Fyziologie působení farmak a toxických látek

Přednáška č. 1

Úvod

Náplň předmětu:

Fyziologie komunikace

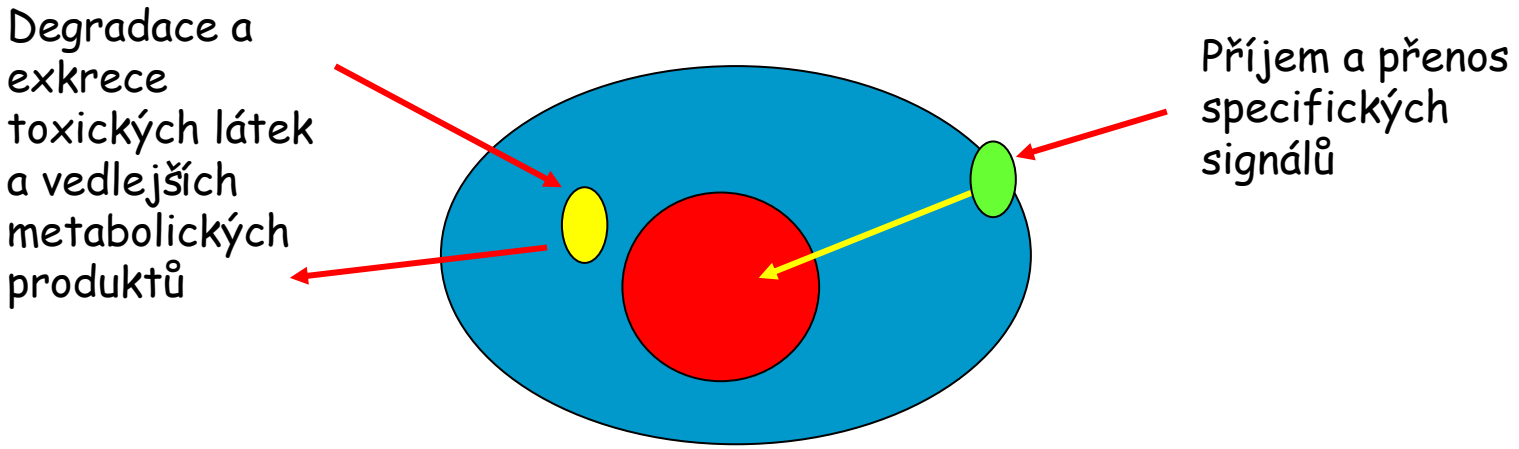
Nízkomolekulární látky přírodního a antropogenního původu:

- Signalizace
- Toxicita
- Fyziologické podmínky vs. lidské zásahy

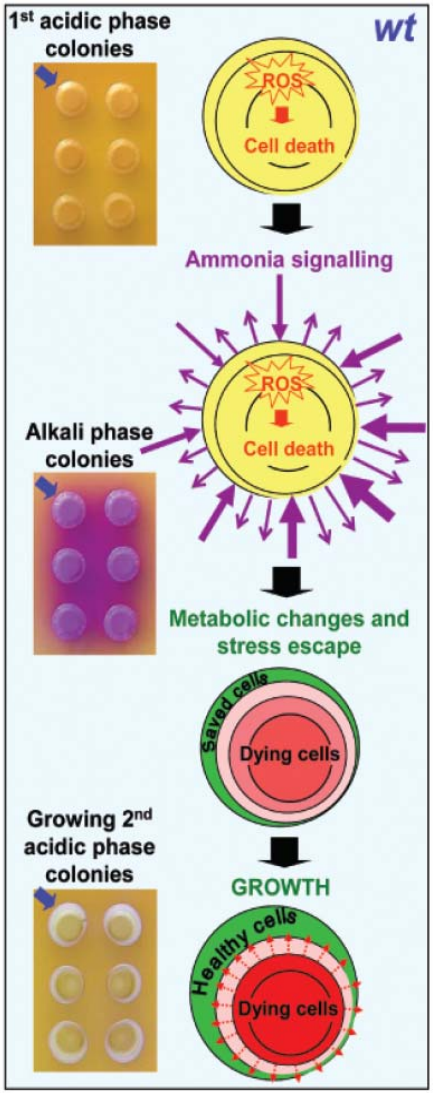
Mechanismy jejich působení na buněčné úrovni

Již na úrovni jednobuněčných organismů je nezbytná schopnost:

1. **Přijímat a identifikovat signály z vnějšího prostředí – např. za účelem výměny genetické informace;**
2. **Eliminovat toxické látky přijímané z vnějšího prostředí/vznikající jak vedlejší produkty metabolismu;**



Modelová forma komunikace – NH_4 jako signální molekula mezi koloniemi kvasinek:



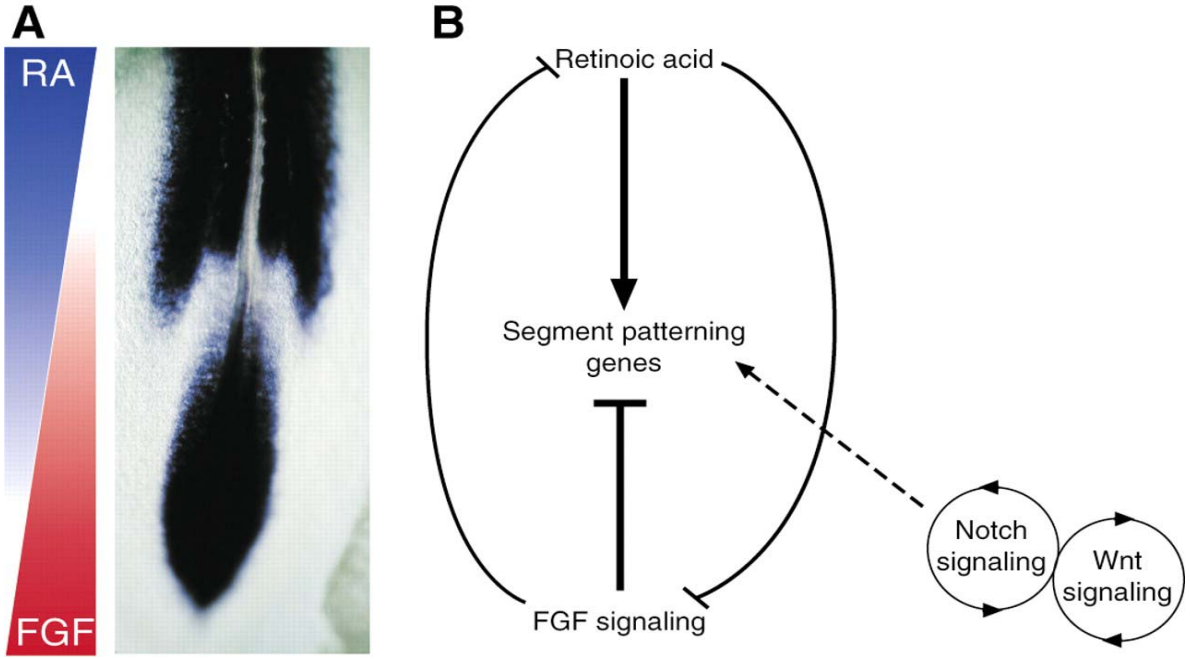
Model of ammonia-triggered differentiation in Saccharomyces cerevisiae colonies. In first-acidic phase colonies, ROS and other harmful products are produced by cells throughout the whole colonies and induce the regulated yeast cell death (YCD). To escape damage, yeast cells start to emit (outgoing violet arrows) and accept (incoming arrows) ammonia signal, which triggers metabolic changes that consequently allow cells to lower their ROS production. Healthy cells located mainly at the colony border (where the concentration of ROS is low) can thus escape cell death. Consequently, at the colony border, there are mainly slowly growing and dividing healthy cells (green) in later developmental phases (second acidic phase), while in the colony centre, dying cells (red) predominate.Compounds released (red arrows) from these cells in late stages of YCD sustain border cell growth and reproduction. The blue arrow indicates the position of the colony considered in the model.

