



Centrum pro výzkum
toxických látek
v prostředí

BIOMARKERS AND TOXICITY MECHANISMS

04 – Mechanisms @membranes

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Tento projekt je spolufinancován Evropským sociálním fondem a státním rozpočtem České republiky.



INVESTICE DO ROZVOJE VZDĚLÁVÁNÍ

Major mechanisms (modes of action) to be discussed in detail

- **Proteins** and inhibition of enzymatic activities
- Mitotic poisons & microtubule toxicity
- **Membrane** nonspecific toxicity (narcosis)
- Toxicity to membrane gradients
- **DNA** toxicity (genotoxicity)
- **Complex** mechanisms
 - Detoxification
 - defence processes as toxicity mechanisms
 - Oxidative stress – redox toxicity
 - Toxicity to signal transduction
 - Ligand competition – receptor mediated toxicity

Cell membrane

Key functions for life

- Primary **barrier** / separation of „living“ inside from „abiotic“ outside
- **Semipermeability** for nutrients / signals
- **Reception** of chemical signals & regulatory molecules
- Keeping **gradients** necessary for life
 - H⁺ - ATP synthesis(mitochondria / bacterial emambrane)
 - K⁺/Na⁺ - neuronal signals
- **Proteosynthesis** (ribosomes) depends on membranes
- Many other **enzymes bound to membranes** (e.g. signaling, detoxification, post-translational modifications)
- Etc.....



Nonspecific (basal, narcotic) toxicity

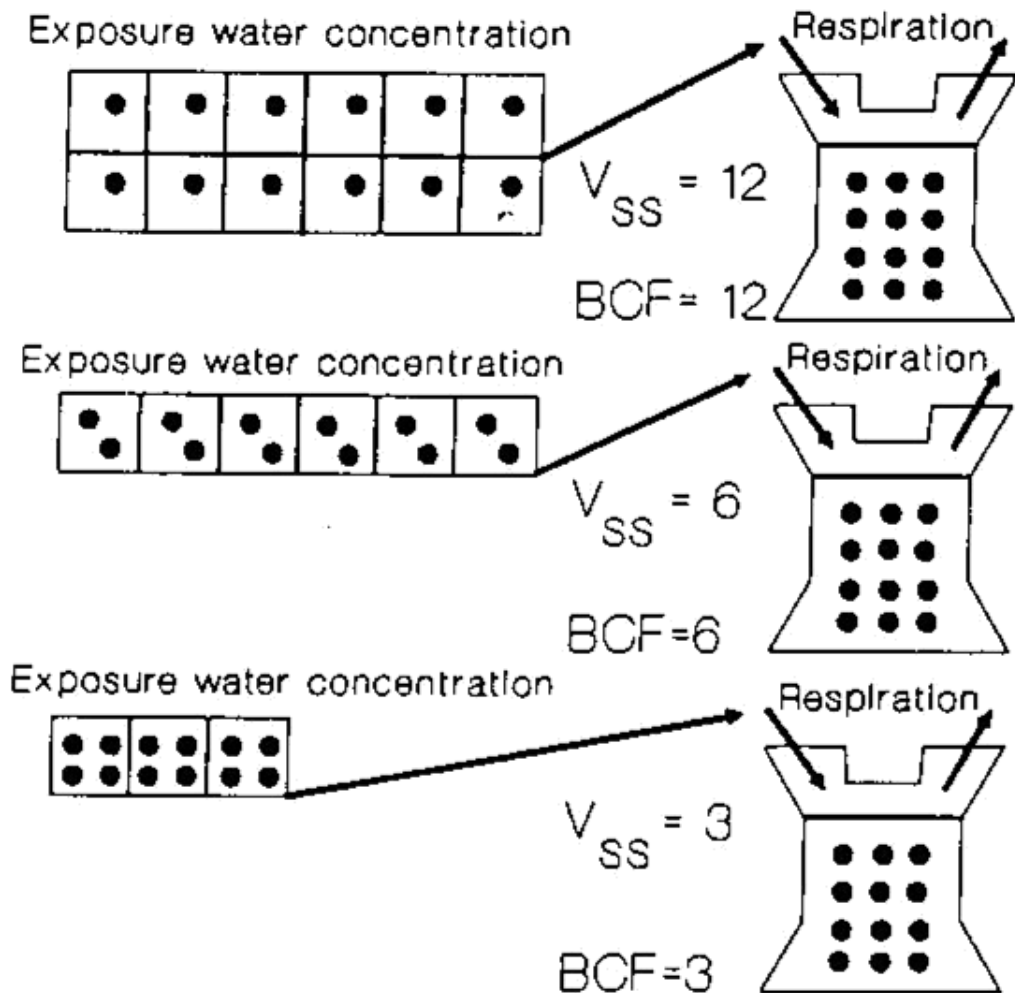
- All organic compounds tend to accumulate in membranes, being “narcotic” at relatively “high” concentrations
- Compounds then affect membranes
 - nonspecific disruption of fluidity
 - and/or disruption of membrane proteins
- Related to lipophilicity (K_{ow}): tendency of compounds to accumulate in body lipids (incl. membranes)

E.g. narcotic toxicity to fish: $\log (1/LC50) = 0.907 \cdot \log K_{ow} - 4.94$

- The toxic effects occur at the same “molar volume” of all narcotic compounds (*volume of distribution principle*)



Volume of distribution principle



BCF – bioconcentration factor

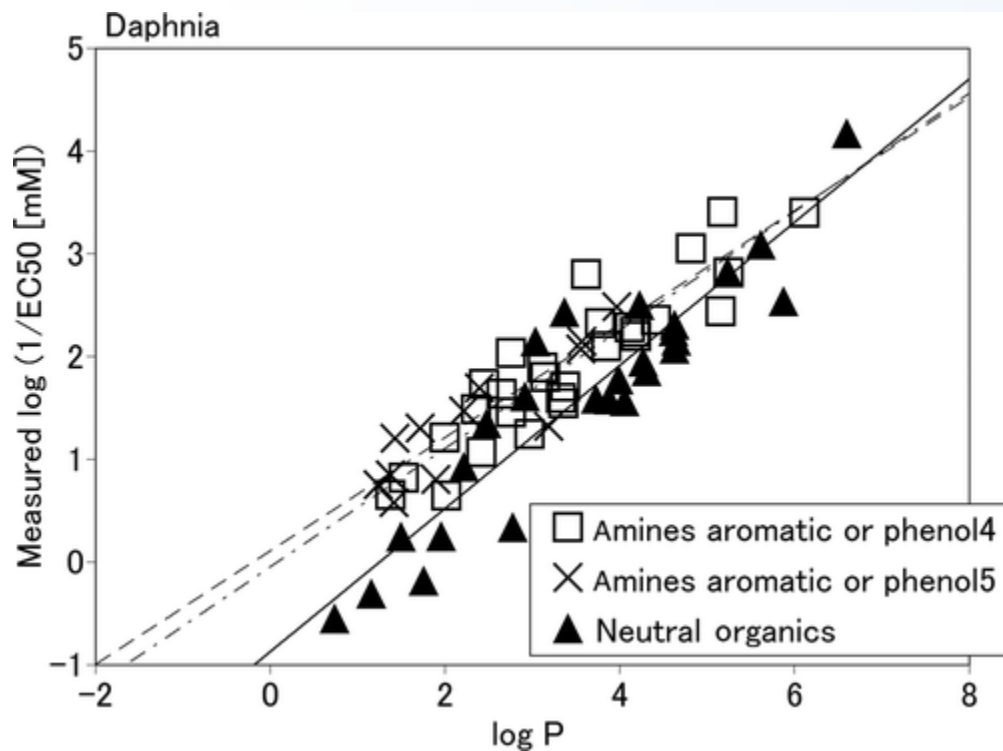
- * Depends on hydrophobicity (i.e. K_{ow})
- * Higher BCF
→ lower concentration is sufficient for bioconcentration to the same “tissue concentration”
→ lower external concentration (IC50) will induce toxic effect
- * *Confirmed by chemical analyses (same molar concentrations of different compounds accumulated in membranes)*



