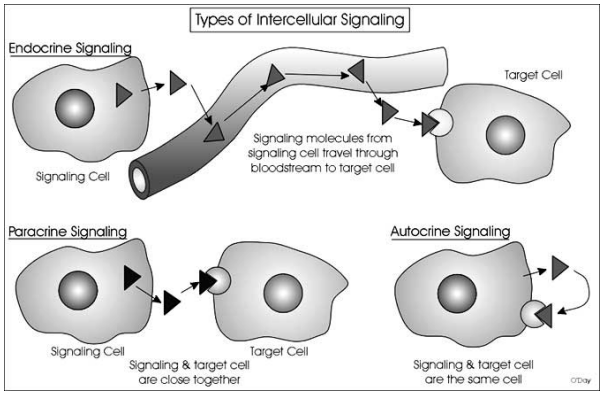
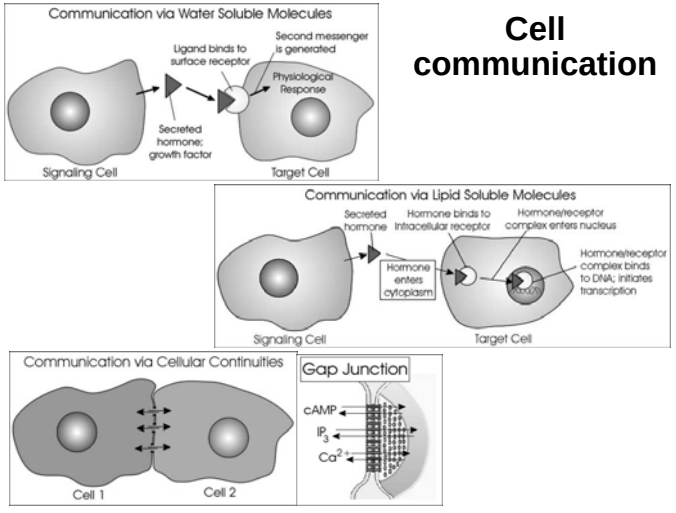
Cell communication & regulation - target of toxicants



Cell communication



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

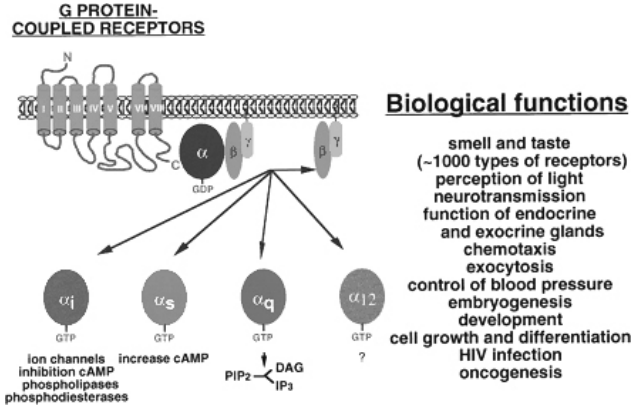
: major processes
- protein-(de)phosphorylation **(PKinases, PPases)**
- secondary messengers (cAMP / IP3, PIP2, DAG, Ca2+, AA)

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

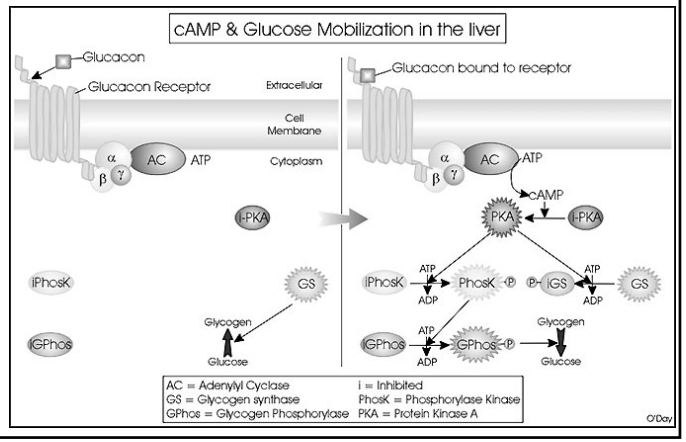
2: Membrane receptors -> PLC / PKC activation
-> PKC activation: IP3, PIP2, DAG, Ca2+, AA