Palková a Váchová, FEMS Microbiol Rev 30 (2006) 806–824

U mnohobuněčných organismů (živočichů) se vyvinuly stovky signálních drah a dalších mechanismů:

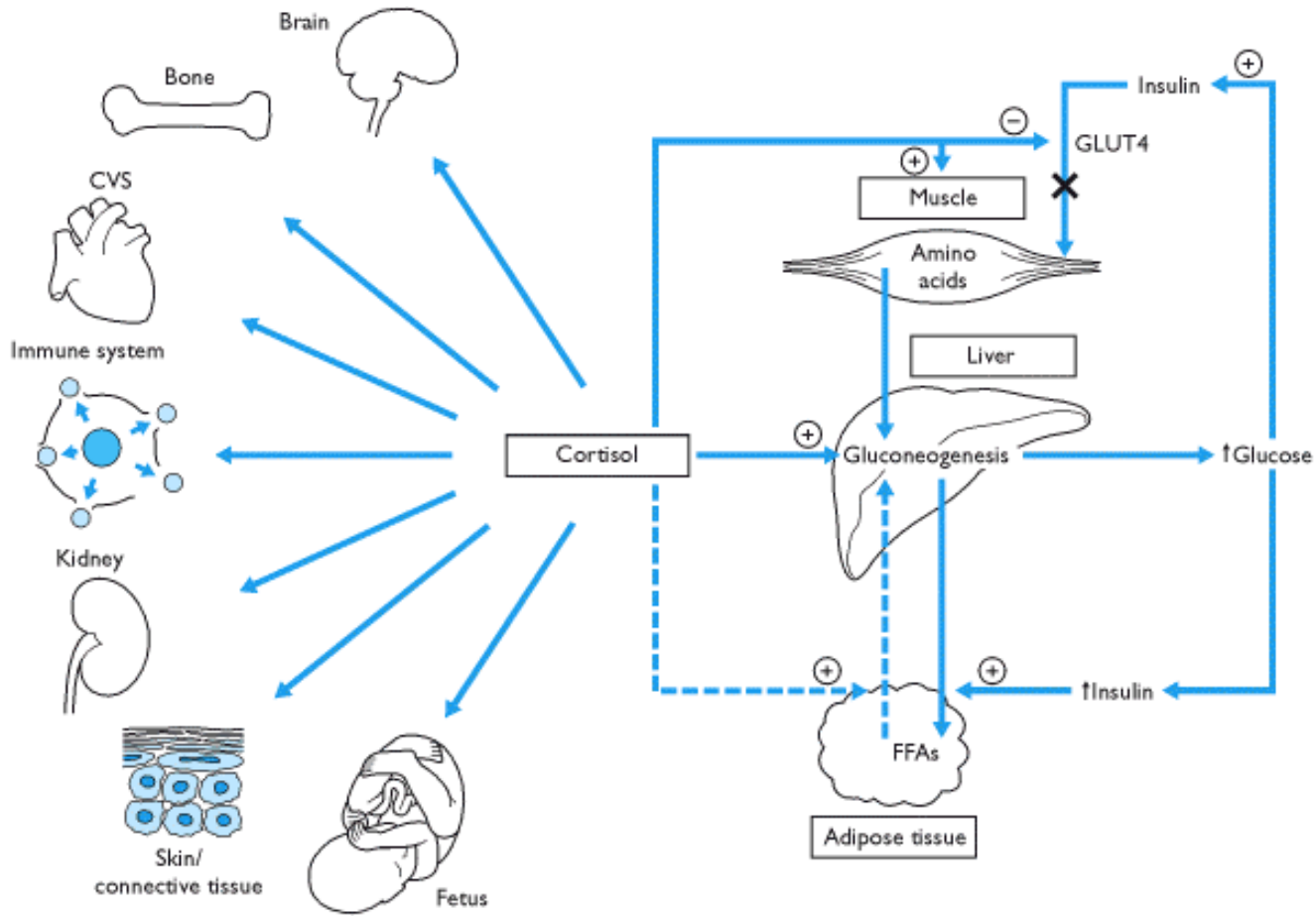
1. Embryonální a postnatální vývoj;
2. Regulace metabolismu a obecně, homeostázy;
3. Pohlavní rozmnožování;
4. Tvorba a degradace signálních molekul i toxických sloučenin; přenos signálu

http://www.luc.edu/faculty/wwasser/dev/zebra.mov



Dubrulle, J. et al. Development 2004;131:5783-5793

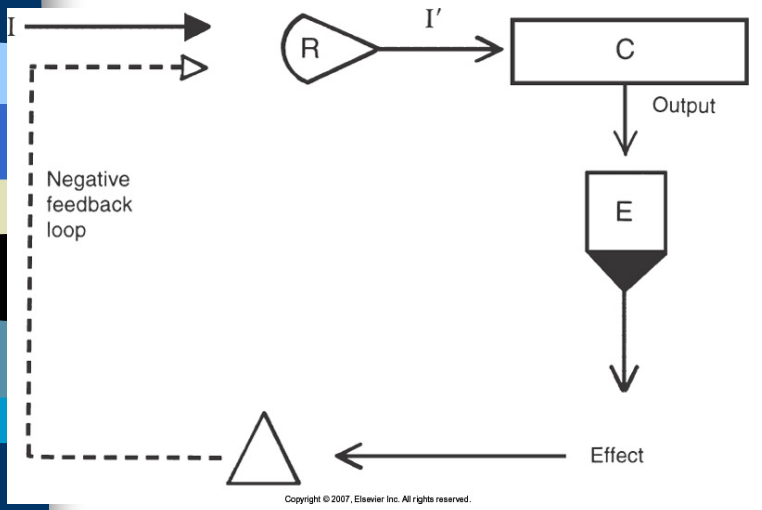
A model for somitogenesis. (A) Double in situ hybridization of a 2-day-old chicken embryo with Raldh2 (retinaldehyde dehydrogenase 2) and Fgf8 (fibroblast growth factor 8) probes. Anterior is towards the top. These genes participate in the establishment of mutually inhibitory, antagonistic gradients of retinoic acid (RA) and fibroblast growth factor (FGF) signaling. (B) Molecular mechanisms leading to a segmental pattern. Segment patterning genes are periodically activated by the segmentation clock, whose main regulators are the Notch and Wnt signaling pathways. The spatial activation of the segment patterning genes is defined by the RA and FGF antagonistic gradients: RA positively regulates their transcription, whereas FGF signaling represses RA activity and inhibits presomitic mesoderm maturation.



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

Endocrinology: An Integrated Approach. Nussey and Whitehead (2001) London: Taylor&Francis

Systém homeostázy



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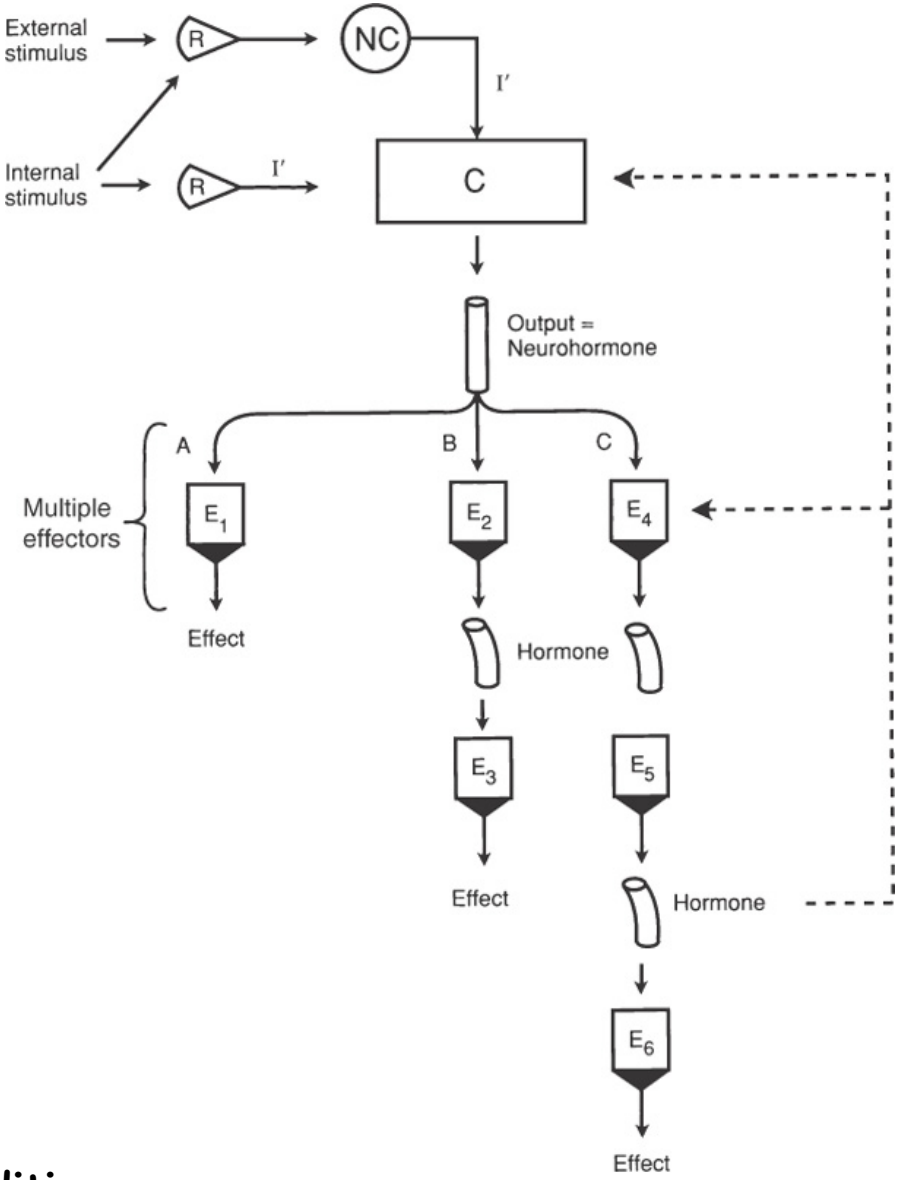