Narcotic toxicity in ecotoxicology

Acute basal toxicity

Direct correlations between $\log K_{ow}$ (= $\log P$) and EC_{50} for aquatic organisms (e.g. *Daphnia magna*)



Example:

Neutral organics

→ **Nonpolar narcosis**

Amines, phenols

→ **Polar narcosis**

(similar $\log P$ → higher toxicity, i.e. higher values of $1/EC_{50}$ in comparison to neutral organics)

→ **More specific** ... In addition to membrane accumulation, direct interactions with proteins are anticipated

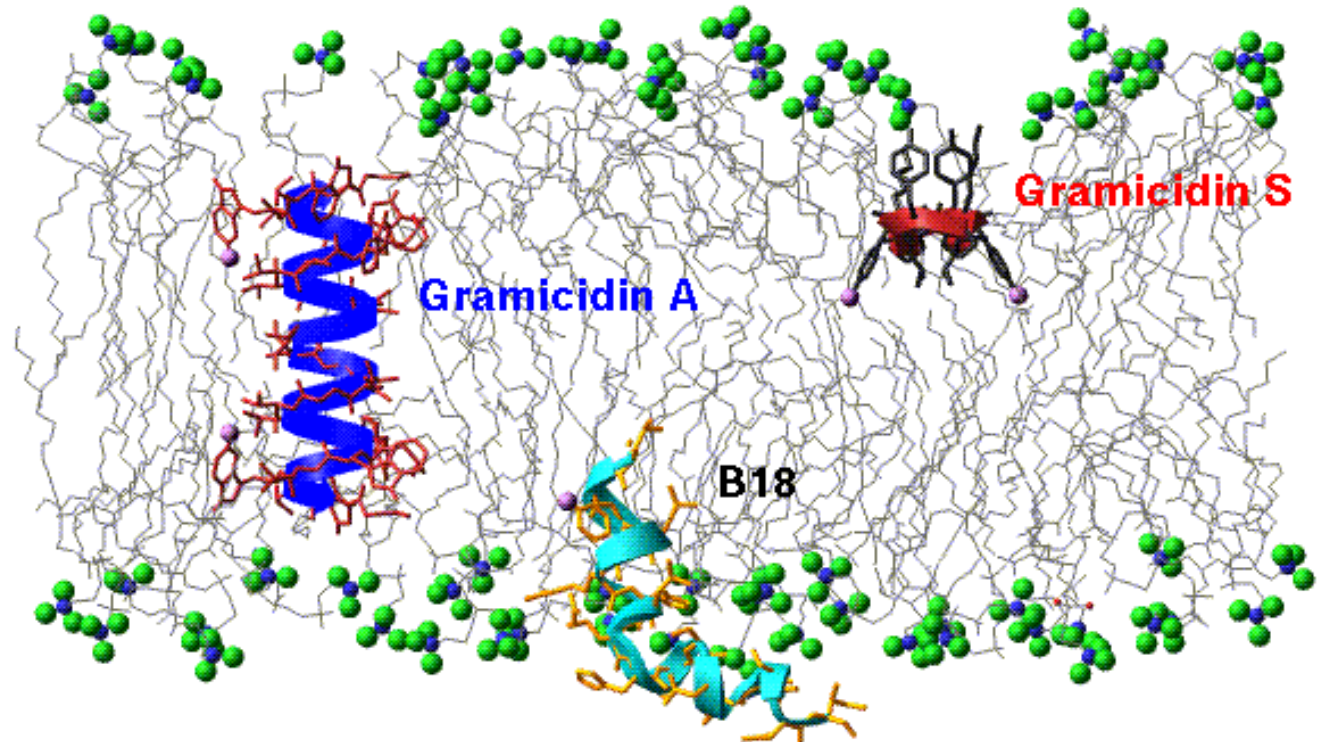
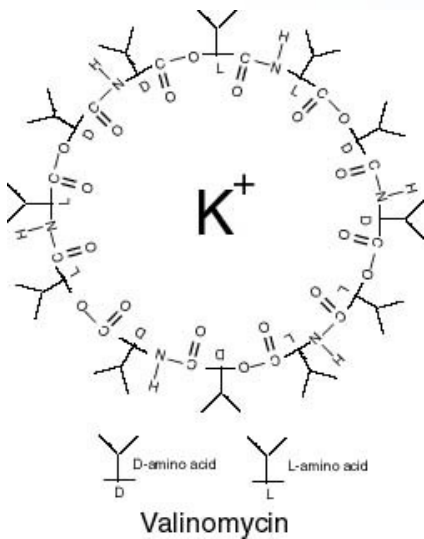
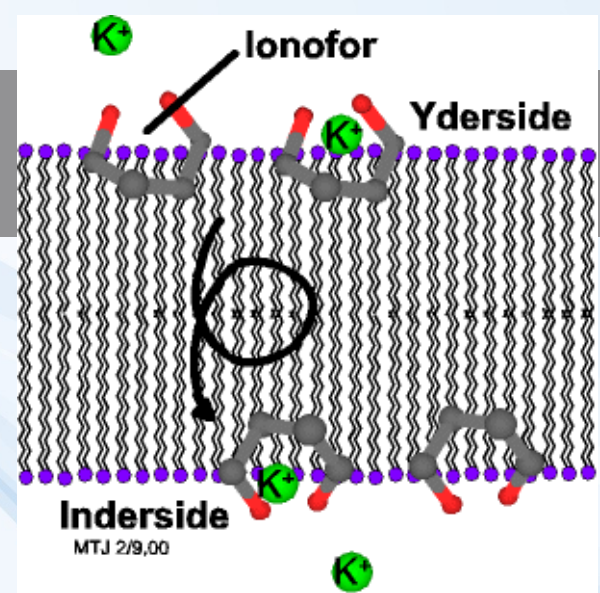
Toxicity to membrane gradients and transport

