Cell communication & regulation: a target for toxicants

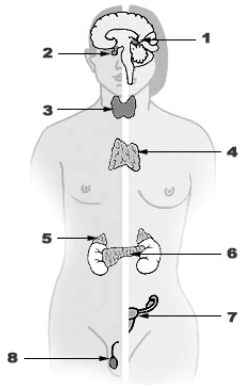
Any sensitively regulated process is susceptible to toxicants

! REGULATIONS & SIGNALLING

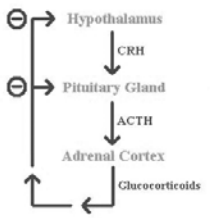
Hierarchy
- systems: neuronal <----> endocrine
- cell-to-cell
  hormonal & neuronal signal transmission
  contact channels
- intracellular signal transduction

HORMONES - fate

1. **Biosynthesis** of a particular hormone in a particular tissue
2. Storage and **secretion** of the hormone
3. **Transport** of the hormone to the target cell(s)
4. **Recognition of the hormone** by an associated cell membrane or intracellular receptor protein.
5. Relay and **amplification of the received hormonal signal** via a signal transduction process -> cellular response.
6. The reaction of the target cells is recognized by the original hormone-producing cells (**negative feedback loop**)
7. **Degradation and metabolism** of the hormone



Endocrine system:
1. Pineal gland, 2. Pituitary gland, 3. Thyroid gland, 4. Thymus, 5. Adrenal gland, 6. Pancreas, 7. Ovary, 8.Testis



Example: feedback loop

HORMONES - actions and controls

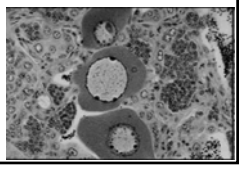
* stimulation or inhibition of growth
* mood swings
* induction or suppression of apoptosis
  (programmed cell death)
* activation or inhibition of the immune system
* regulation of metabolism
* preparation for fighting, fleeing, mating …
* preparation for a new phase of life
  (puberty, caring for offspring, and menopause)
* control of the reproductive cycle

TOXICITY TO HORMONAL ACTION = ENDOCRINE DISRUPTION

ED & EDCs - major problem in environmental toxicology

- Effects at **all levels of hormonal action**
  (*synthesis, transport, action ….)*
- **Multiple effects** (! Not only „xenoestrogenicity“ & feminization)
  (*immunotoxicity, reproduction …*)

(WILL BE DISCUSSED FURTHER)



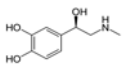
Intersex roach testis
containing both oocytes and spermatozoa,
caused by exposure to environmental oestrogens

HORMONES - chemicals (vertebrates)

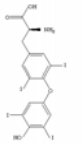
* **Amine-derived hormones** are derivatives of the amino acids tyrosine and tryptophan. Examples are catecholamines and thyroxine.

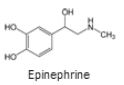
(small molecules - similar to organic toxicants - TOXIC EFFECTS)

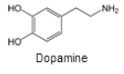
Adrenalin

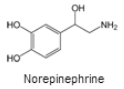


Thyroxin









Further:
* *Peptide hormones*
* *Lipid and phospholipid-derived hormones*

HORMONES - chemicals (vertebrates)

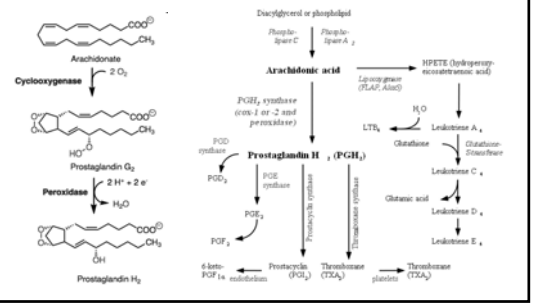
* **Peptide hormones** chains of amino acids. - small: TRH and vasopressin; proteins: insulin, growth hormone, luteinizing hormone, follicle-stimulating hormone and thyroid-stimulating hormone).

