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.

EVROPSKÁ UNIE

MINISTERSTVO ŠKOLSTVÍ, MLÁDEŽE A TĚLOVÝCHOVY

OP Vzdělávání pro konkurenceschopnost

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
  - Detoxificiation
    - defence processes as toxicity mechanisms
  - Oxidative stress – redox toxicity
  - Toxicity to signal transduction
  - Ligand competition – receptor mediated toxicity

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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….

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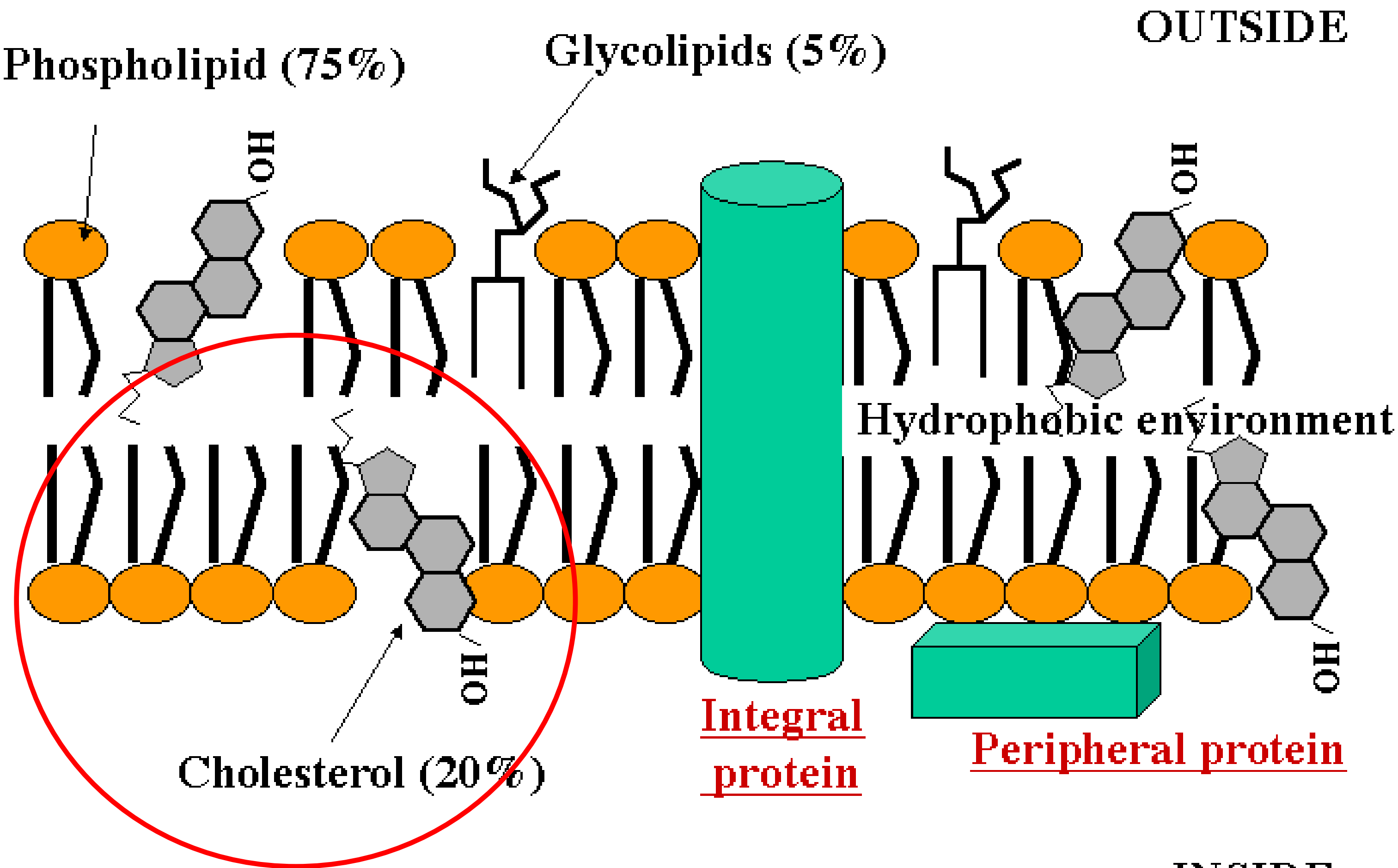
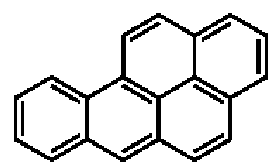
Plasma membrane