- **Semipermeability of membranes and key functions**
 - **cytoplasmic membrane:**
signalling, neural cells Na^+/K^+ gradient
 - **mitochondrial membrane:**
electron flow \rightarrow ATP synthesis
 - **endoplasmatic reticulum**
 Ca^{2+} signalling



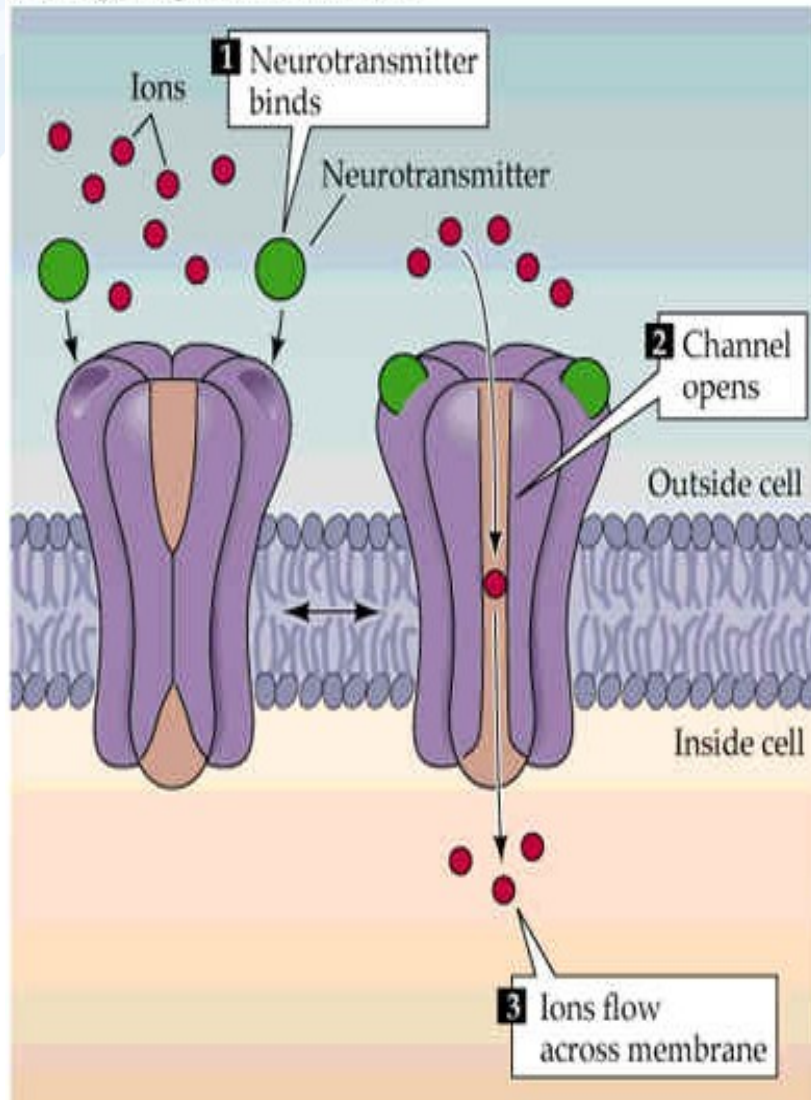
Direct membrane gradient disruption

Ion transfer ("**ionofores**")
e.g. antibiotics
(K^+ , Ca^{2+} , Mg^{2+})