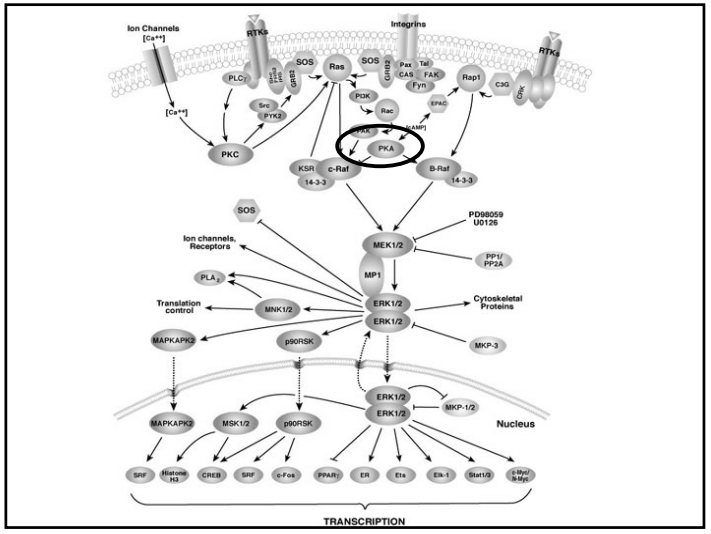
3: Cytoplasmic (nuclear) receptors

Membrane receptors (PKs): G-proteins

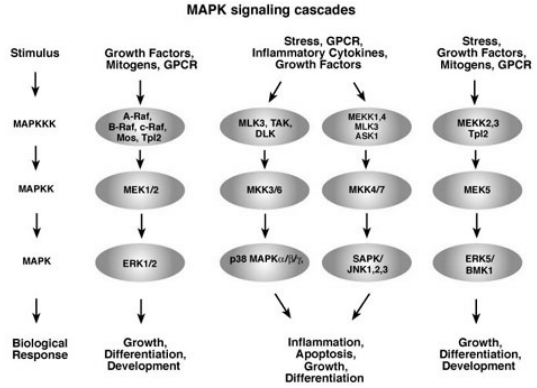


1: Membrane receptors (PKs)
-> Adenylate cyclase -> cAMP -> PKA – modulation

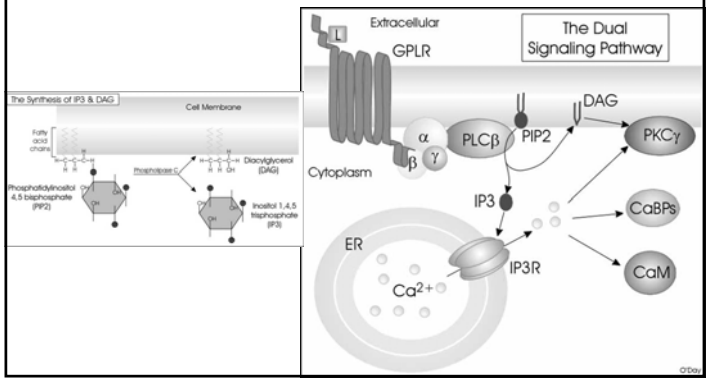


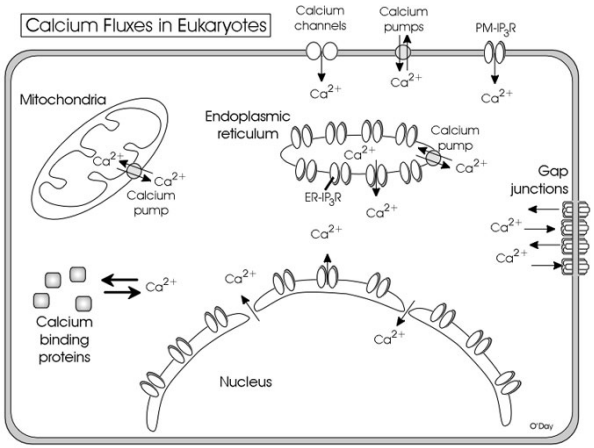


Mitogen Activated Protein Kinases (MAPK) – dependent effects

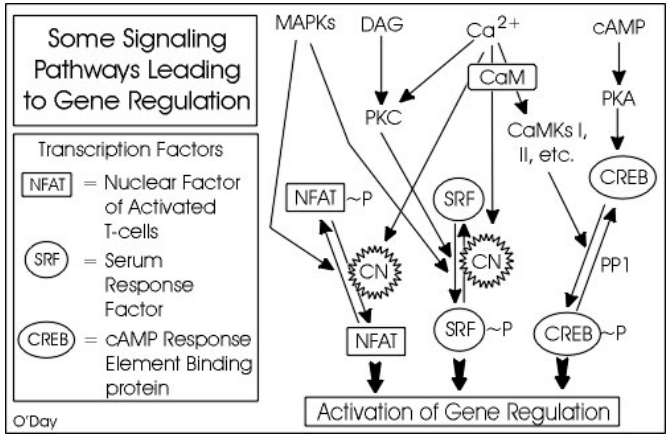


2: Membrane receptors
-> Phospholipase C:
PIPs -> DAG -> PKC / arachidonic acid
+ IP3 -> Ca^{2+}





Crosstalk



Examples

ER-dependent estrogenicity (DDE) [other lecture]

xenoestrogenicity, binding to ER + activation

ER-independent estrogenicity (PAHs)