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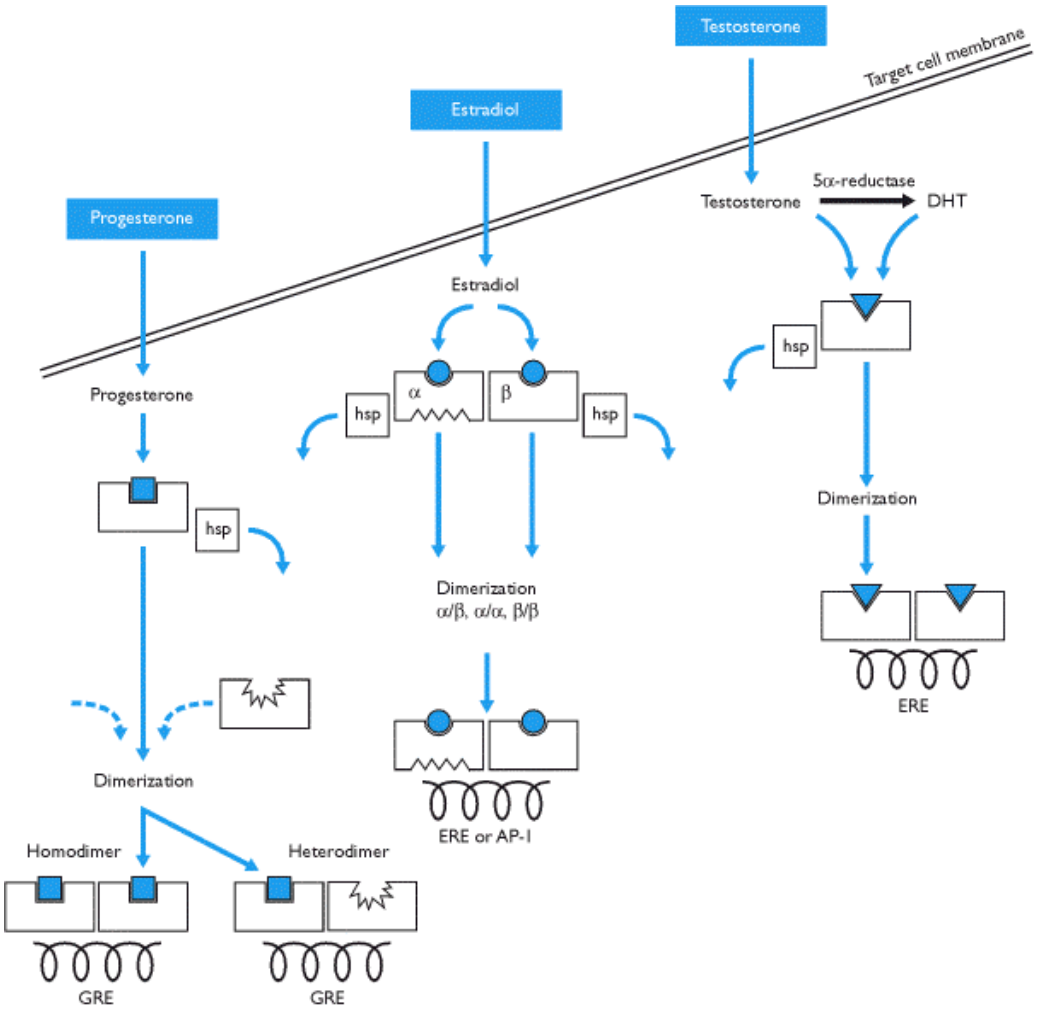
Vertebrate Endocrinology. 4th Edition.
David Norris; Academic Press, 2006



Vedle tohoto základního schematu je třeba si představit celou řadu dalších regulačních modulů:

- **transportní proteiny;**
- **syntéza a degradace hormonů;**
- **regulace hladiny steroidních hormonů;**

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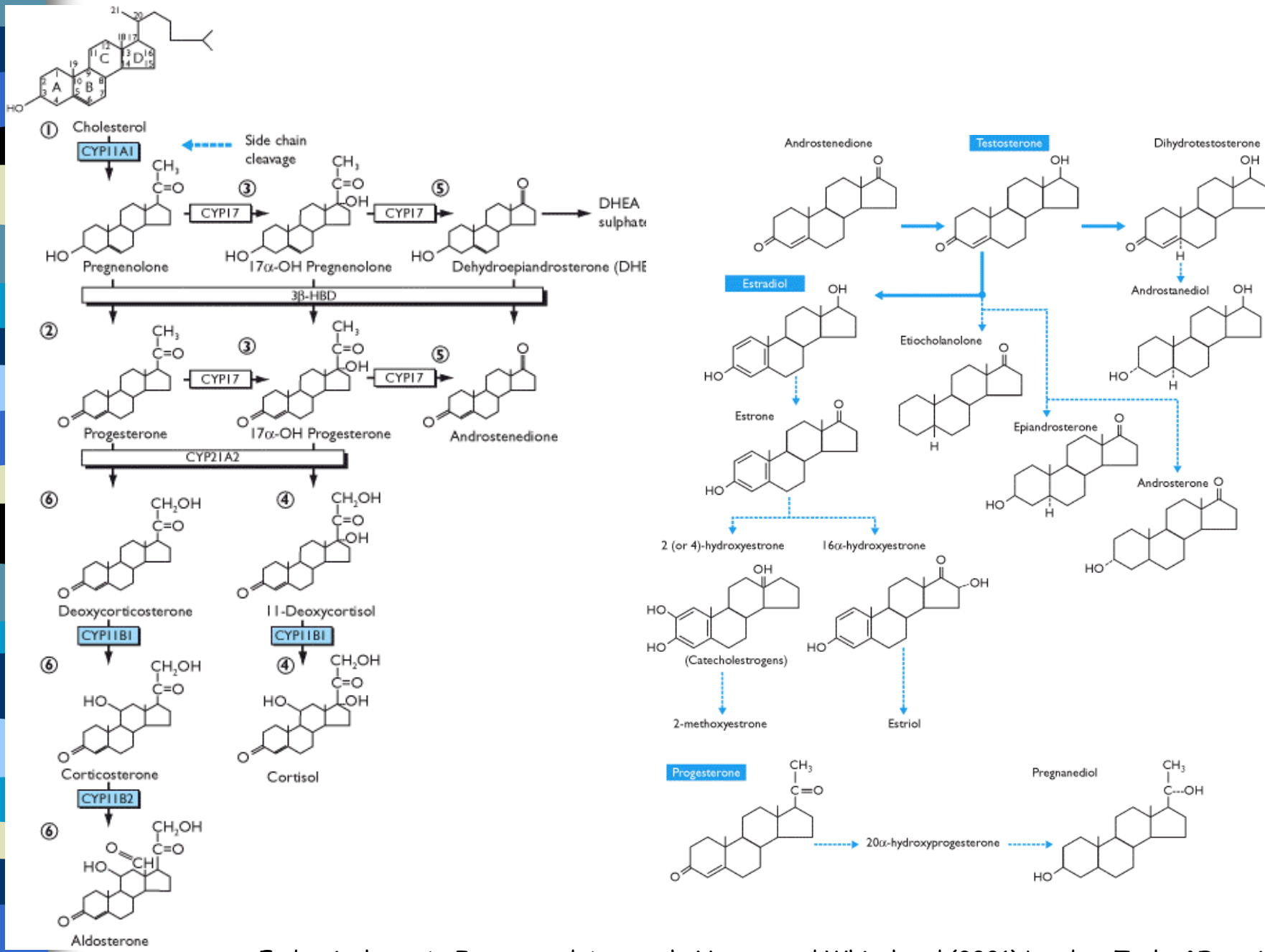
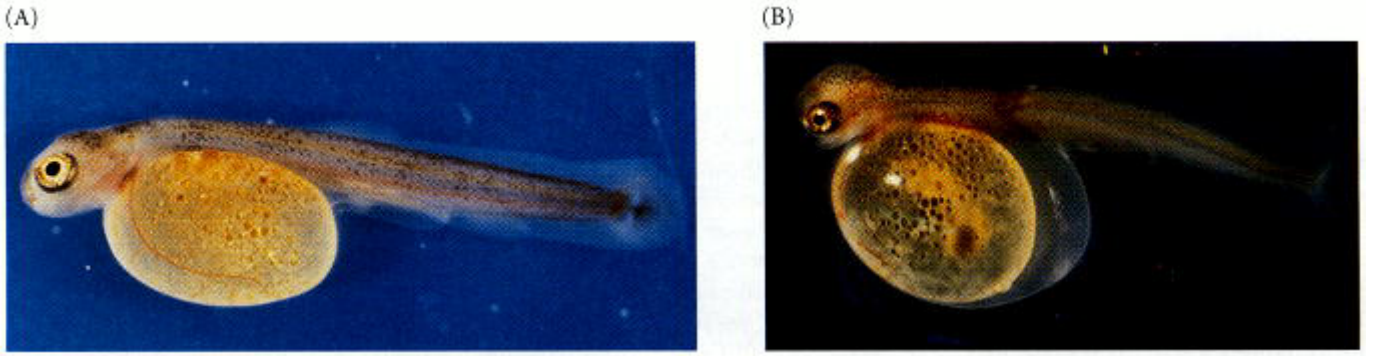