Note: *cholesterol – structural/size similarity to toxic organics e.g. Benzo[a]pyrene*



Nonspecific (basal, narcotic) toxicity

- **All <u>organic</u> 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 (Kow): tendency of compounds to accumulate in body lipids (incl. membranes)**

  E.g. narcotic toxicity to fish: log (1/LC50) = 0.907 . log Kow - 4.94

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

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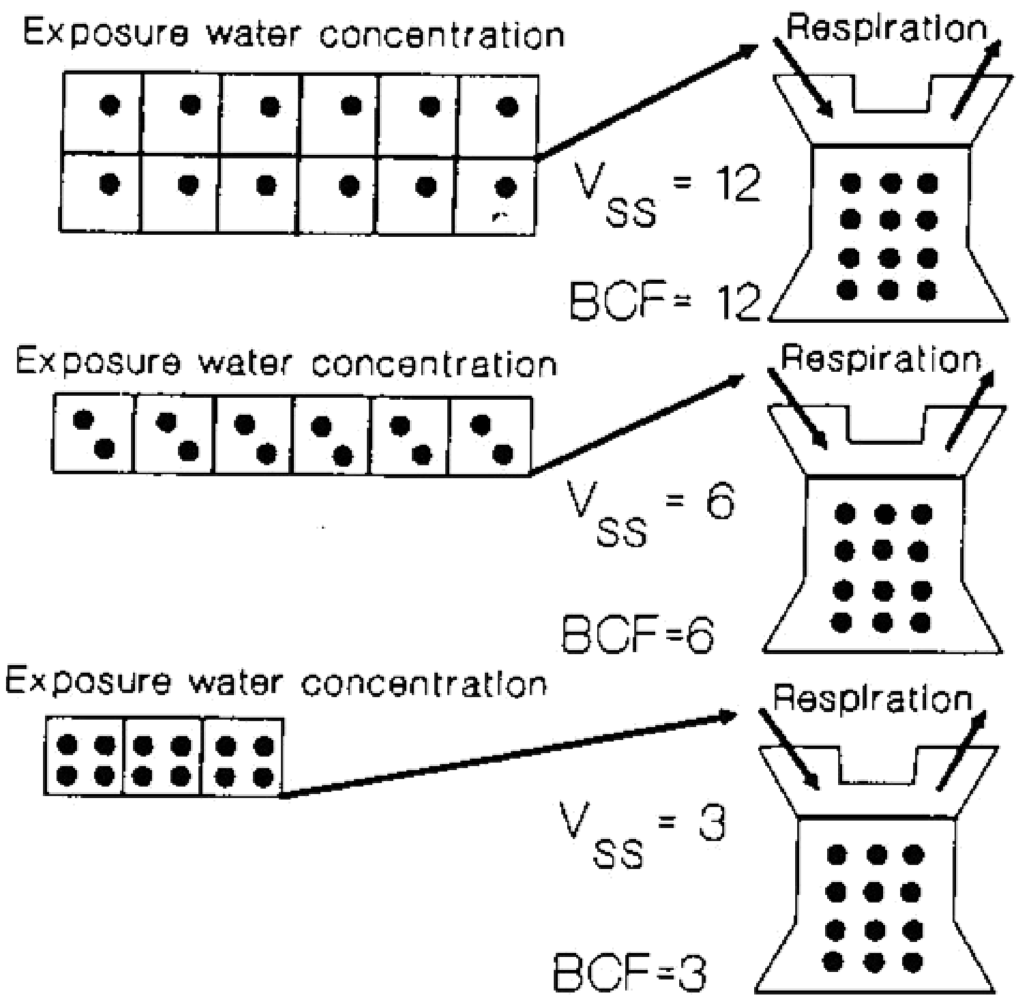
Volume of distribution principle



BCF – bioconcentration factor

* Depends on hydrophobicity (i.e. Kow)