Large molecules; receptors on surfaces of the cells
*(Interactions with toxic chemicals **less likely**)*

Example - insulin

HORMONES - chemicals (vertebrates)

Lipid derived hormones (1) (from linoleic acid, arachidonic acid)
- prostaglandins



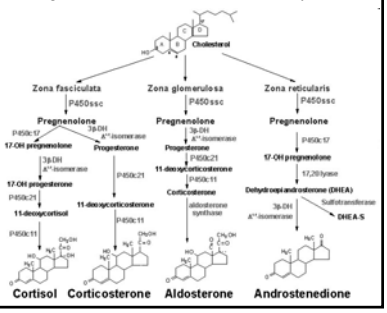
HORMONES - chemicals (vertebrates)

Lipid derived hormones (2)

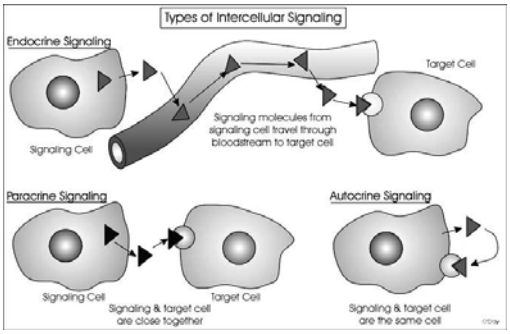
(small molecules - similar to organic toxicants - TOXIC EFFECTS)

- steroid hormones
(from cholesterol)

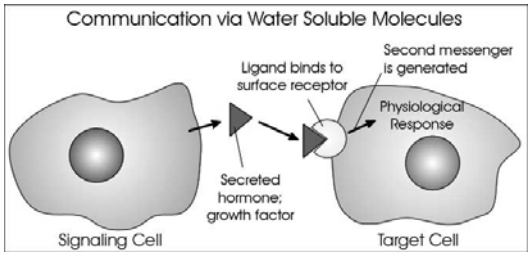
testosterone,
cortisol,
estradiol …



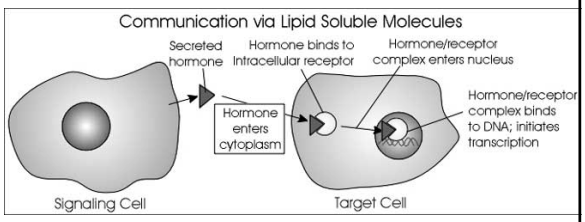
Cell communication & regulation: a target for toxicants



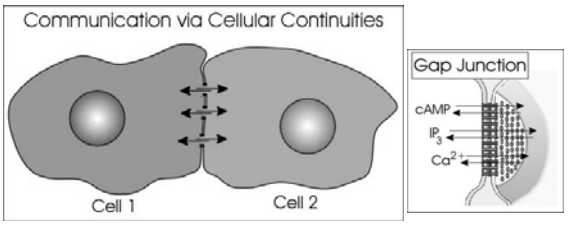
Cell communication (1)



Cell communication (2)



Cell communication (3)



Signal transduction - target of toxicants

- Regulation of cell life / death (apoptosis)
- metabolism
- proliferation
- differentiation
- death (apoptosis)

- Signalling
- "network" of general pathways
- similar in all cells / different cell-specific effects

Signalling disruption

- **Consequences of signalling disruption**
  - unwanted changes in proliferation / differentiation / apoptosis

-> cell transformation (carcinogenicity)
-> embryotoxicity
-> immunotoxicity
-> reproduction toxicity
.... *other chronic types of toxicity*

Signal transduction - principles

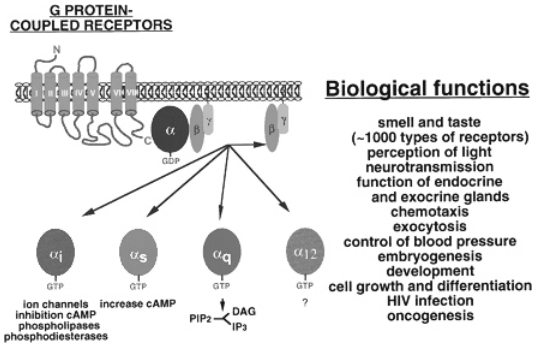
: major processes
– protein-(de)phosphorylation **(PKinases, PPases)**
- **secondary messengers** (cAMP / IP3, PIP2, DAG, Ca2+, AA)