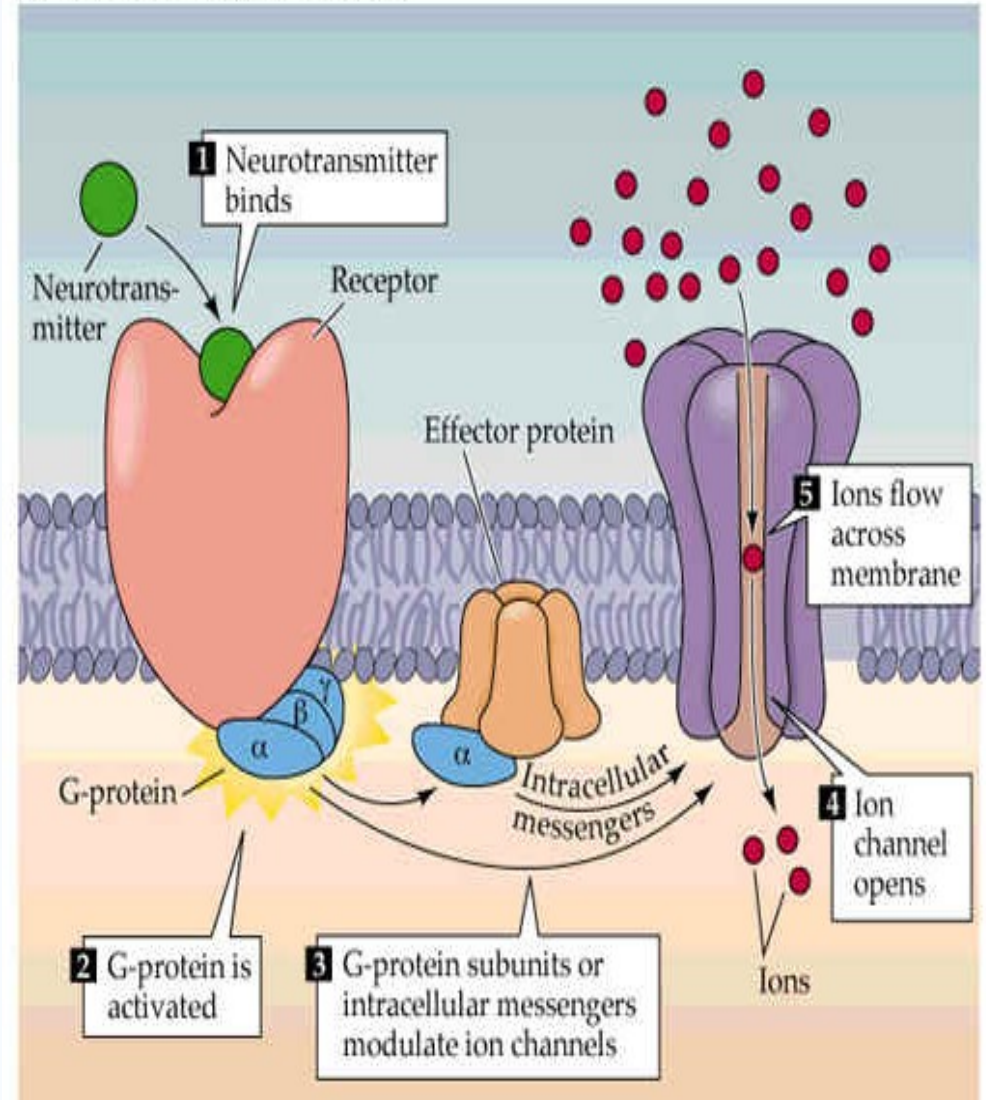


Principal types of channel activation

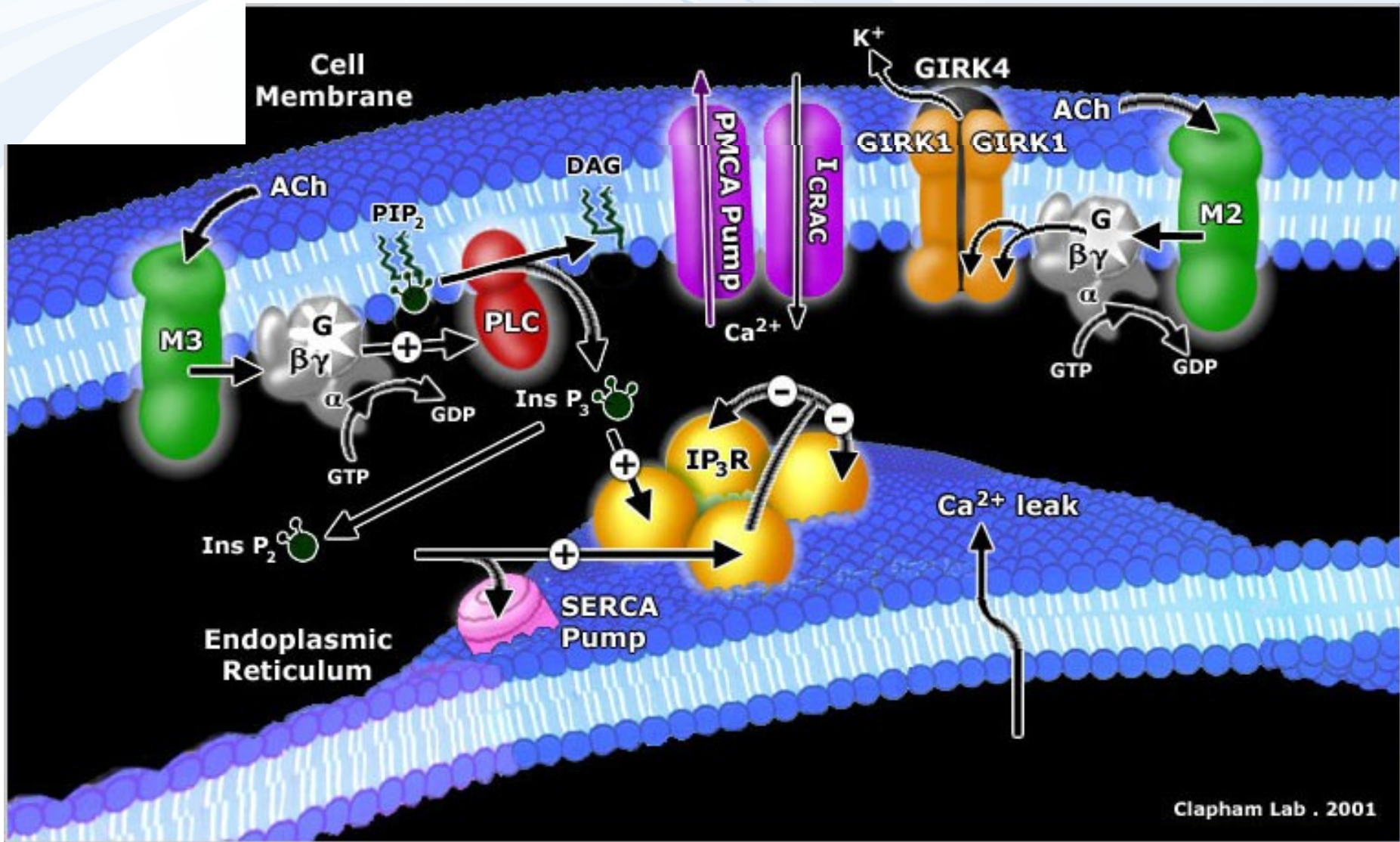
