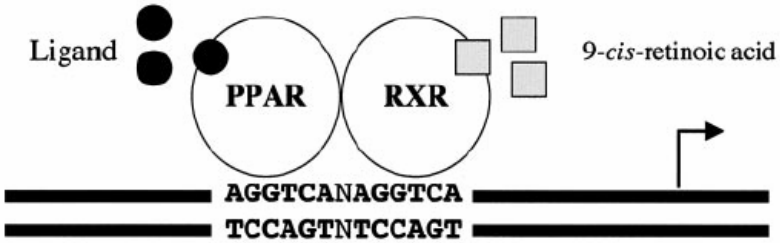

Androstenedione
Testosterone
Dihydrotestosteron
aromatáza
Estradiol
Androstanediol
Etiocholanolone
Estrone
Epiandrosterone
Androsterone
2 (or 4)-hydroxyestrone
16α-hydroxyestrone
(Catecholestrogens)
2-methoxyestrone
Estriol
Progesterone
20α-hydroxyprogesterone
Pregnanediol

Modelový příklad 4:
Metabolismus mastných kyselin


PPAR
Acetyl CoA
Fatty Acids
CYP4A
ABCB4,D2,D4
RAR
RXR
CYP26
Retinoic Acids
Plants
Isoprenoids
Diet
Diet
Lanosterol
CYP27B1
7-Dehydro-
Cholesterol
1,25-Dihydroxy-
Vitamin D3
CYP24
VDR
Cholesterol
Insects
20-Hydroxy-
Ecdysone
26OHase
E23
EcR
Xenobiotics
CYP3A
CYP2B
ABCB1,C2,C3
PXR
CAR
CYP7A1
Oxysterols
LXR
ABCA1,G1,G5,G8
Steroids
Bile Acids
FXR
CYP7A1
CYP8B1
ABCB11

Receptory aktivované peroxizómovými proliferátory (PPAR)





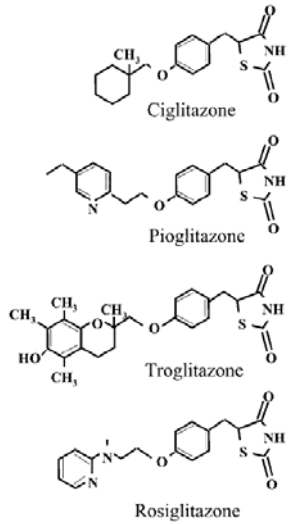
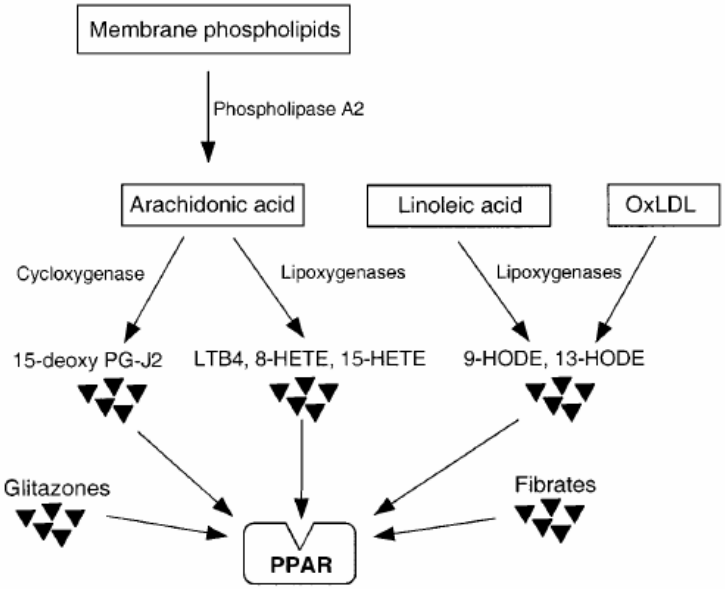
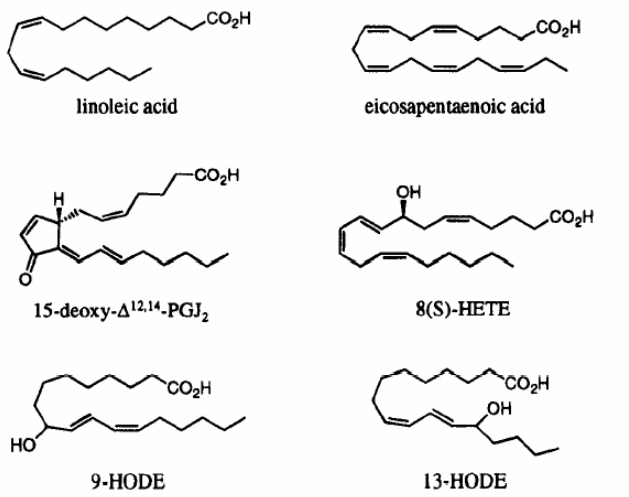


FIG. 1. General structure and mechanism of action of PPARs. PPAR isoforms share a common domain structure and molecular mechanism of action.