1: Membrane receptors (G-protein, kinases)
-> PKA activation: cAMP

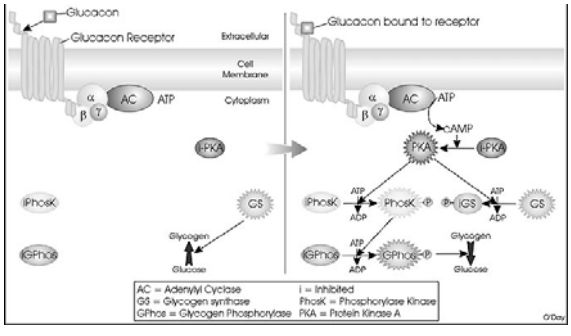
2: Membrane receptors -> PLC / PKC activation
-> PKC activation: IP3, PIP2, DAG, Ca2+, AA

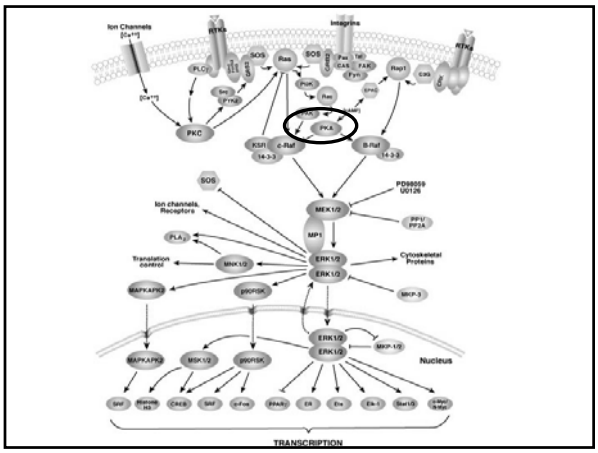
3: Cytoplasmic (nuclear) receptors

Membrane receptors (PKs): G-proteins (GPCRs)

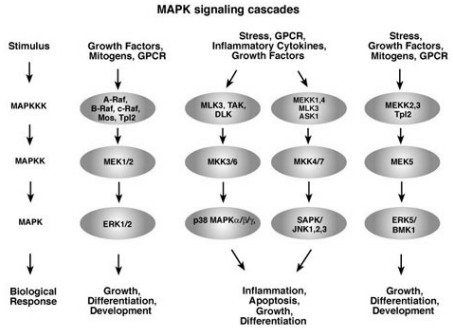


1: Membrane receptors (PKs)
-> Adenylate cyclase -> cAMP -> PKA – modulation





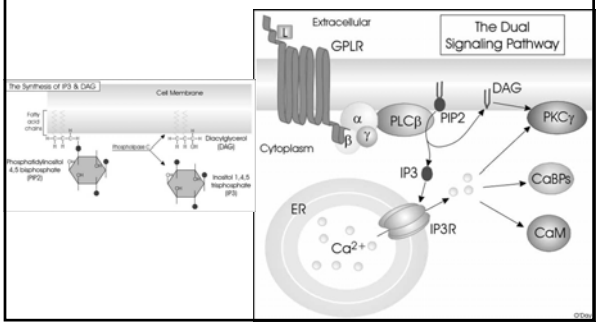
(!!!) Mitogen Activated Protein Kinases (MAPK) – dependent effects