* 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)*

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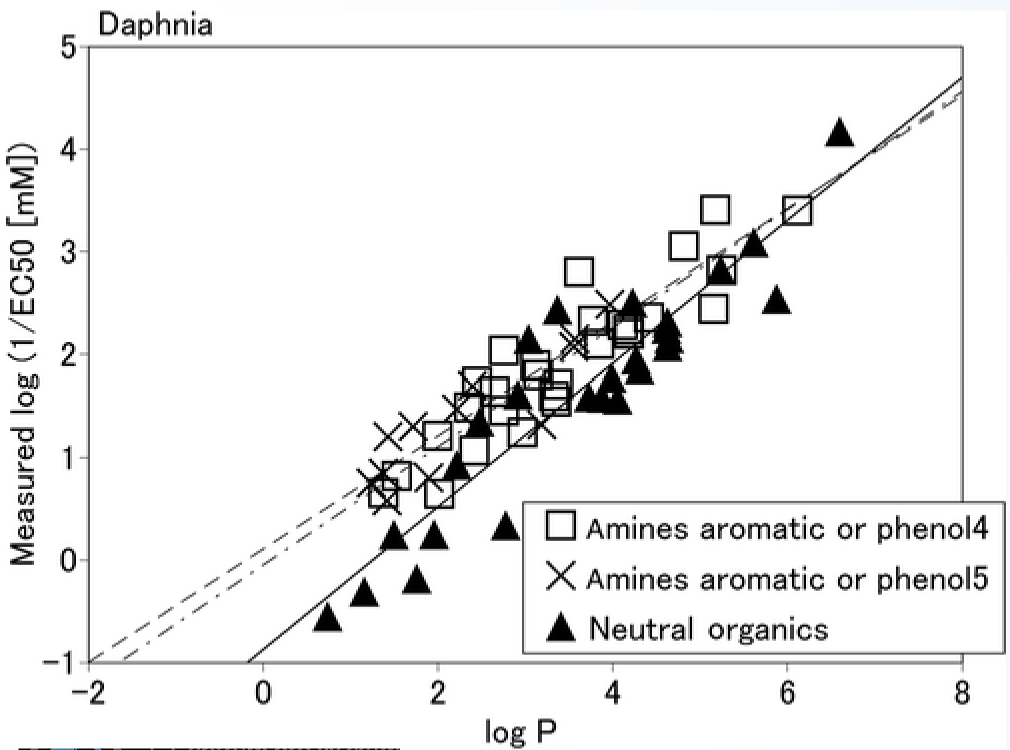
Acute basal toxicity

Direct correlations between logKow (=logP) and EC50 for aquatic organisms (e.g. *Daphnia magna)*



Example:

Neutral organics

→**Nonpolar narcosis**

Amines, phenols

→**Polar narcosis**

(similar logP → higher toxicity, i.e. higher Values of 1/EC50 in comparison to neutral organics)

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

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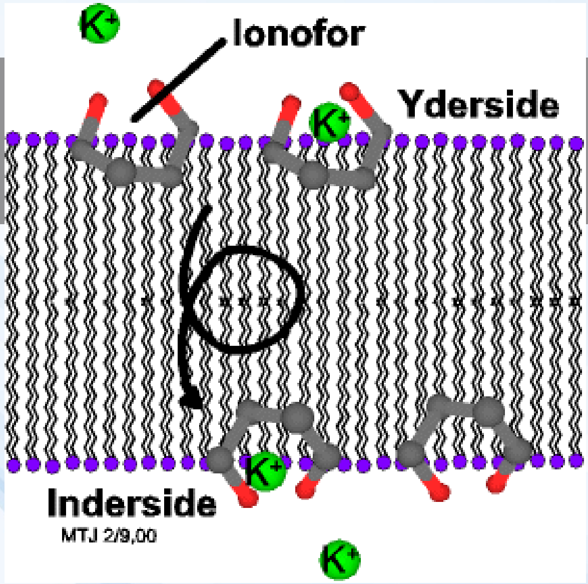
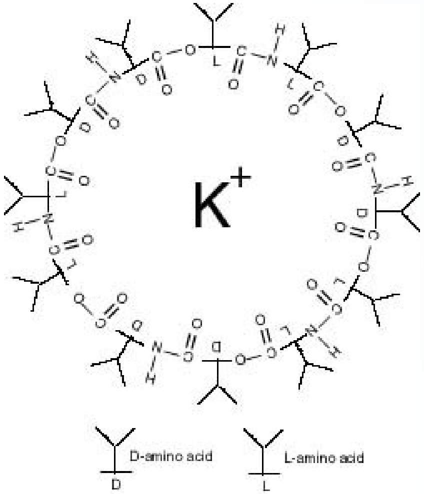
Toxicity to membrane gradients and transport