(A) Ligand-gated ion channels



(B) G-protein-coupled receptors

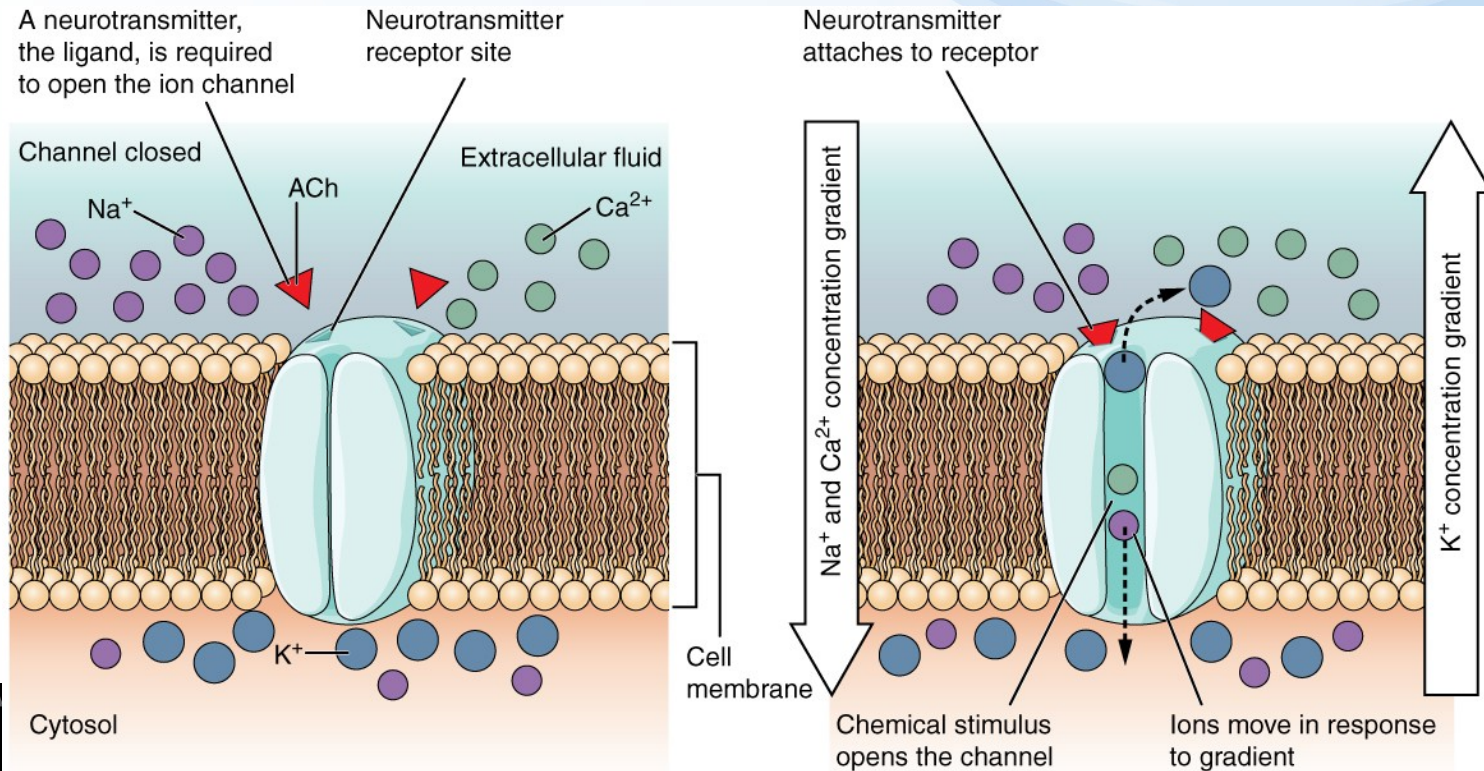
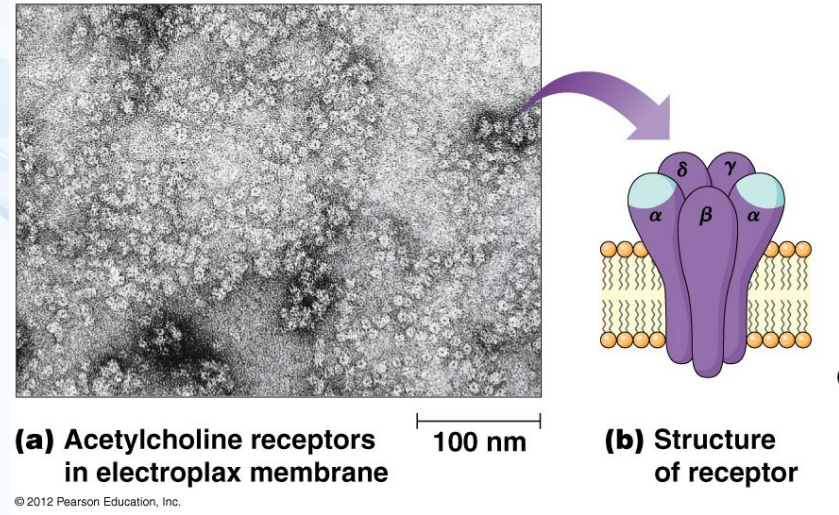