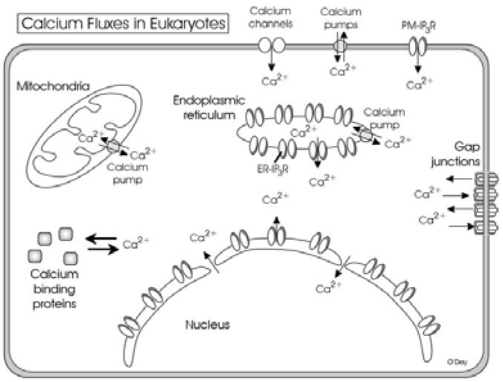


2: Membrane receptors

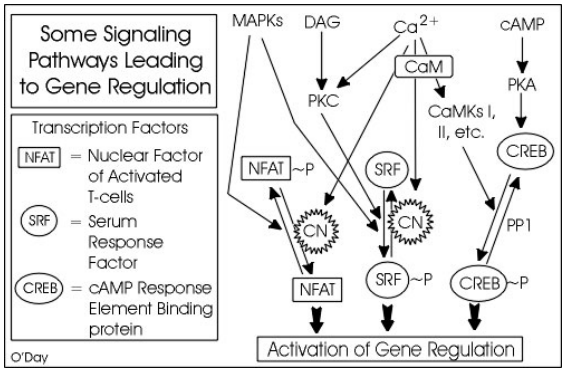
-> Phospholipase C:

PIPs -> DAG -> PKC / arachidonic acid
+ IP3 -> Ca^{2+}





Signalling crosstalk

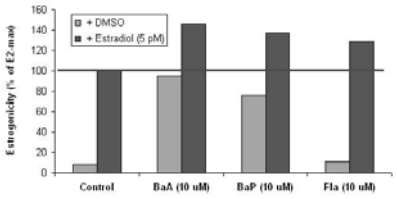


Examples

ER-independent estrogenicity (PAHs)

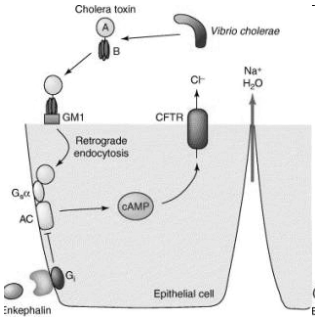
modulation of PKs/PPases: phosphorylation
-> activation of ER-dependent genes

PAHs significantly potentiate the effect of 17β-estradiol (*via increased phosporylation of ER)*

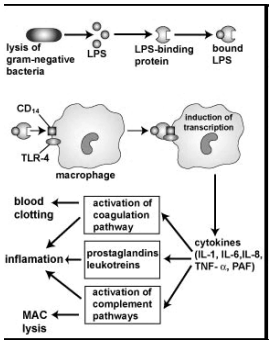


Vondráček et al. 2002 Toxicol Sci 70(2) 193

Cholera toxin - activation of adenylate cyclase



Lipopolysaccharide (bacteria) - immunotoxicity



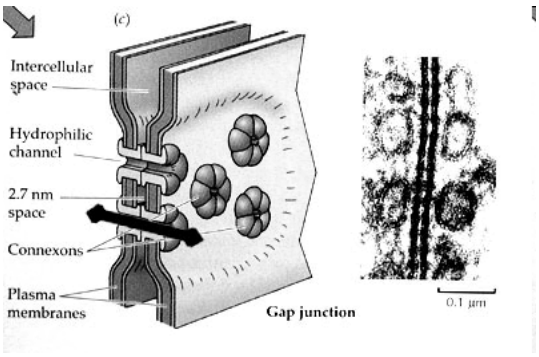
Examples - other lectures

ER-dependent estrogenicity (DDE) [other lectures]
xenoestrogenicity, binding to ER + activation

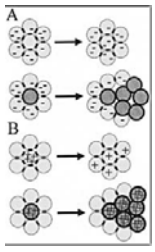
AhR-dependent anti-estrogenicity, retinoid toxicity, modulation of estrogen / retinoid levels [other lectures]
AhR -> CYPs -> steroid-metabolism
PAHs/POPs -> inhibition of Aromatase (CYP19)

Microcystins -> liver tumor promotion
inhibition of PPases [other lecture]

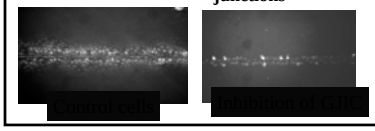
Gap junctions and cellular continuum
(Gap Junctional Intercellular Communication - GJIC)