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

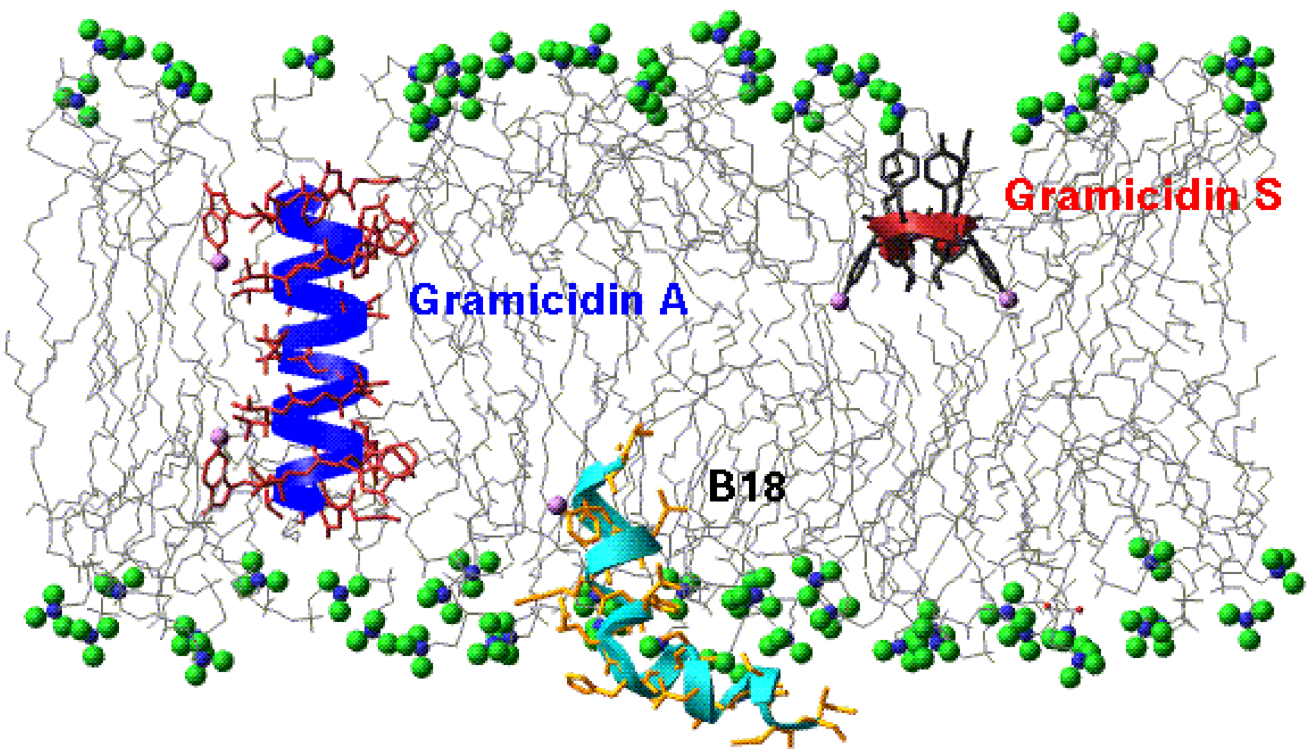
Direct membrane gradient disruption



Ion transfer ("ionofores")
e.g. antibiotics
(K+, Ca2+, Mg2+)