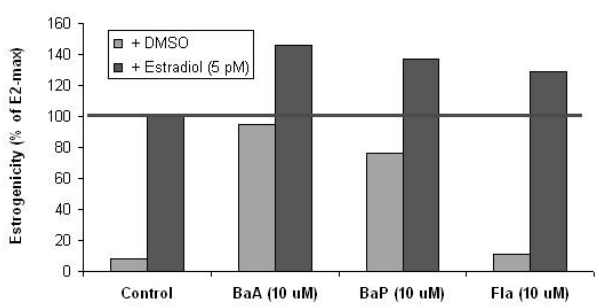
modulation of PKs/PPases: phosphorylation
-> activation of ER-dependent genes

AhR-dependent anti-estrogenicity, retinoid toxicity

modulation of estrogen / retinoid levels
[other lectures]

AhR -> CYPs -> steroid-metabolism
PAHs/POPs -> inhibition of Aromatase (CYP19)

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



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

Examples

Microcystins -> liver tumor promotion

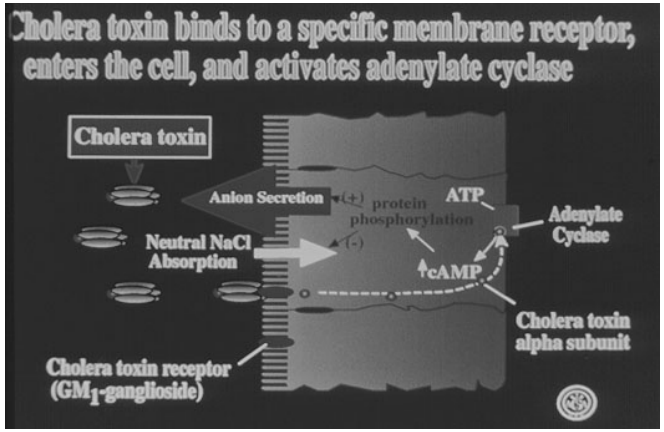
inhibition of PPases [other lecture]

Immunotoxicity

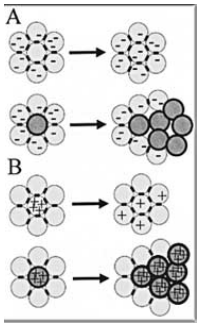
- (Cyano)bacterial lipopolysaccharides, heavy metals ...
- Cholera toxin
  - AC: cAMP -> effects