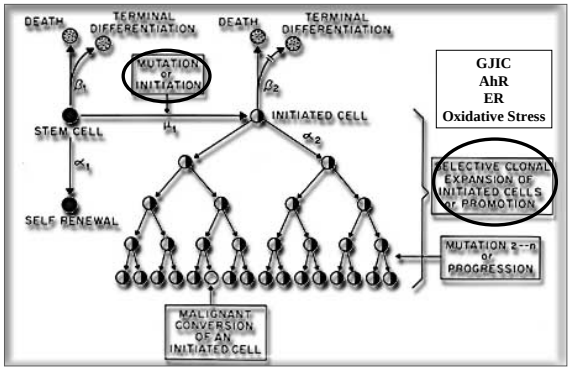
Inhibition of GJIC - mechanism of tumor promotion



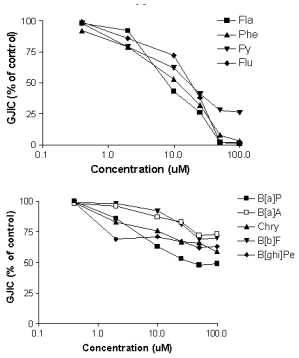
- gap-junctional intercellular communication (GJIC) - transfer of small signalling molecules via protein channels (*gap junctions)*
- regulation of proliferation, differentiation, apoptosis
- inhibition of GJIC -> proliferation ~ tumor promotion
- **relevance: tumors *in vivo* have inhibited gap-junctions**



from Trosko and Ruch 1998, Frontiers in Bioscience 3:d208



PAHs as tumor promoters
- inhibition of GJIC -



- Several PAHs inhibits GJIC within 30 min exposure (IC_{50} ~ 10-40 μM)

- Low MW and bay/bay-like regions promotes the effect

-Fluoranthene
:non-mutagenic
:non-AhR-inducing
:tumor promoter *in vivo* (!)

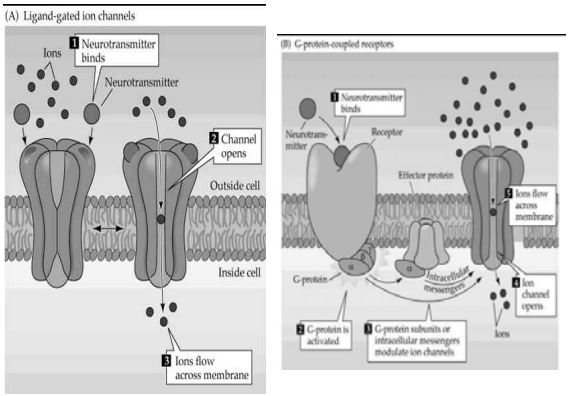
Bláha et al. 2002 Toxicol Sci 65: 43

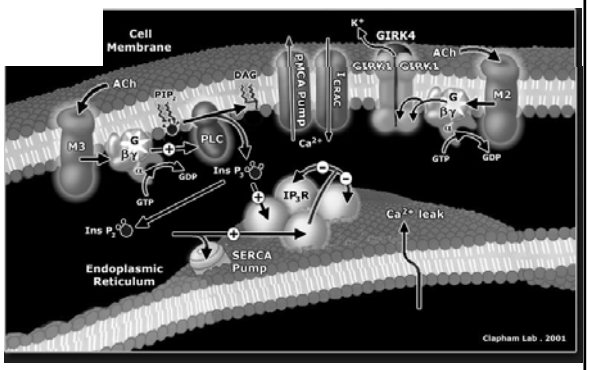
Toxicity to membrane gradients and transport

- Semipermeability of membranes: several key functions

- cytoplasmic membrane:
signalling, neural cells Na+/K+ gradient
- mitochondrial membrane:
electrone flow -> ATP synthesis
- endoplasmatic reticulum
Ca^{2+} signalling

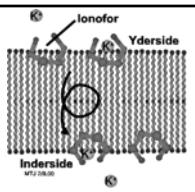
- Membrane fusion / transport
neurotransmitter release