Endocrinology: An Integrated Approach. Nussey and Whitehead (2001) London: Taylor&Franci

Zásahy z vnějšího prostředí:

1. Produkty sekundárního metabolismu rostlin a hub;
2. Zásahy člověka – cílené – aplikace chemických látek jako jsou pesticidy, syntetické feromony; terapie;
3. Zásahy člověka – nezamýšlené – toxické sloučeniny; odpad.



Lake trout 4 weeks after hatching. (A) Normal larva with its golden yellow yolk sac. (B) Dioxin-exposed larva exhibiting a blue yolk sac. The yolk sac has swelled with water and has numerous sites of hemorrhage. Such fish often have reduced growth, as well as heart and facial anomalies. (Photograph courtesy of R. E. Peterson.)

Developmental Biology. 6th ed. Gilbert, Scott F. Sunderland (MA): Sinauer Associates, Inc.; 2000.

Co všechno se dá najít v odpadních vodách:

(Kolpin et al., ENVIRONMENTAL SCIENCE & TECHNOLOGY / VOL. 36, NO. 6, 2002)

chemical (method)	CASRN	*N*	RL (μg/L)	freq (%)	max (μg/L)	med (μg/L)	use	MCL or *HAL* (*23*) (μg/L)	lowest LC_{50} for the most sensitive indicator species (μg/L)/no. of aquatic studies identified (*24*)
Veterinary and Human Antibiotics									
carbodox (1)	6804-07-5	104	0.10	0	ND	ND	antibiotic	–	–/1
chlortetracycline (1)	57-62-5	115	0.05	0	ND	ND	antibiotic	–	88000[a]/3
chlortetracycline (2)	57-62-5	84	0.10	2.4	0.69	0.42	antibiotic	–	88000[a]/3
ciprofloxacin (1)	85721-33-1	115	0.02	2.6	0.03	0.02	antibiotic	–	–/0
doxycycline (1)	564-25-0	115	0.1	0	ND	ND	antibiotic	–	–/0
enrofloxacin (1)	93106-60-6	115	0.02	0	ND	ND	antibiotic	–	40[b]/29
erythromycin-H_2O (1)	114-07-8	104	0.05	21.5	1.7	0.1	erythromycin metabolite	–	665000[b]/35
lincomycin (1)	154-21-2	104	0.05	19.2	0.73	0.06	antibiotic	–	–/0
norfloxacin (1)	70458-96-7	115	0.02	0.9	0.12	0.12	antibiotic	–	–/6
oxytetracycline (1)	79-57-2	115	0.1	0	ND	ND	antibiotic	–	102000[a]/46
oxytetracycline (2)	79-57-2	84	0.10	1.2	0.34	0.34	antibiotic	–	102000[a]/46
roxithromycin (1)	80214-83-1	104	0.03	4.8	0.18	0.05	antibiotic	–	–/0
sarafloxacin (1)	98105-99-8	115	0.02	0	ND	ND	antibiotic	–	–/0
sulfachloropyridazine (2)	80-32-0	84	0.05	0	ND	ND	antibiotic	–	–/0
sulfadimethoxine (1)	122-11-2	104	0.05	0	ND	ND	antibiotic	–	–/5
sulfadimethoxine (2)	122-11-2	84	0.05	1.2	0.06	0.06	antibiotic	–	–/5
sulfamerazine (1)	127-79-7	104	0.05	0	ND	ND	antibiotic	–	100000[c]/17
sulfamerazine (2)	127-79-7	84	0.05	0	ND	ND	antibiotic	–	100000[c]/17
sulfamethazine (1)	57-68-1	104	0.05	4.8	0.12	0.02	antibiotic	–	100000[c] 17
sulfamethazine (2)	57-68-1	84	0.05	1.2	0.22	0.22	antibiotic	–	100000[c]/17
sulfamethizole (1)	144-82-1	104	0.05	1.0	0.13	0.13	antibiotic	–	–/0
sulfamethoxazole (1)	723-46-6	104	0.05	12.5	1.9	0.15	antibiotic	–	–/0
sulfamethoxazole (3)	723-46-6	84	0.023	19.0	0.52	0.066	antibiotic	–	–/0
sulfathiazole (1)	72-14-0	104	0.10	0	ND	ND	antibiotic	–	–/0
sulfathiazole (2)	72-14-0	84	0.05	0	ND	ND	antibiotic	–	–/0
tetracycline (1)	60-54-8	115	0.05	0	ND	ND	antibiotic	–	550000[b]/3
tetracycline (2)	60-54-8	84	0.10	1.2	0.11	0.11	antibiotic	–	550000[b]/3
trimethoprim (1)	738-70-5	104	0.03	12.5	0.71	0.15	antibiotic	–	3000[c]/4
trimethoprim (3)	738-70-5	84	0.014	27.4	0.30	0.013	antibiotic	–	3000[c]/4
tylosin (1)	1401-69-0	104	0.05	13.5	0.28	0.04	antibiotic	–	–/0
virginiamycin (1)	21411-53-0	104	0.10	0	ND	ND	antibiotic	–	–/0

Prescription Drugs									
albuterol (salbutamol) (3)	18559-94-9	84	0.029	0	ND	ND	antiasthmatic	–	–/0
cimetidine (3)	51481-61-9	84	0.007	9.5	0.58[d]	0.074[d]	antacid	–	–/0
codeine (3)	76-57-3	46	0.24	6.5	0.019	0.012	analgesic	–	–/0
codeine (4)	76-57-3	85	0.1	10.6	1.0[d]	0.2[d]	analgesic	–	–/0
dehydronifedipine (3)	67035-22-7	84	0.01	14.3	0.03	0.012	antianginal	–	–/0
digoxin (3)	20830-75-5	46	0.26	0	ND[d]	ND[d]	cardiac stimulant	–	10000000[a]/24
digoxigenin (3)	1672-46-4	84	0.008	0	ND	ND	digoxin metabolite	–	–/0
diltiazem (3)	42399-41-7	84	0.012	13.1	0.049	0.021	antihypertensive	–	–/0
enalaprilat (3)	76420-72-9	84	0.15	1.2	0.046[d]	0.046[d]	enalapril maleate (antihypertensive) metabolite	–	–/0
fluoxetine (3)	54910-89-3	84	0.018	1.2	0.012[d]	0.012[d]	antidepressant	–	–/0
gemfibrozil (3)	25812-30-0	84	0.015	3.6	0.79	0.048	antihyperlipidemic	–	–/0
metformin (3)	657-24-9	84	0.003	4.8	0.15[d]	0.11[d]	antidiabetic	–	–/0
paroxetine metabolite (3)	–	84	0.26	0	ND[d]	ND[d]	paroxetine (antidepressant) metabolite	–	–/0
ranitidine (3)	66357-35-5	84	0.01	1.2	0.01[d]	0.01[d]	antacid	–	–/0
warfarin (3)	81-81-2	84	0.001	0	ND	ND	anticoagulant	–	16000[c]/ 33
Nonprescription Drugs									
acetaminophen (3)	103-90-2	84	0.009	23.8	10	0.11	antipyretic	–	6000[a]/ 14
caffeine (3)	58-08-2	84	0.014	61.9	6.0	0.081	stimulant	–	40000[e]/ 77
caffeine (4)	58-08-2	85	0.08	70.6	5.7	0.1	stimulant	–	40000[e]/ 77
cotinine (3)	486-56-6	84	0.023	38.1	0.90	0.024	nicotine metabolite	–	–/0
cotinine (4)	486-56-6	54	0.04	31.5	0.57	0.05	nicotine metabolite	–	–/0
1,7-dimethylxanthine (3)	611-59-6	84	0.018	28.6	3.1[d]	0.11[d]	caffeine metabolite	–	–/0
ibuprofen (3)	15687-27-1	84	0.018	9.5	1.0	0.20	antiinflammatory	–	–/0