PAHs -> Inhibition of Gap-junctions

- Gap-junctional intercellular communication



Inhibition of GJIC - biomarker of tumor promotion

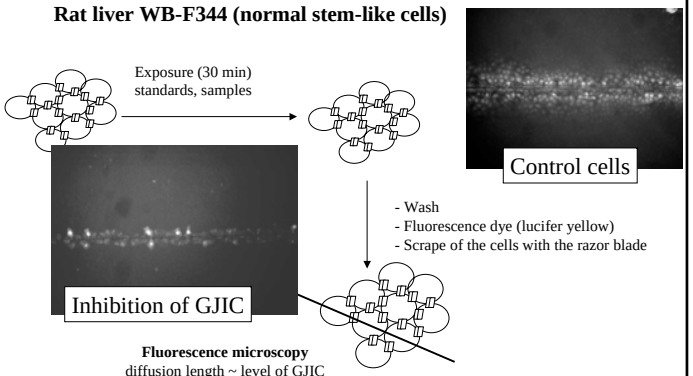


- gap-junctional intercellular communication (GJIC) - transfer of signalling molecules via protein channels (*gap junctions)*
- regulation of proliferation, differentiation, apoptosis
- inhibition of GJIC -> proliferation ~ tumor promotion
- **relevance: tumors *in vivo* have inhibited gap-junctions**

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

Scrape loading / dye transfer assay (GJIC inhibition)

Rat liver WB-F344 (normal stem-like cells)

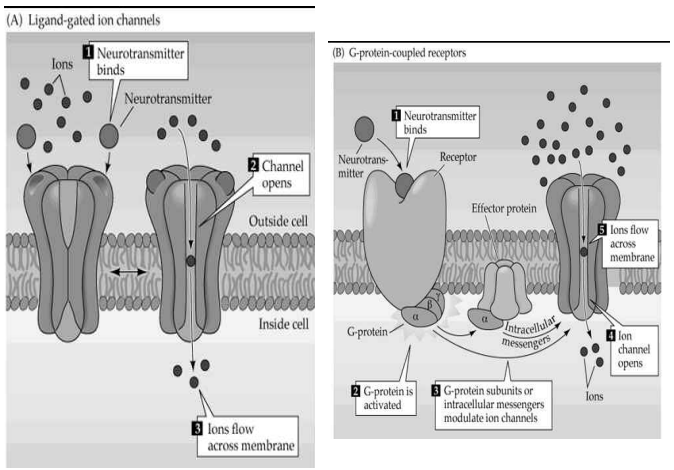


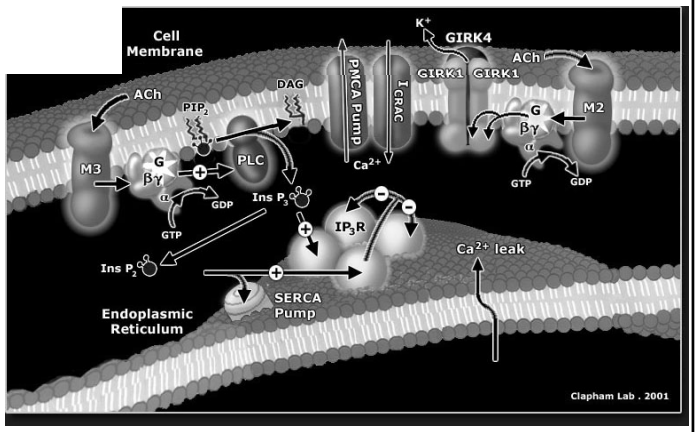
Fluorescence microscopy
diffusion length ~ level of GJIC

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

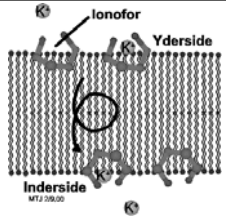
- Membrane fusion / transport
neurotransmitter release