Various membrane channels - examples

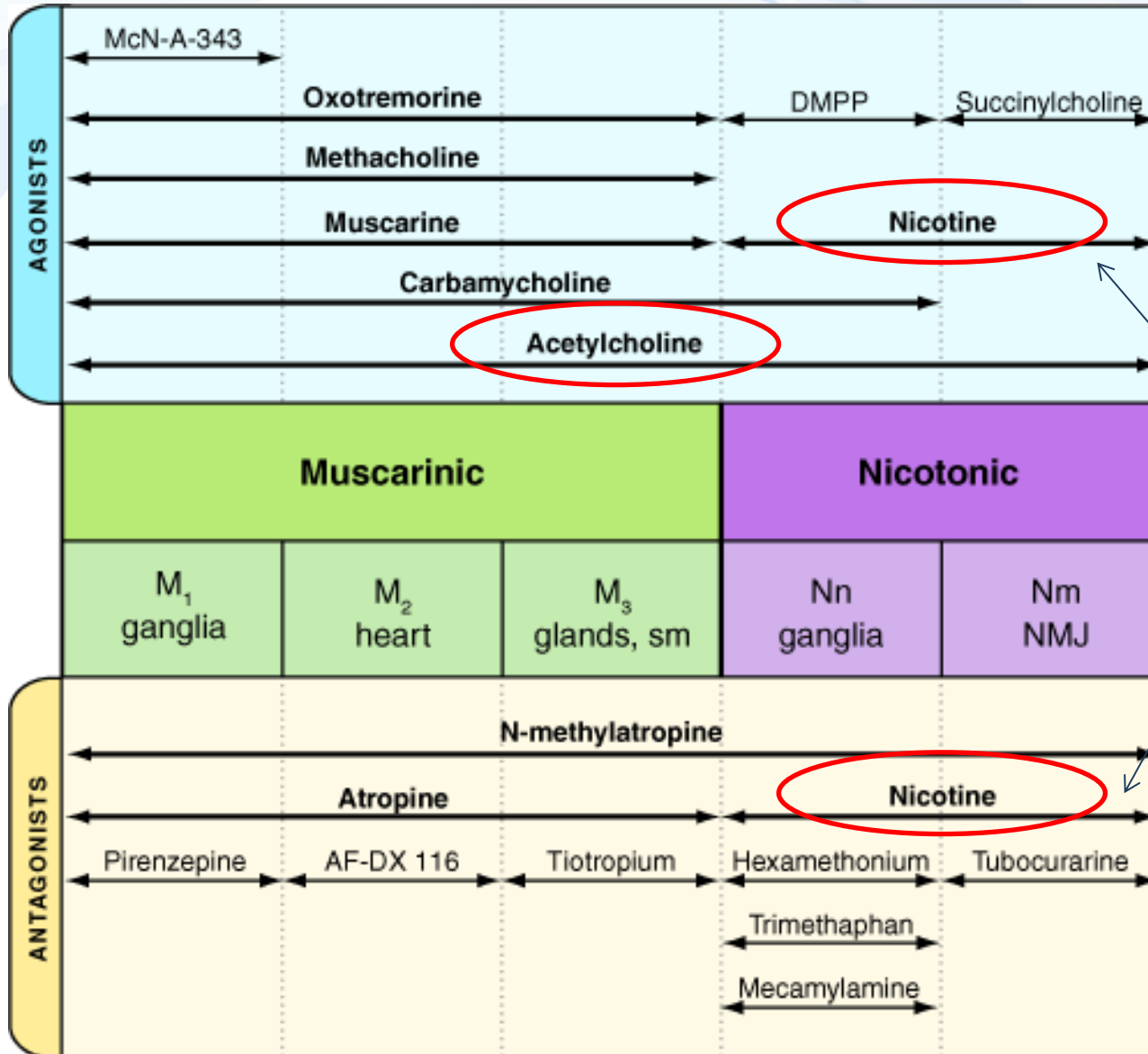


Activation of AcChol receptors

→ Disruption of membrane gradients



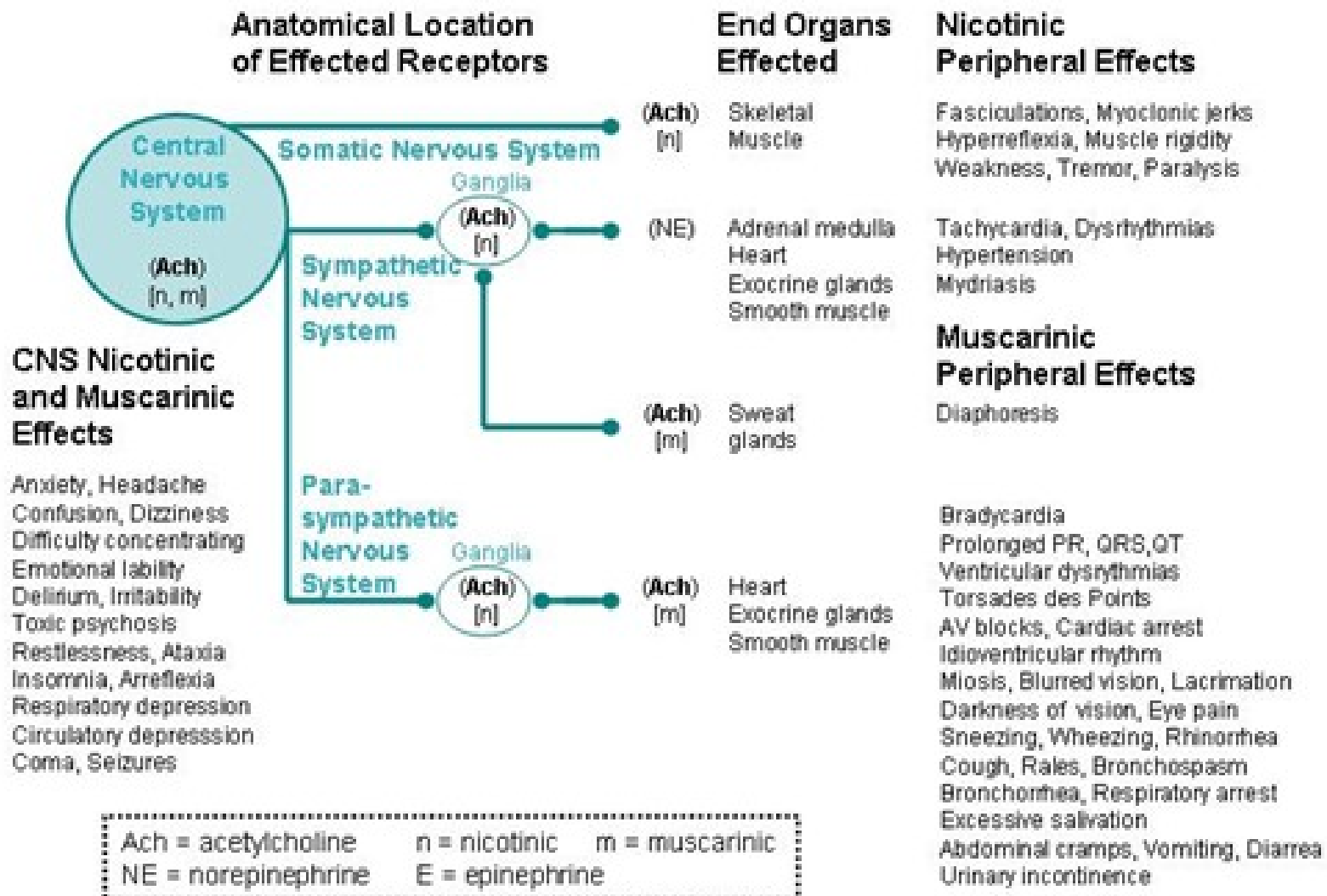
Activation / inhibition of ligand-gated channels



Concentration-dependent action

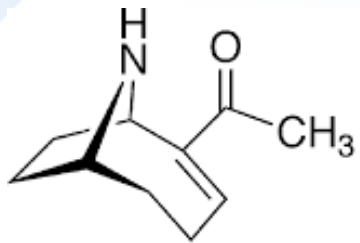
Activation / inhibition of ligand-gated channels

Nicotinic and Muscarinic Effects of Cholinesterase Inhibitors

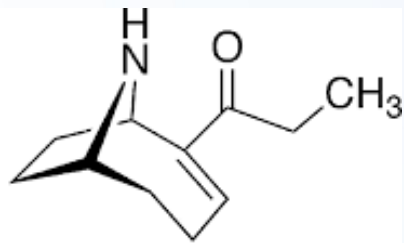


Environmentally relevant ion channel activators

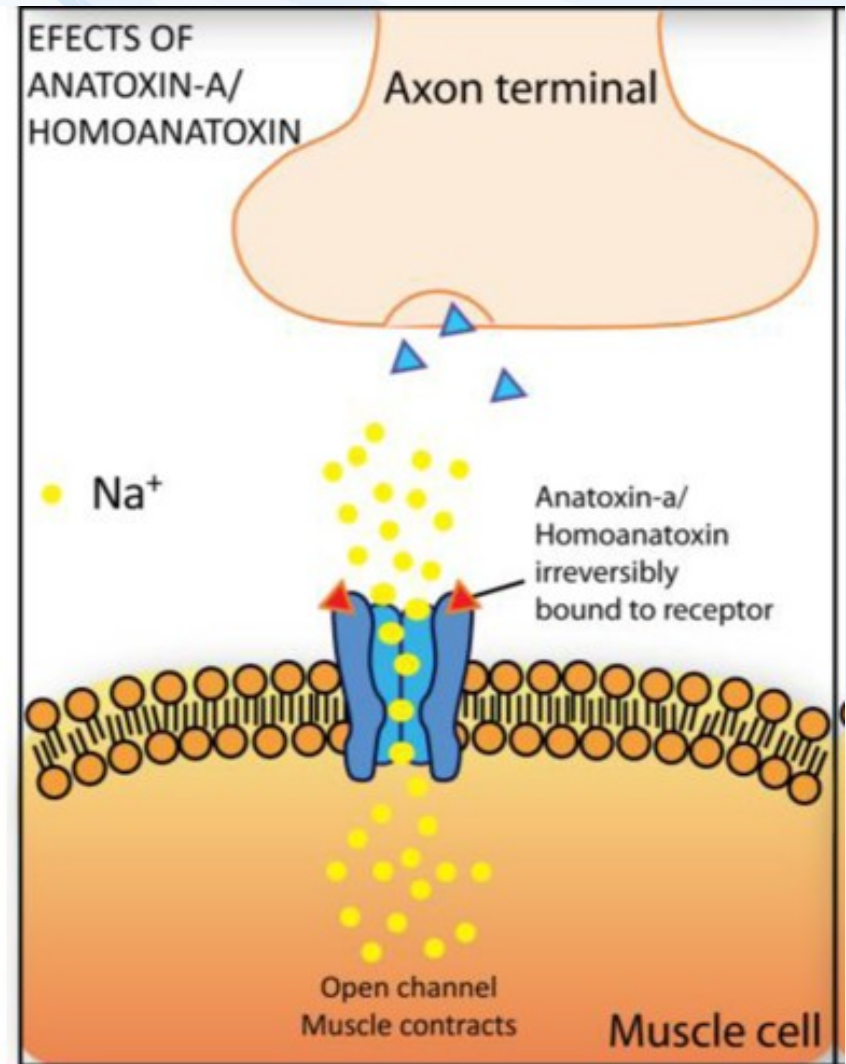
Neurotoxins (cyanobacterial)