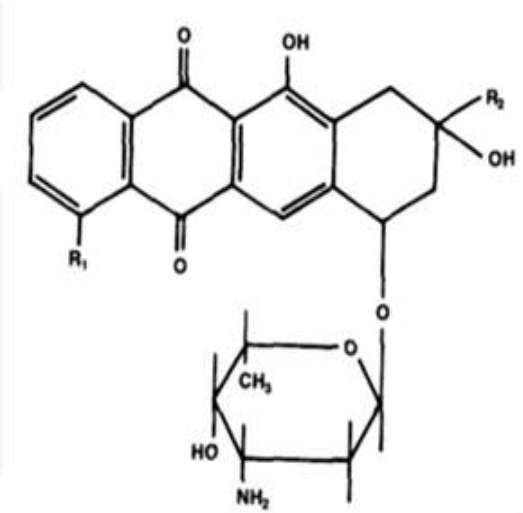
Other Wastewater-Related Compounds

1,4-dichlorobenzene (4)	106-46-7	85	0.03	25.9	4.3	0.09	deodorizer	*75*	1100[c]/190
2,6-di-*tert*-butylphenol (4)	128-39-2	85	0.08	3.5	0.11[d]	0.06[d]	antioxidant	–	–/2
2,6-di-*tert*-butyl-1,4-benzoquinone (4)	719-22-2	85	0.10	9.4	0.46	0.13	antioxidant	–	–/0
5-methyl-1H-benzotriazole (4)	136-85-6	54	0.10	31.5	2.4	0.39	antiocorrosive	–	–/0
acetophenone (4)	98-86-2	85	0.15	9.4	0.41	0.15	fragrance	–	155000[e]/21
anthracene (4)	120-12-7	85	0.05	4.7	0.11	0.07	PAH	–	5.4[e]/188
benzo[*a*]pyrene (4)	50-32-8	85	0.05	9.4	0.24	0.04	PAH	0.2	1.5[a]/428
3-*tert*-butyl-4-hydroxy anisole (4)	25013-16-5	85	0.12	2.4	0.2[d]	0.1[d]	antioxidant	–	870[c]/14
butylated hydroxy toluene (4)	128-37-0	85	0.08	2.4	0.1[d]	0.1[d]	antioxidant	–	1440[a]/15
bis(2-ethylhexyl) adipate (4)	103-23-1	85	2.0	3.5	10[f]	3[f]	plasticizer	400	480[a]/9
bis(2-ethylhexyl) phthalate (4)	117-81-7	85	2.5	10.6	20[f]	7[f]	plasticizer	6	7500[a]/309
bisphenol A (4)	80-05-7	85	0.09	41.2	12	0.14	plasticizer	–	3600[e]/26
carbaryl (4)	63-25-2	85	0.06	16.5	0.1[d]	0.04[d]	insecticide	*700*	0.4[a]/1541
***cis*-chlordane** (4)	5103-71-9	85	0.04	4.7	0.1	0.02	insecticide	2	7.4[b]/28
chlorpyrifos (4)	2921-88-2	85	0.02	15.3	0.31	0.06	insecticide	*20*	0.1[a]/1794
diazinon (4)	333-41-5	85	0.03	25.9	0.35	0.07	insecticide	*0.6*	0.56[a]/1040
dieldrin (4)	60-57-1	85	0.08	4.7	0.21	0.18	insecticide	0.2	2.6[c]/1540
diethylphthalate (4)	84-66-2	54	0.25	11.1	0.42	0.2	plasticizer	–	12000[c]/129
ethanol,2-butoxy-phosphate (4)	78-51-3	85	0.2	45.9	6.7	0.51	plasticizer	–	10400[e]/7
fluoranthene (4)	206-44-0	85	0.03	29.4	1.2	0.04	PAH	–	74[e]/216
lindane (4)	58-89-9	85	0.05	5.9	0.11	0.02	insecticide	0.2	30[c]/1979
methyl parathion (4)	298-00-0	85	0.06	1.2	0.01	0.01	insecticide	*2*	12[a]/888
4-methyl phenol (4)	106-44-5	85	0.04	24.7	0.54	0.05	disinfectant	–	1400[a]/74
naphthalene (4)	91-20-3	85	0.02	16.5	0.08	0.02	PAH	*20*	910[c]/519
N,*N*-diethyltoluamide (4)	134-62-3	54	0.04	74.1	1.1	0.06	insect repellant	–	71250[c]/9
4-nonylphenol (4)	251-545-23	85	0.50	50.6	40[g]	0.8[g]	nonionic detergent metabolite	–	130[e]/135
4-nonylphenol monoethoxylate (4)	–	85	1.0	45.9	20[g]	1[g]	nonionic detergent metabolite		14450[a]/4
4-nonylphenol diethoxylate (4)	–	85	1.1	36.5	9[g]	1[g]	nonionic detergent metabolite	–	5500[a]/6
4-octylphenol monoethoxylate (4)	–	85	0.1	43.5	2[g]	0.2[g]	nonionic detergent metabolite	–	–/0
4-octylphenol diethoxylate (4)	–	85	0.2	23.5	1[g]	0.1[g]	nonionic detergent metabolite	–	–/0
phenanthrene (4)	85-01-8	85	0.06	11.8	0.53	0.04	PAH	–	590[a]/192
phenol (4)	108-95-2	85	0.25	8.2	1.3[f]	0.7[f]	disinfectant	*400*	4000[c]/2085
phthalic anhydride (4)	85-44-9	85	0.25	17.6	1[f]	0.7[f]	plastic manufacturing	–	40400[c]/5
pyrene (4)	129-00-0	85	0.03	28.2	0.84	0.05	PAH	–	90.9[a]/112
tetrachloroethylene (4)	127-18-4	85	0.03	23.5	0.70[d]	0.07[d]	solvent, degreaser	5	4680[c]/147
triclosan (4)	3380-34-5	85	0.05	57.6	2.3	0.14	antimicrobial disinfectant	–	180[e]/3
tri(2-chloroethyl) phosphate (4)	115-96-8	85	0.04	57.6	0.54	0.1	fire retardant	–	66000[b]/8
tri(dichlorisopropyl) phosphate (4)	13674-87-8	85	0.1	12.9	0.16	0.1	fire retardant	–	3600[b]/9
triphenyl phosphate (4)	115-86-6	85	0.1	14.1	0.22	0.04	plasticizer	–	280[c]/66