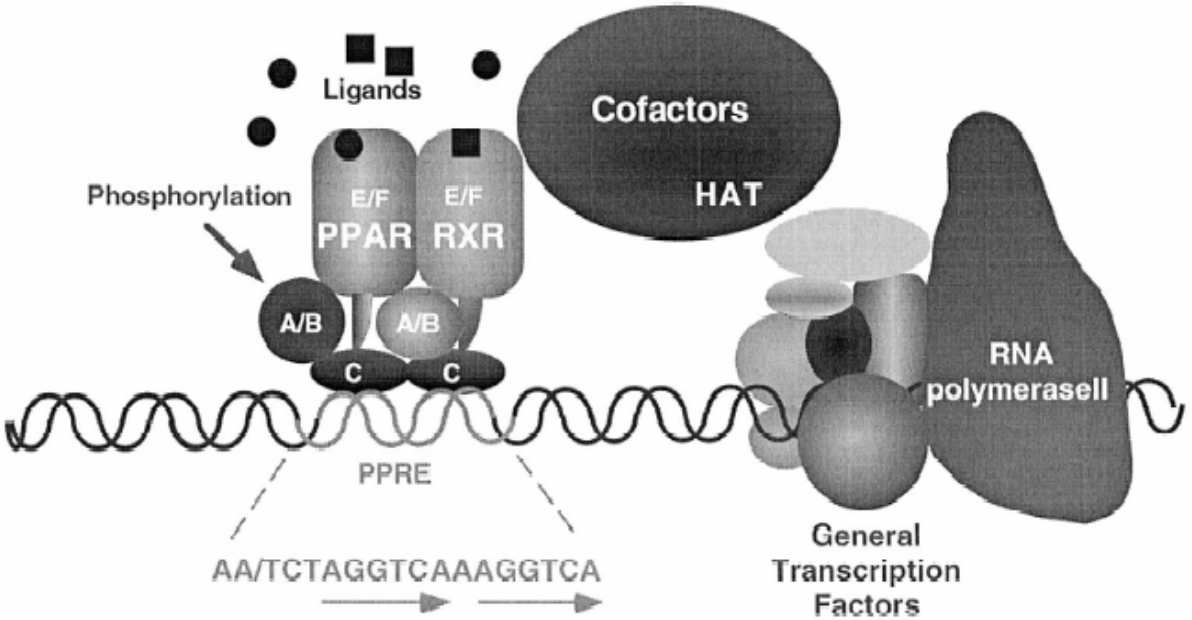


Fig. 3. Mechanisms of transactivation. The PPAR/RXR heterodimer binds to a PPRE (PPAR-response elements) located in the promoter of target genes through the C domain (DNA-binding domain) of PPAR and RXR. Receptor activity is regulated by both phosphorylation of A/B domain and ligand-binding by E/F domain (ligand-binding domain). The activated PPAR/RXR heterodimer associates with cofactors containing histone acetyl-transferase activity (HAT), modifying nucleosome structure and contacting general transcription factors.

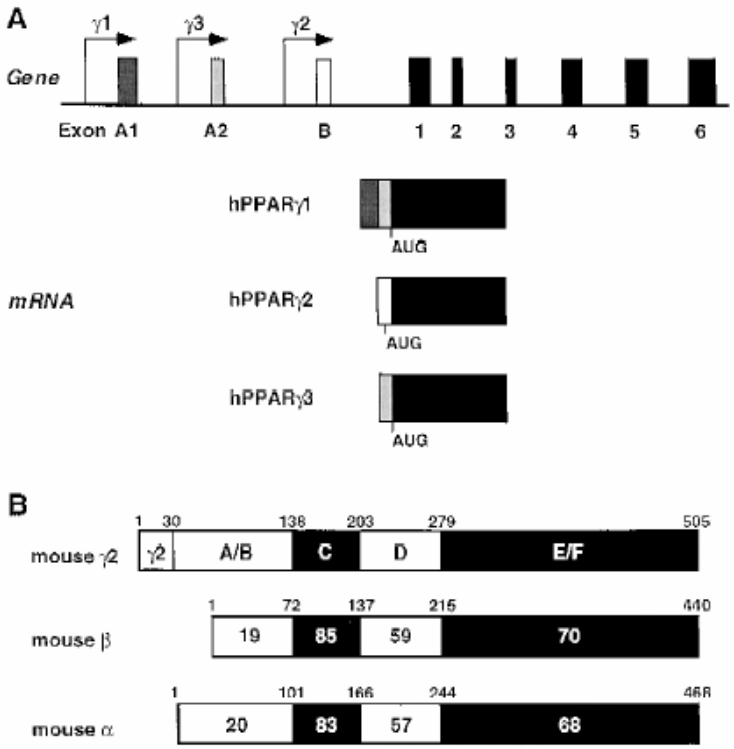


Fig. 1. Structure of PPARs. (A) Genomic organization of the human PPARγ gene (not drawn to scale). Alternative promoter usage and splicing results in three different transcripts. PPARγ1, PPARγ2 and PPARγ3 are transcribed from promoters located upstream of exons A1, B and A2, respectively. PPARγ1 and PPARγ3 mRNAs encode the same protein. (B) Structural and functional domains of PPARs. γ2: PPARγ2-specific N-terminus of A/B domain. A/B: N-terminal A/B domain containing a ligand-independent activation function 1 (AF-1). (C) DNA-binding domain. (D) Hinge region. (E/F): C-terminal ligand-binding domain containing the ligand-dependent activation function 2 (AF-2). Sequence similarities were determined by the BESTFIT program (GCG package) using reported mouse PPARα [8], PPARβ [14], PPARγ1 [14] and PPARγ2 [32] sequences.