Anatoxin-a



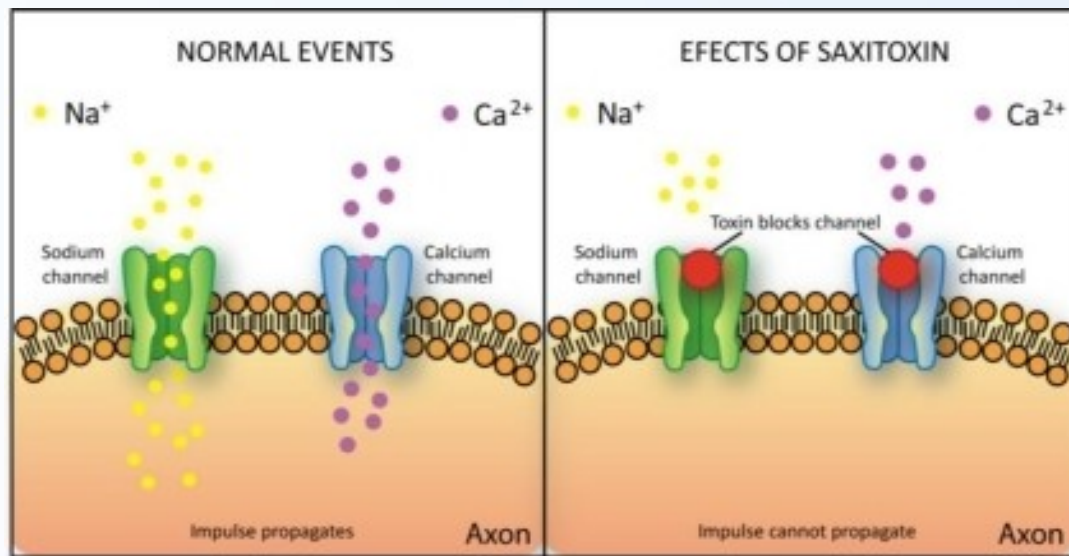
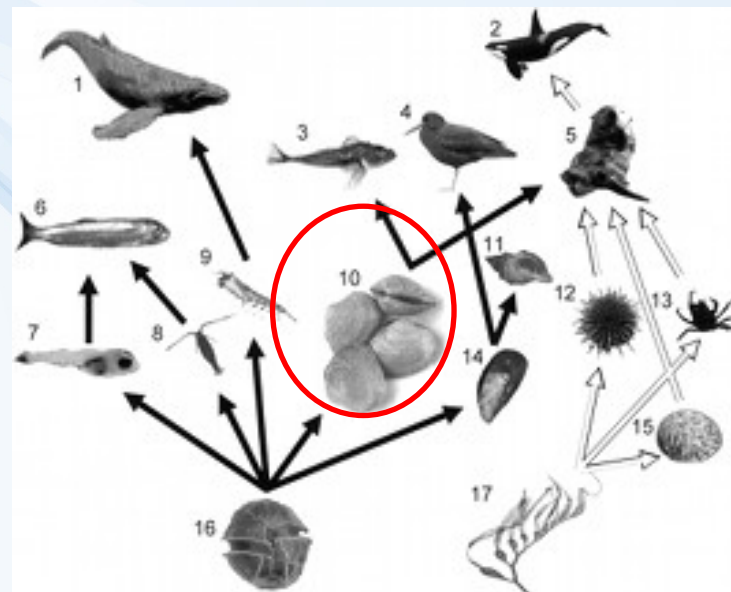
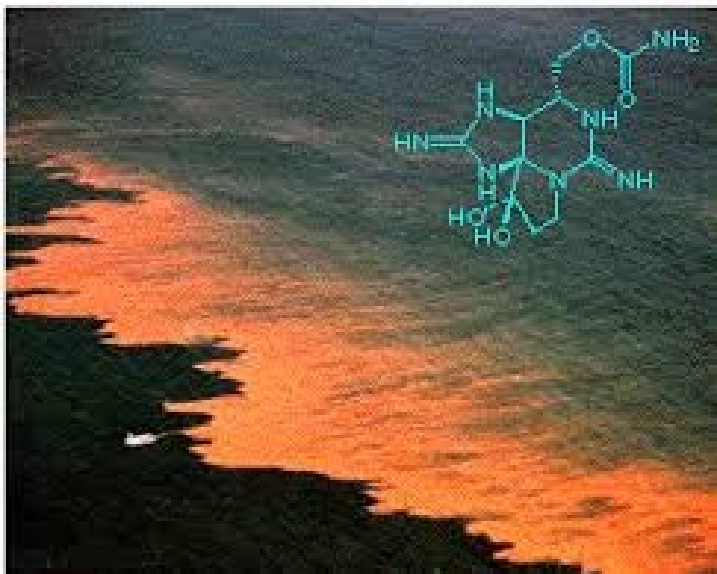
Homoanatoxin-a



Environmentally relevant ion channel activators

SAXITOXINS

- Produced by **dinoflagelates** and **cyanobacteria**
- (toxic blooms, „red tides“)



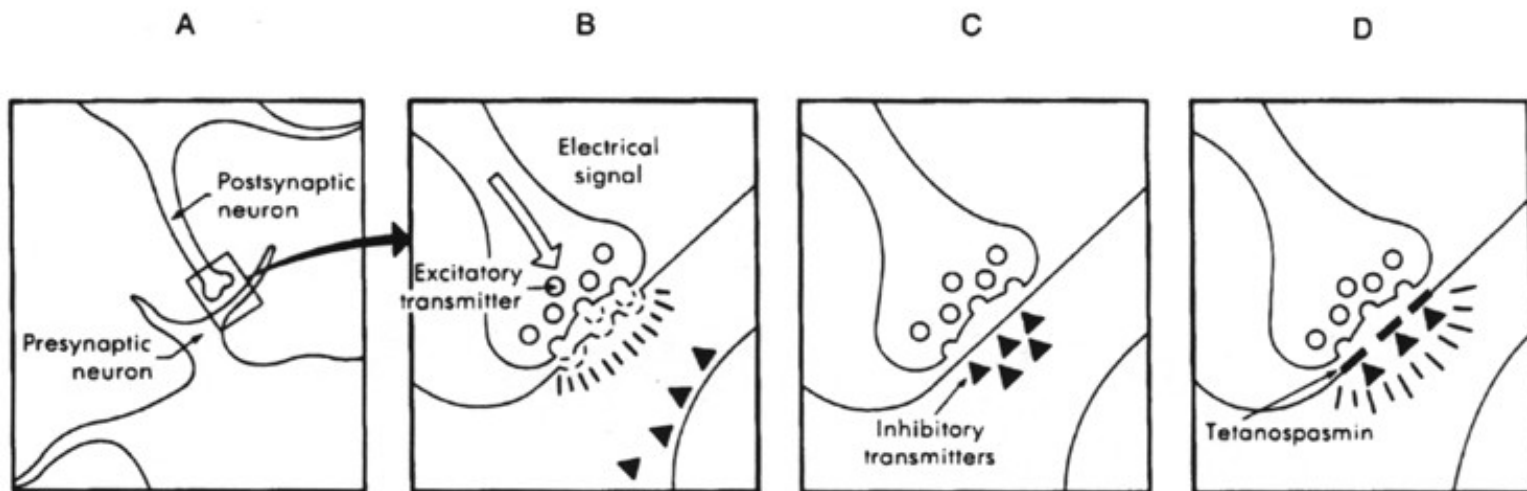
Botulinum and Tetanus toxins

(Clostridium botulinum, Clostridium tetani)