Valinomycin



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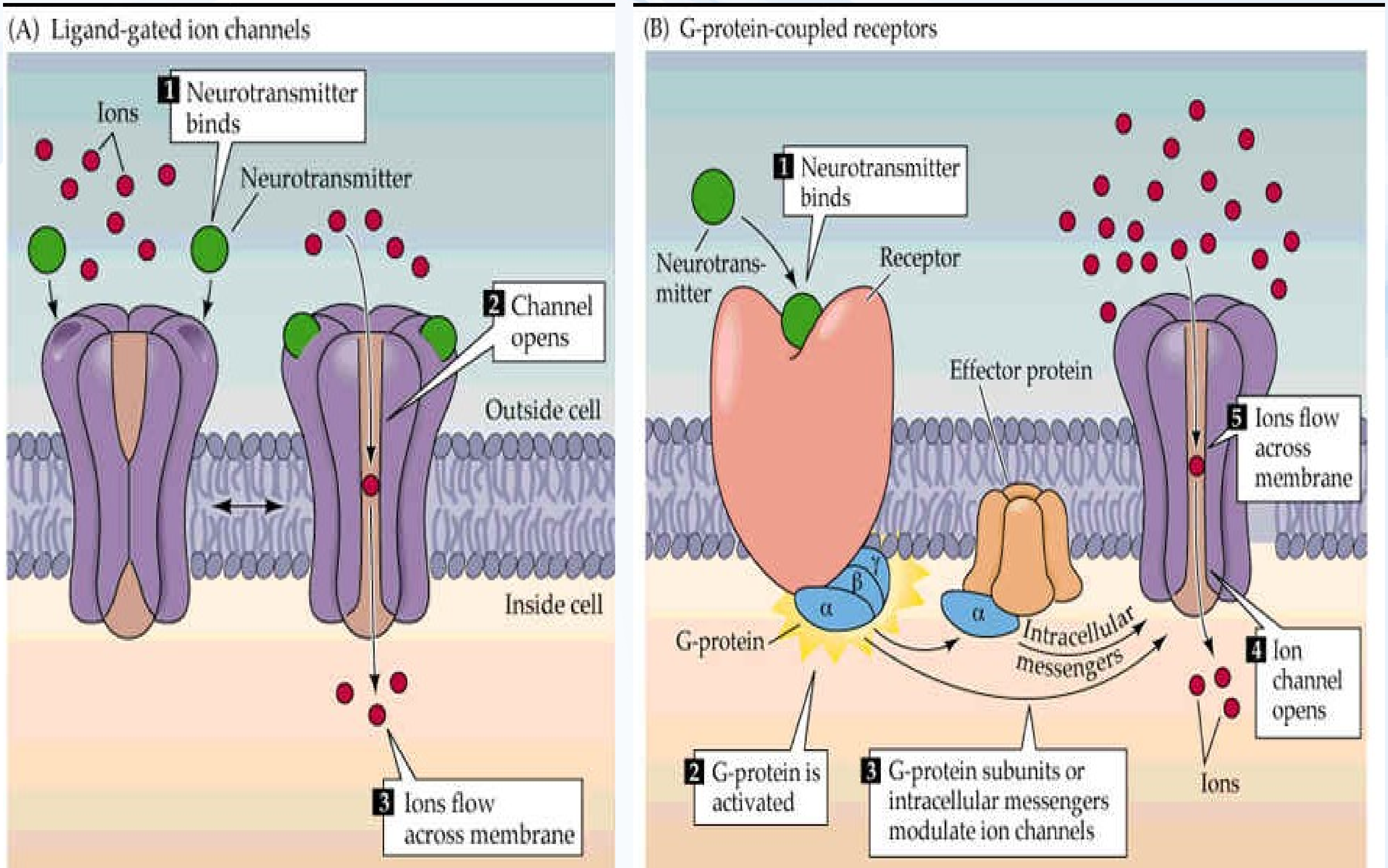