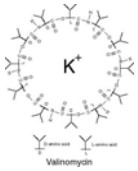


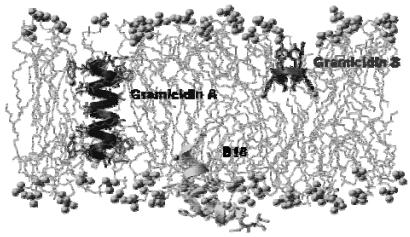


Membrane gradient disruption

Ion transfer ("ionofors")
antibiotics
(K+, Ca2+, Mg2+)

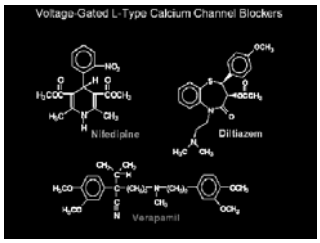




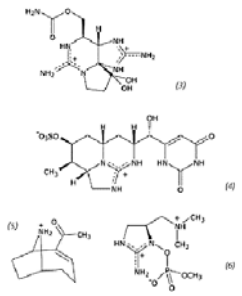


Ion Channel BLOCKERS / ACTIVATORS

Neuromodulators (drugs)



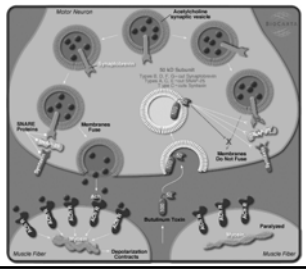
Neurotoxins (cyanobacterial)



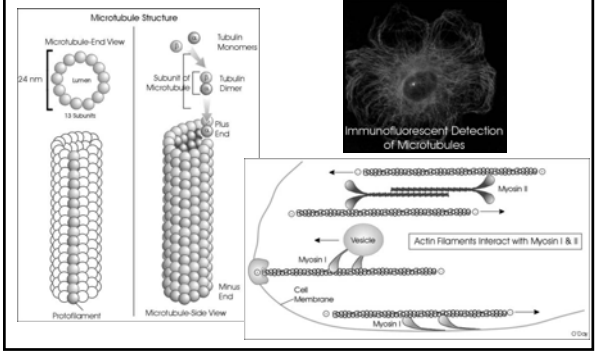
Botulinum and Tetanus toxins
(Clostridium botulinum, Clostridium tetani)

Toxins = enzymes - proteases (!)
- cleavage of proteins involved in vesicle formation
- selective inhibition of neutrotransmitter release

neurotoxicity

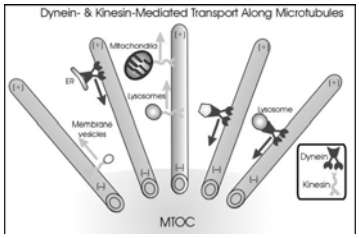


Cytoskeleton as target of toxicants
microtubules / actin-myosin

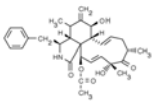


Cytoskeleton – function

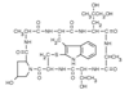
- intracellular transport
- cell replication and division (mitosis:chromosomes)
- muscle movement
- membrane (vesicles) fusion



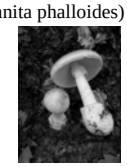
TOXINS: effects on (DE)POLYMERIZATION

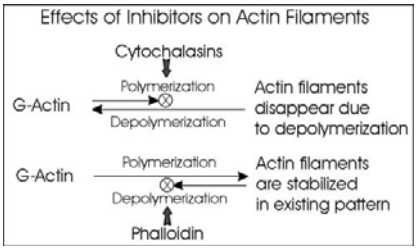


cytochalasin D
(fungal toxin)

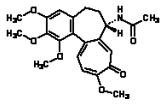


Phalloidin
(death cap - Amanita phalloides)

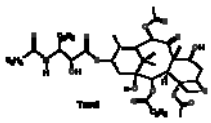




TOXINS: effects on (DE)POLYMERIZATION



Colchicine



taxol