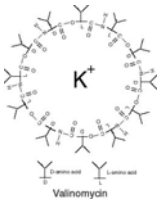


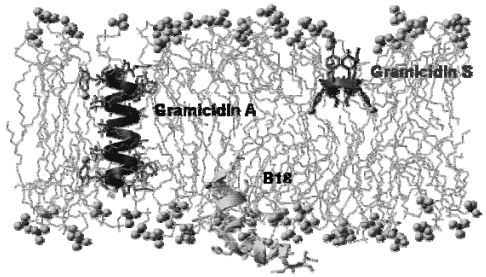


Membrane gradient disruption

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

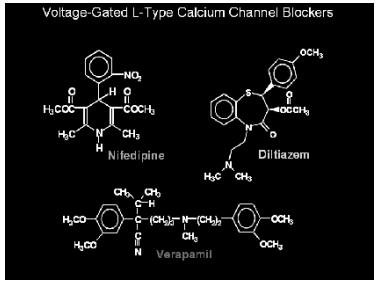




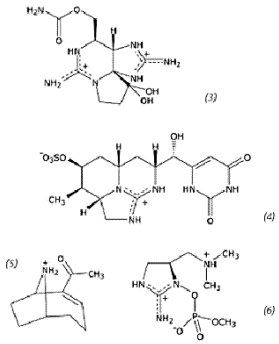


Ion Channel BLOCKERS / ACTIVATORS

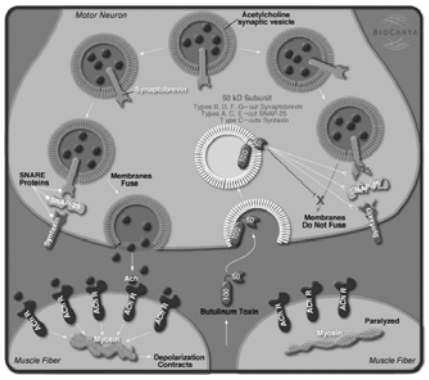
Neuromodulators (drugs)



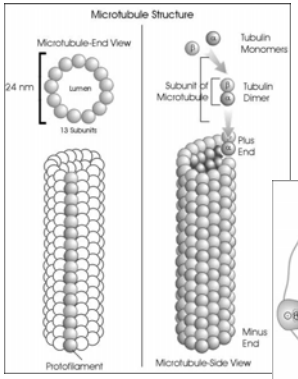
Neurotoxins (cyanobacterial)

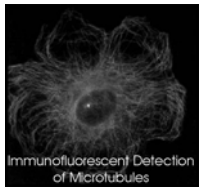


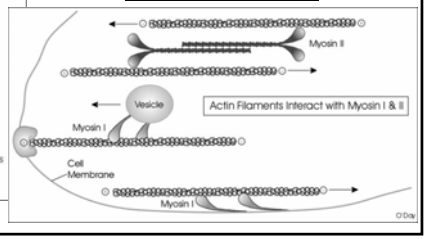
Botulotoxin, Tetanotoxin
- proteases (!)
- selective inhibition of neutrotransmitter release (membrane vesicles)



Cytoskeleton as target of toxicants
microtubules / actin-myosin

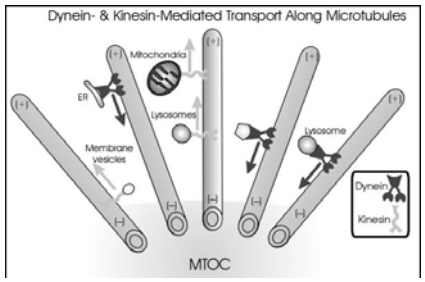






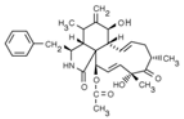
Cytoskeleton – function

- intracellular transport
- cell replication and division (mitotic poisons)
- muscle movement
- membrane (vesicles) fusion

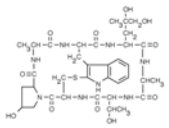


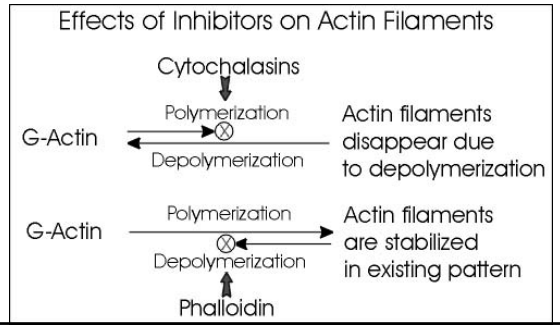
TOXINS: effects on (DE)POLYMERIZATION

cytochalasin D

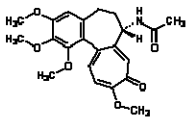


phalloidin





TOXINS: effects on (DE)POLYMERIZATION



N-[(7S)-(5,6,7,9-Tetrahydro-1,2,3,10-tetramethoxy-9-oxobenzo[a] heptalen-7-yl)] acetamide

colchicine

taxol