Steroids and Hormones									
***cis*-androsterone** (5)	53-41-8	70	0.005	14.3	0.214	0.017	urinary steroid	–	–/0
cholesterol (4)	57-88-5	85	1.5	55.3	10[d]	1[d]	plant/animal steroid	–	–/0
cholesterol (5)	57-88-5	70	0.005	84.3	60[h]	0.83	plant/animal steroid	–	–/0
coprostanol (4)	360-68-9	85	0.6	35.3	9.8[d]	0.70[d]	fecal steroid	–	–/0
coprostanol (5)	360-68-9	70	0.005	85.7	150[h]	0.088	fecal steroid	–	–/0
equilenin (5)	517-09-9	70	0.005	2.8	0.278	0.14	estrogen replacement	–	–/0
equilin (5)	474-86-2	70	0.005	1.4	0.147	0.147	estrogen replacement	–	–/0
17α-ethynyl estradiol (5)	57-63-6	70	0.005	15.7	0.831	0.073	ovulation inhibitor	–	–/22
17α-estradiol (5)	57-91-0	70	0.005	5.7	0.074	0.03	reproductive hormone	–	–/0
17β-estradiol (4)	50-28-2	85	0.5	10.6	0.2[d]	0.16[d]	reproductive hormone	–	–/0
17β-estradiol (5)	50-28-2	70	0.005	10.0	0.093	0.009	reproductive hormone	–	–/0
estriol (5)	50-27-1	70	0.005	21.4	0.051	0.019	reproductive hormone	–	–/0
estrone (5)	53-16-7	70	0.005	7.1	0.112	0.027	reproductive hormone	–	–/11
mestranol (5)	72-33-3	70	0.005	10.0	0.407	0.074	ovulation inhibitor	–	–/0
19-norethisterone (5)	68-22-4	70	0.005	12.8	0.872	0.048	ovulation inhibitor	–	–/0
progesterone (5)	57-83-0	70	0.005	4.3	0.199	0.11	reproductive hormone	–	–/0
stigmastanol (4)	19466-47-8	54	2.0	5.6	4[d]	2[d]	plant steroid	–	–/0
testosterone (5)	58-22-0	70	0.005	2.8	0.214	0.116	reproductive hormone	–	–/4

Náplň předmětu:

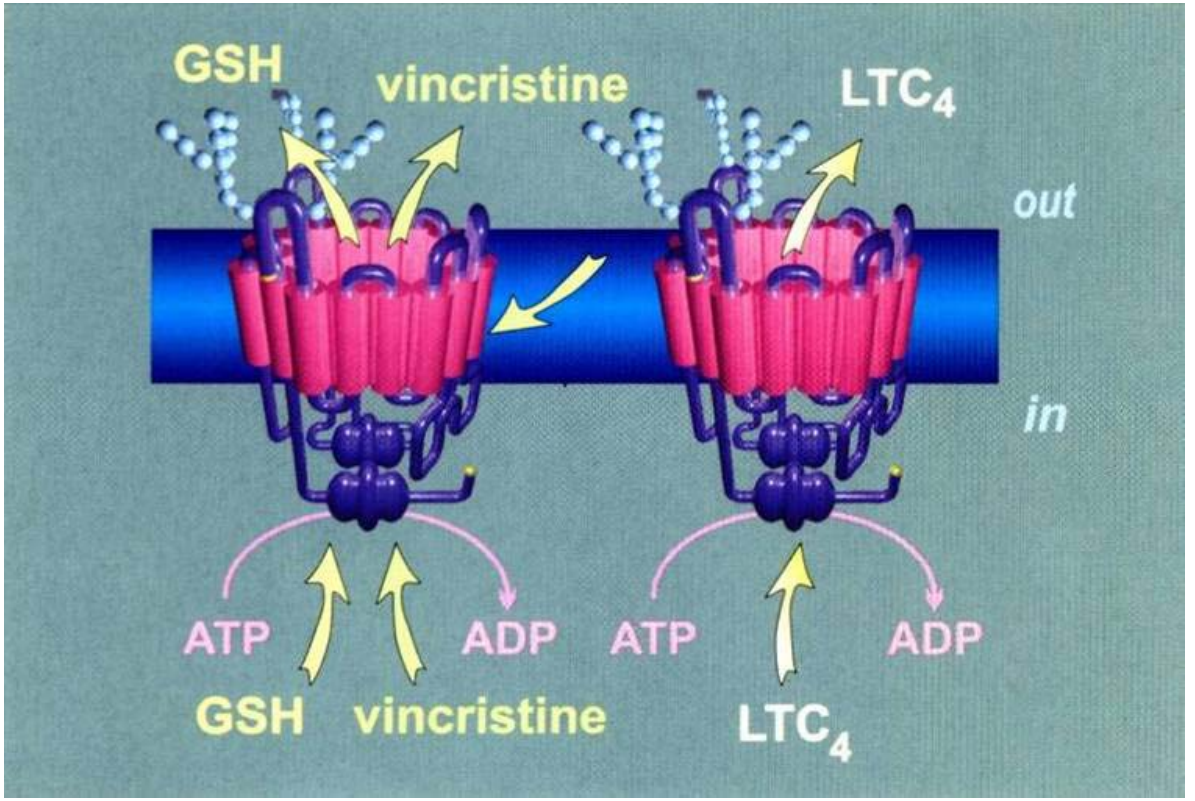
- Základní přehled chemických látek, které mohou cíleně nebo náhodně narušovat normální fyziologické procesy – antropogenní organické polutanty, farmaka, sekundární metabolity (dietární látky a neantropogenní toxiny);



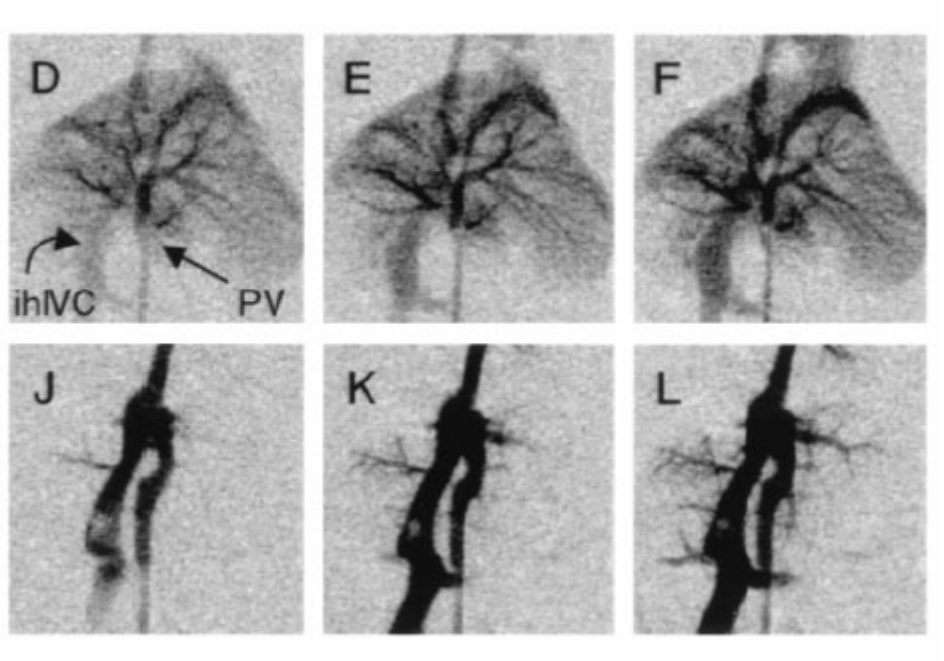
R_1	R_2	
$-CH_3O$	$-COCH_3$	– daunorubicin
$-CH_3O$	$-COCH_2OH$	– adriamycin
$-CH_3O$	$-C(CH_3)=N-NH-CO-C_6H_5$	– rubidazon
$-OH$	$-COCH_3$	– karminomycin
$-H$	$-COCH_3$	– 4-demetoxydaunorubicin

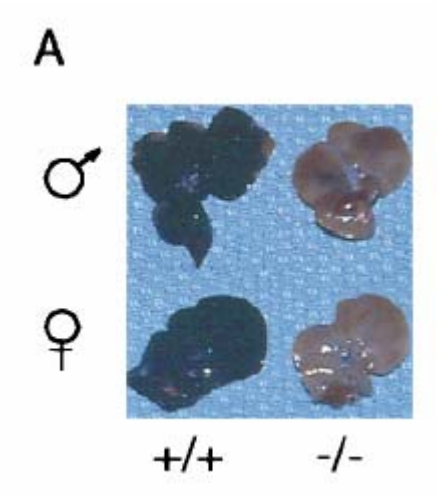
antracyklinová antibiotika

- Principy regulace metabolismu, transportu a akumulace cizorodých látek v těle, enzymy I. a II. fáze biotransformace, antioxidační enzymy/antioxidanty, enzymy/proteiny III. fáze.