Gene	Localization of PPRE	PPRE	function of gene product
ACO	(-570/-558)	TGACCTtTGTCCT	First step in fatty acid β-oxidation
	(-214/-202)	TGACCTtCTACCT	
HD	(-2939/-2927)	TGACCTatTGAACTaTTACCT	Second and third step in fatty acid β-oxidation
C-ACS	(-175/-154)	TGACTGaTGCCCTgaaAGACCT	Conversion of fatty acids into acyl-CoA derivatives
CYP4A6	(-650/-662)	TCACTTtTGCCCTAGTTCA	Formation of dicarboxylic acids by ω-oxidation
	(-728/-740)	GGACCCTGGCCTtTGTCCT	
	(-27/-1)	TGACCTtTGCCCA	
HMG-CoAS	(-104/-92)	AGACCTtTGGCCC	Liver ketogenesis
MCAD	(-301/-336)	TGGTCAgcctTCACCT-TTACCCggagagaa AGGTCA	First step in β-oxidation of medium-chain fatty acids
L-FABP	(-68/-56)	TGACCTaTGGCCT	Liver fatty acid binding protein
aP2	(-5222/-5209)	GGATCAgAGTTCA	Adipose tissue fatty acid binding protein
ME	(-328/-340)	TCAACTtTGACCC	Malate decarboxylation, providing NADPH for fatty acid synthesis
PEPCK	(-999/-987)	AGACCT-TATCCC	Gluconeogenesis and glyceroneogenesis
LPL	(-169/-157)	TGCCCTtTCCCCC	Hydrolysis of triglyceride-rich particles
apo A-I	(-212/-197)	TGAACCctTGACCCcTGCCCT	Protein component HDL, co-factor LCAT
apoA-II	(-734/-716)	CAACCTtTACCCT	Protein component HDL
Consensus		TGACCT[c/a]TGACCT	

Fig. 2. Functional PPREs. The DR-1s are indicated by a solid arrow which is indicated above the sequence when the coding strand is depicted; a dotted arrow indicates eventual additional half sites located adjacent to the DR-1 element. Abbreviations used in this figure include: ACO, acyl-CoA oxidase; ACS, acyl-CoA synthetase; aP2, adipocyte fatty acid binding protein P2; apo, apolipoprotein; L-FABP, liver fatty acid binding protei[n]; HD, enoyl-CoA hydratase-3-hydroxyacyl-CoA dehydrogenase; HMG-CoAS, HMG-CoA synthase; LPL, lipoprotein lipase; MCAD, medium-chain acyl-CoA dehydrogenase; ME, malic enzyme.

The **peroxisome proliferator-activated receptors (PPAR α, γ, δ)** are activated by polyunsaturated fatty acids, eicosanoids, and various synthetic ligands. Consistent with their distinct expression patterns, gene-knockout experiments have revealed that each PPAR subtype performs a specific function in fatty acid homeostasis.

PPARα is a global regulator of fatty acid catabolism. PPARα activation up-regulates the transcription of liver fatty acid–binding protein, which buffers intracellular fatty acids and delivers PPARα ligands to the nucleus. In addition, expression of two members of the adrenoleukodystrophy subfamily of ABC transporters, ABCD2 and ABCD3, is similarly up-regulated to promote transport of fatty acids into peroxisomes where catabolic enzymes promote β-oxidation. The hepatocyte CYP4A enzymes complete the metabolic cascade by catalyzing ϖ-oxidation, the final catabolic step in the clearance of PPARα ligands.

PPARγ was identified initially as a key regulator of adipogenesis, but it also plays an important role in cellular differentiation, insulin sensitization, atherosclerosis, and cancer. Ligands for PPARγ include fatty acids and other arachidonic acid metabolites, antidiabetic drugs (e.g., thiazolidinediones), and triterpenoids. In contrast to PPARα, PPARγ promotes fat storage by increasing adipocyte differentiation and transcription o a number of important lipogenic proteins.

Ligands for **PPARδ** include long-chain fatty acids and carboprostacyclin. Pharmacological activation of PPARδ in macrophages and fibroblasts results in up-regulation of the ABCA1 transporter, and because of its widespread expression, PPARδ may affect lipid metabolism in peripheral tissues can be antagonized by other small lipophilic agents, including 22(*S*)-hydroxycholesterol, certain unsaturated fatty acids, and

Nízkomolekulární lipofilní sloučeniny jako ligandy = aktivita jaderných receptorů je do značné míry závislá na syntéze a degradaci ligandů a naopak

Toxické látky, farmaka

?????