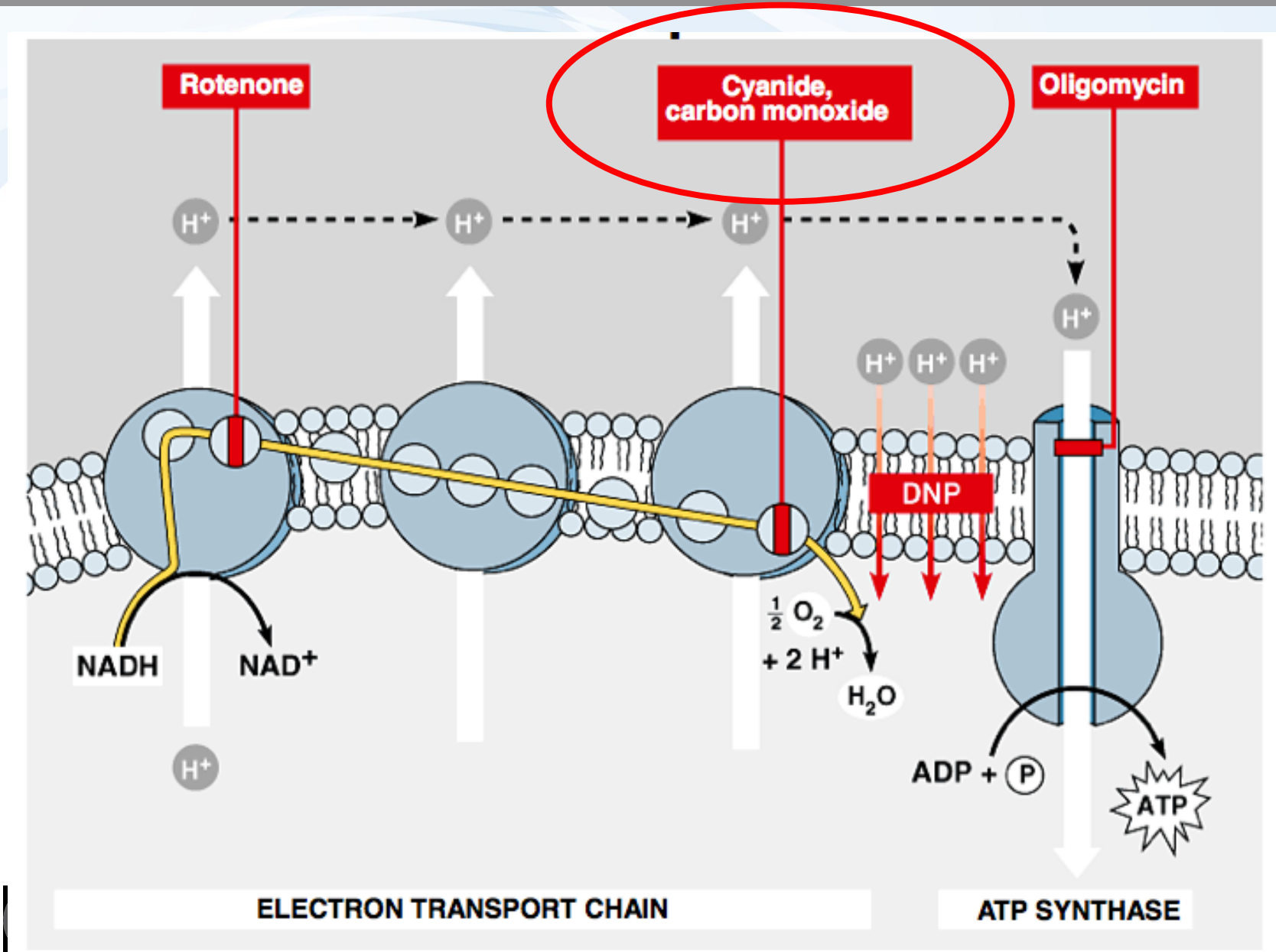
TETANUS TOXIN (tetanospasmin)

blocks release of INHIBITORY NEUROTRANSMITTERS
(γ -aminobutyric acid (GABA) in CNS

→ neurotoxicity – permanent contraction

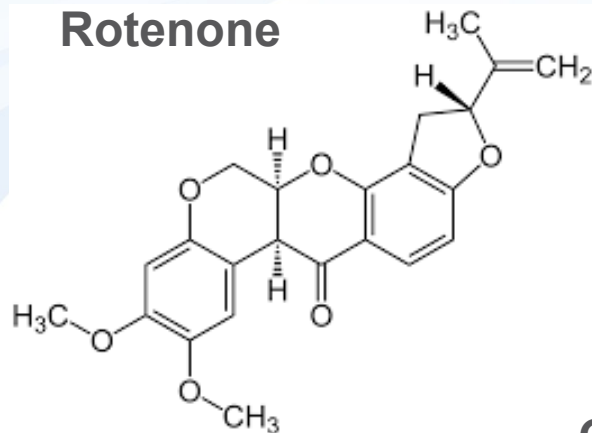


Gradient of H⁺ → ATP generation & its disruption

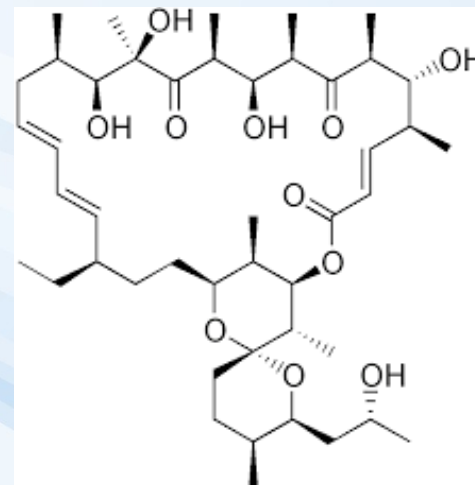


Gradient of H⁺ → ATP generation & its disruption

Rotenone



Oligomycin



CO (carbon monoxide)
CN (cyanide)
→ Binding to haem structures