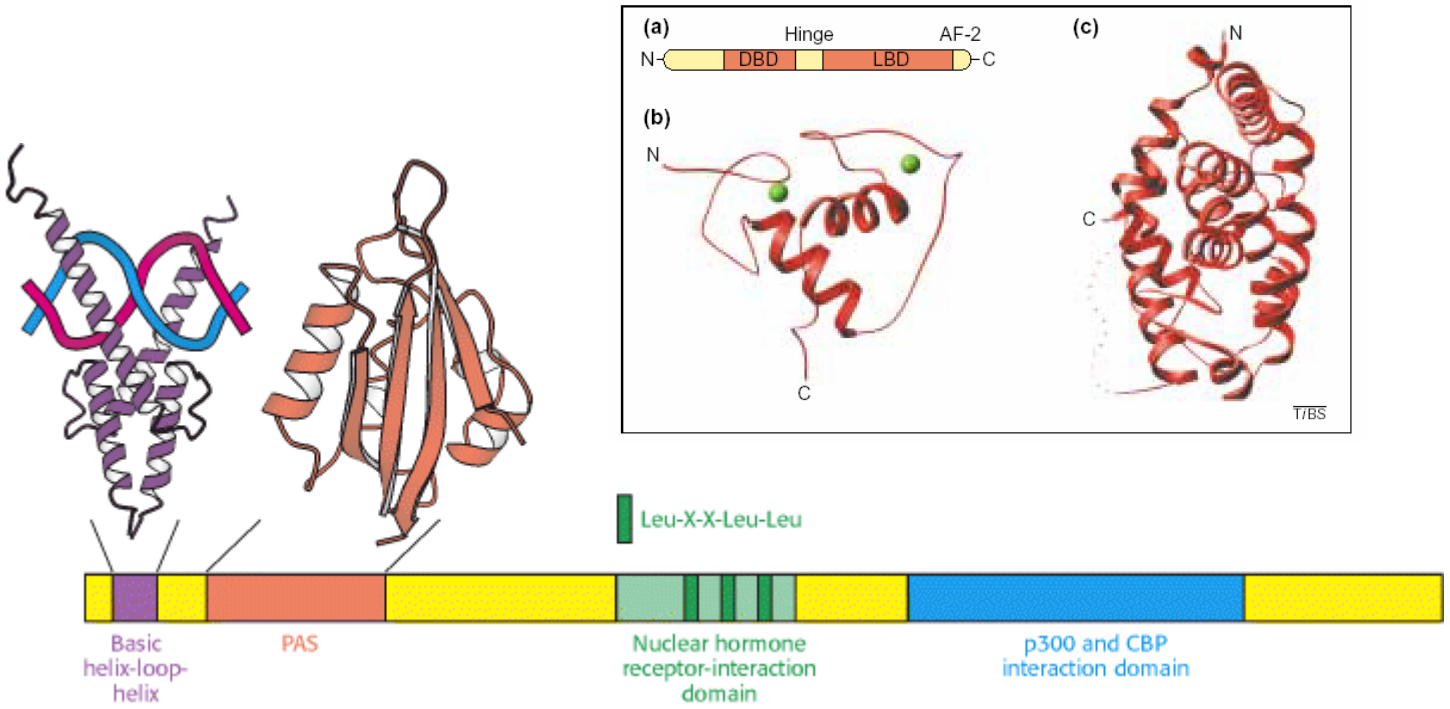


- Základní typy toxických efektů cizorodých látek (genotoxicita, hepatotoxicita, neurotoxicita, imunotoxicita, nádorová promoce, endokrinní disrupce).

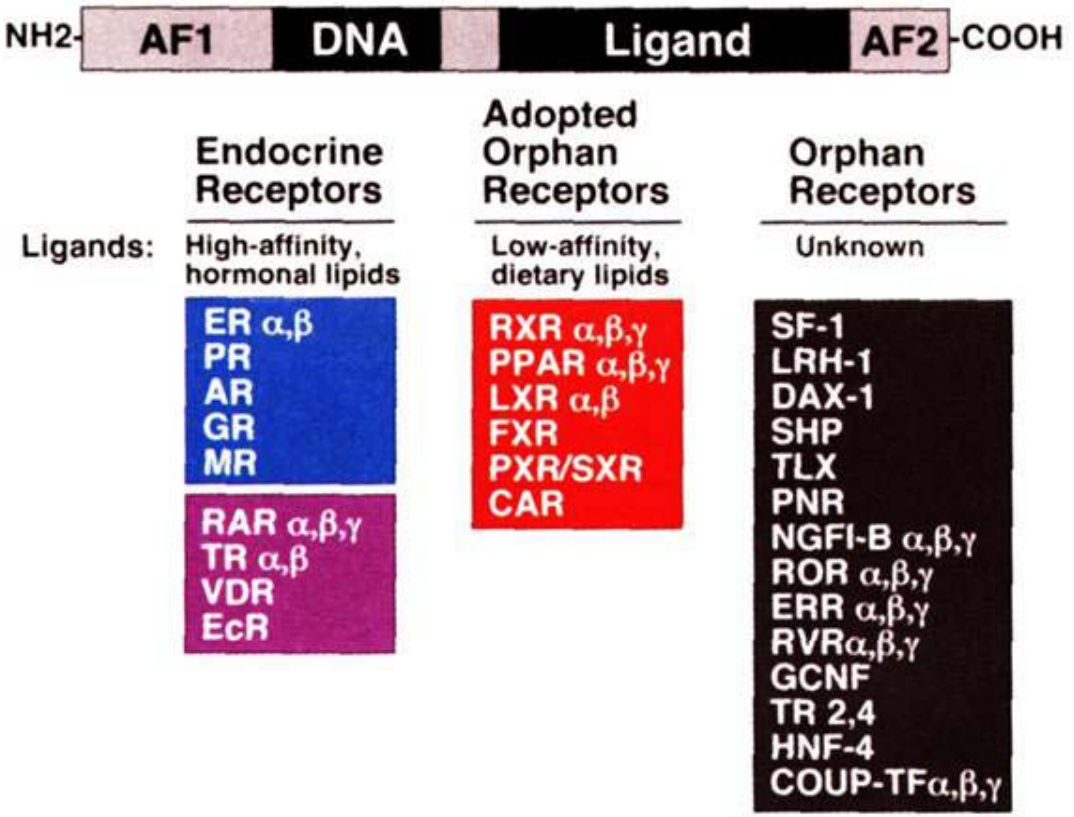




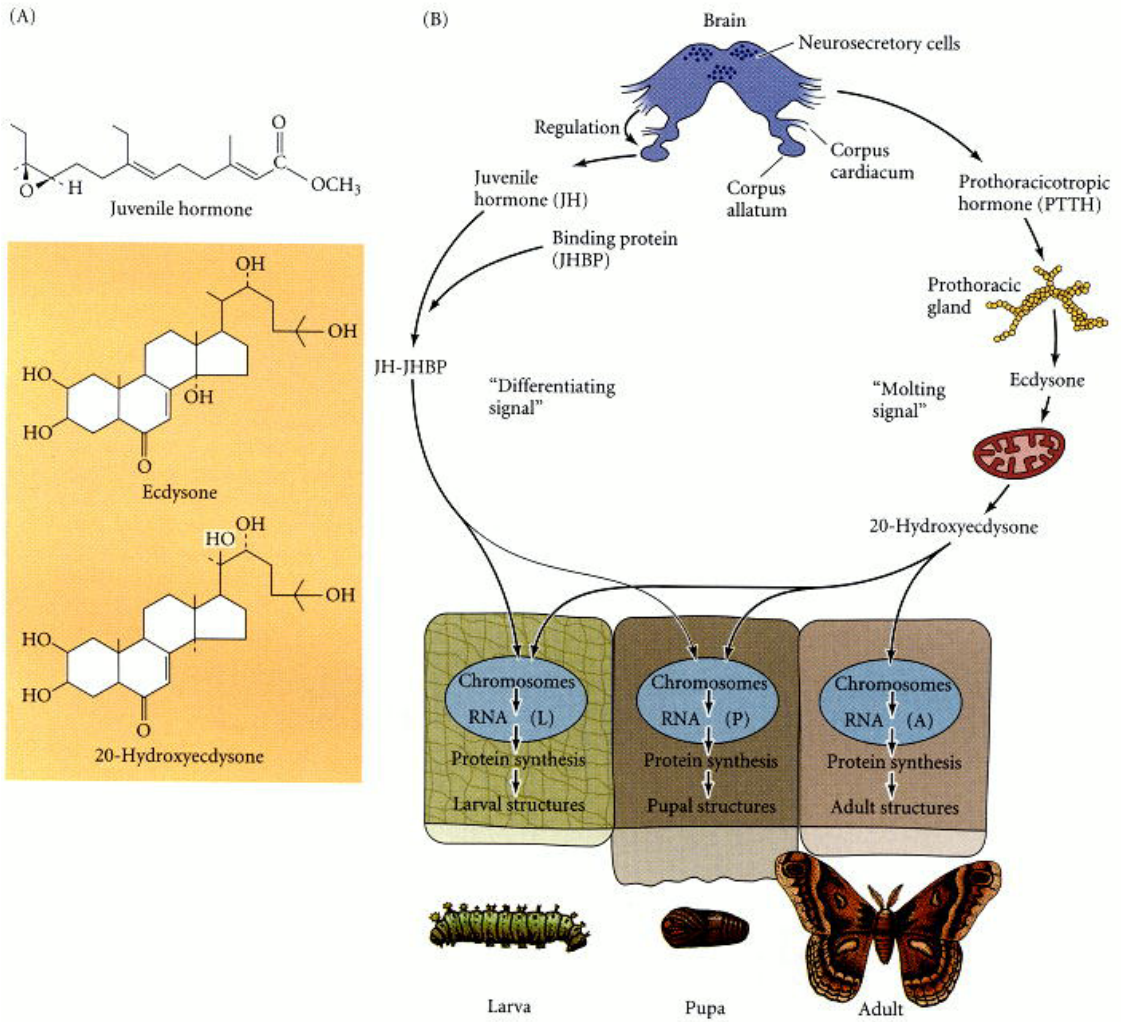
- HLH/PAS rodina proteinů – HIF1α, Ah receptor a jeho signalizační dráha.
- Jaderné receptory (ER, AR, PR, GR, TR, RAR/RXR, CAR, PXR, PPAR) – jejich ligandy, jejich úloha v regulaci metabolismu, fyziologické funkce zprostředkované modulací cílových genů.



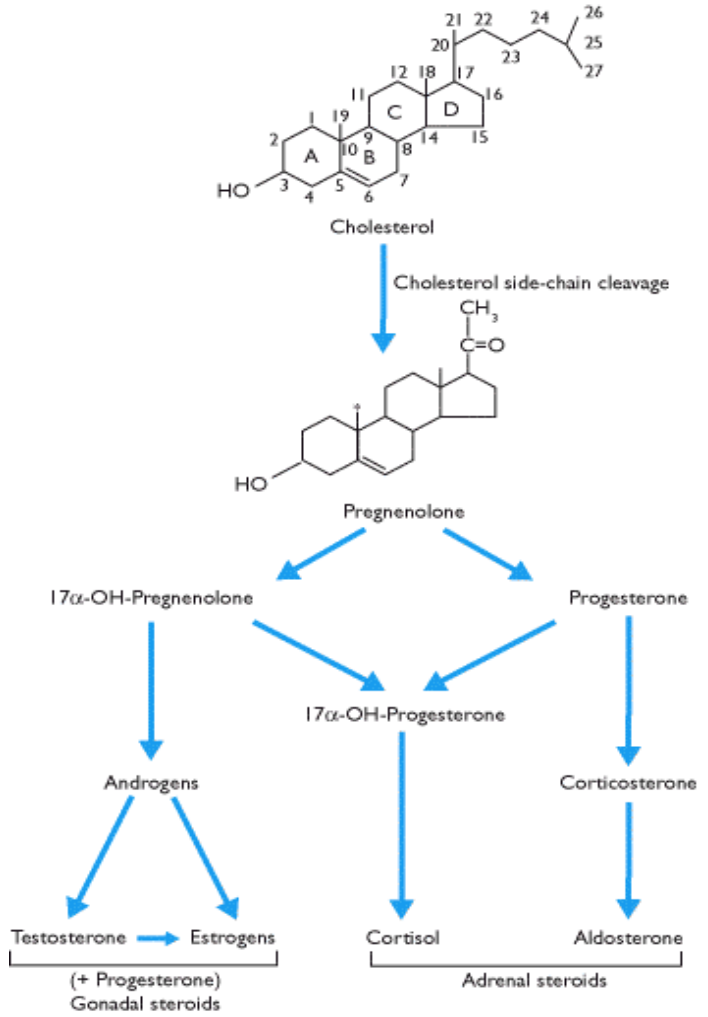
- Biosyntéza a metabolismus přirozených ligandů NR (steroidy, mastné kyseliny, lipidové mediátory); hormonální regulace biosyntézy.



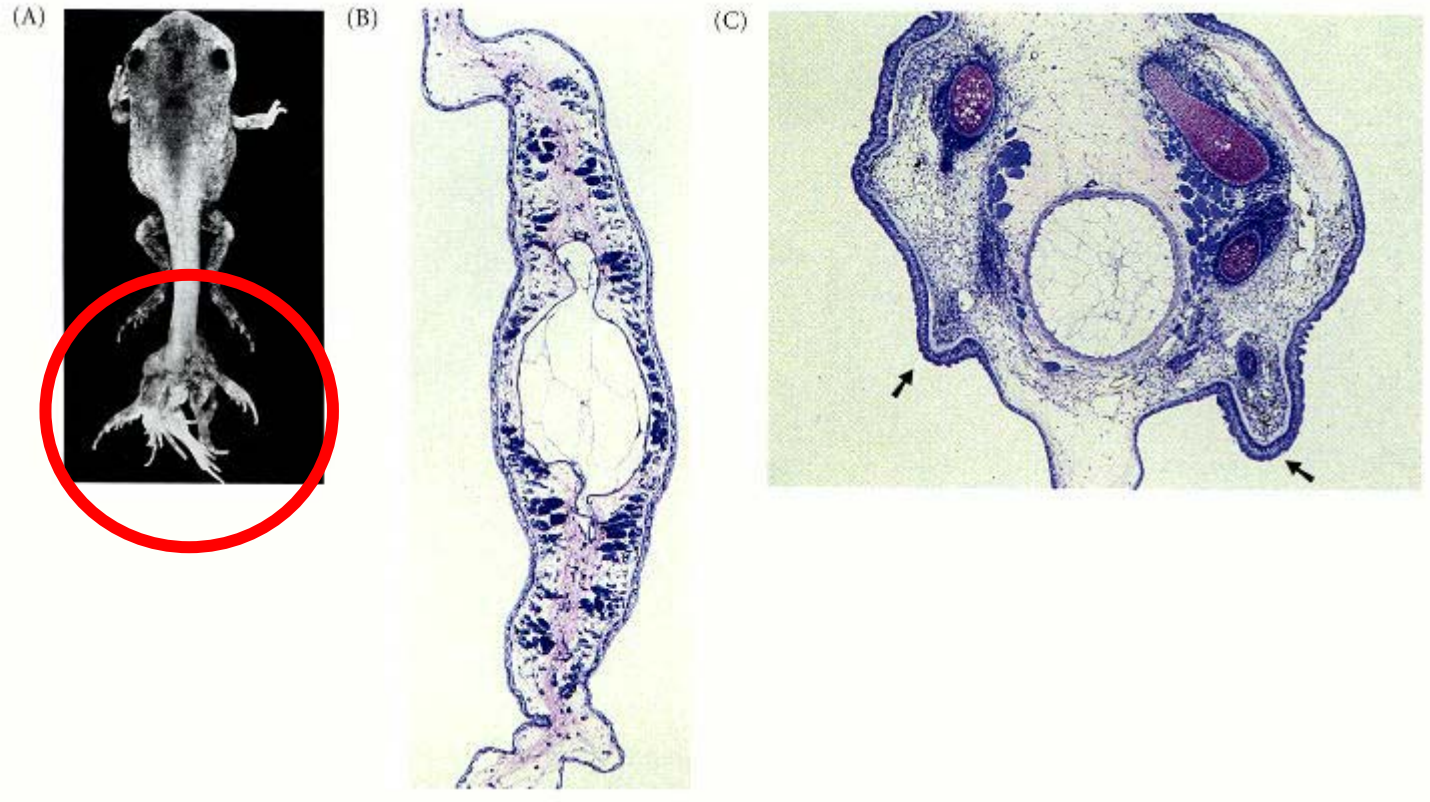
Principy hormonální regulace a chemické komunikace – bezobratlí.



Endokrinní regulace – obratlovci – ER, AR, PR, GR.



- Endokrinní regulace embryonálního a postnatálního vývoje – obratlovci – RAR, RXR, PPAR, TR.



Přednáška bude probíhat každé úterý od 10:00.

Dr. Machala přednáší 6., 13. a 27.3.
(20.3. výuka odpadá)

Dr. Vondráček přednáší 3., 10., 17., 24.4. a 15.5.
(1. a 8. 5. výuka odpadá)

Ukončení – písemný test.