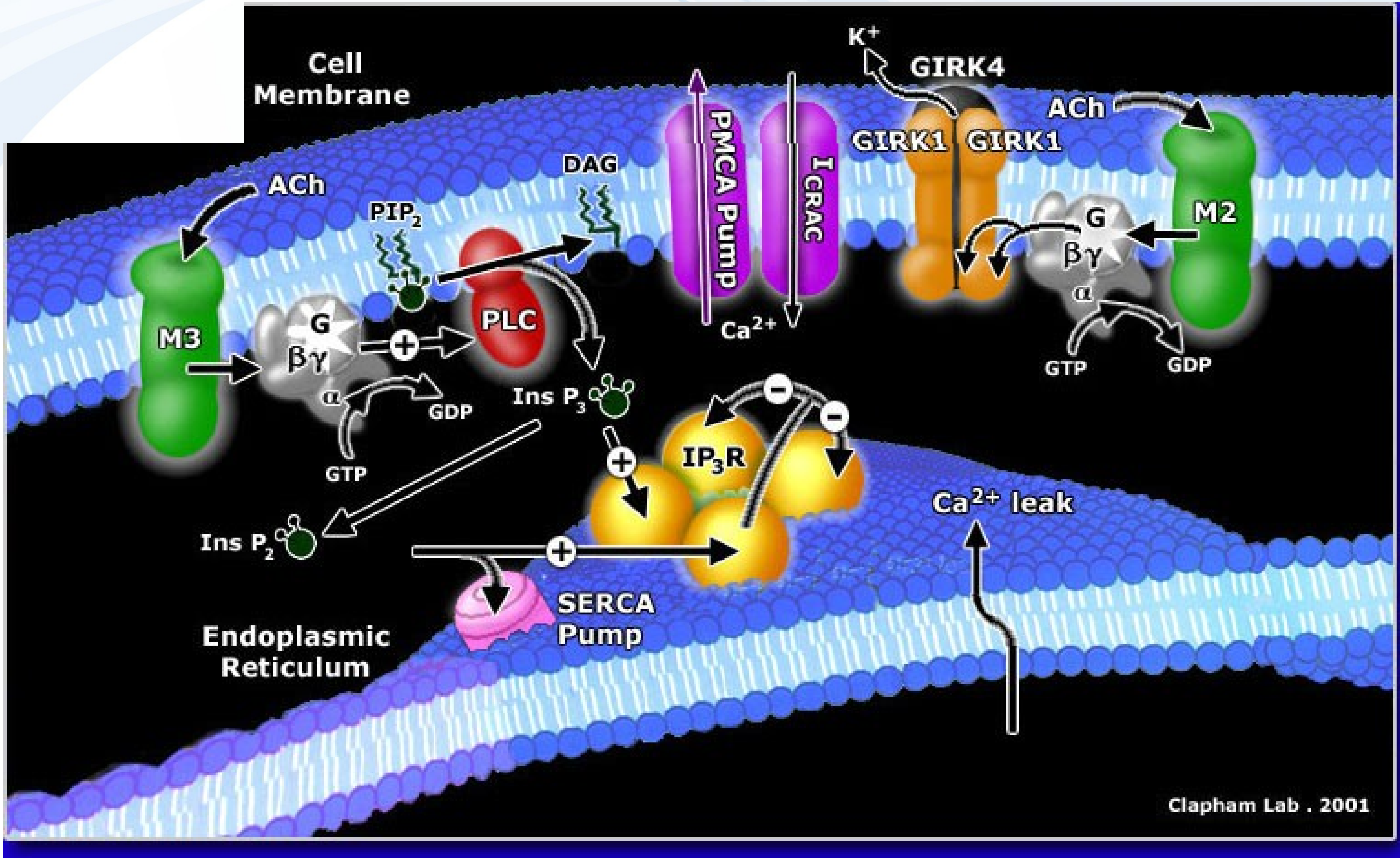
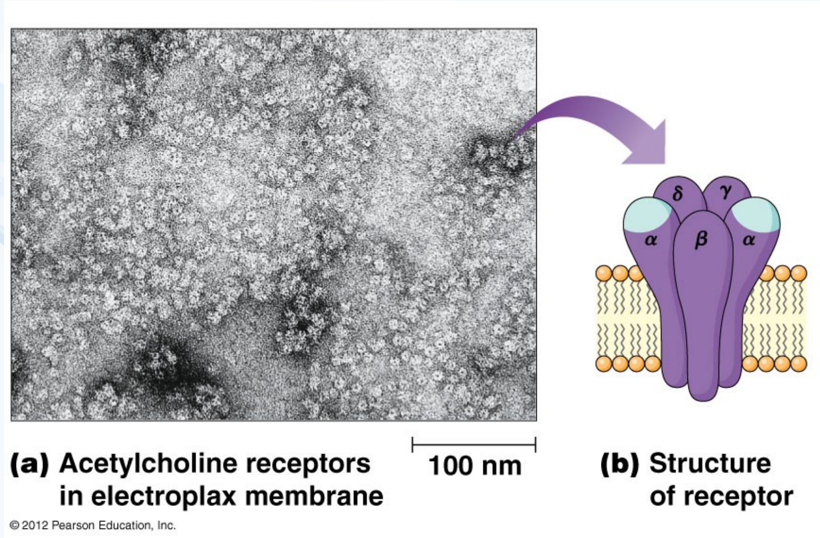
Principal types of channel activation

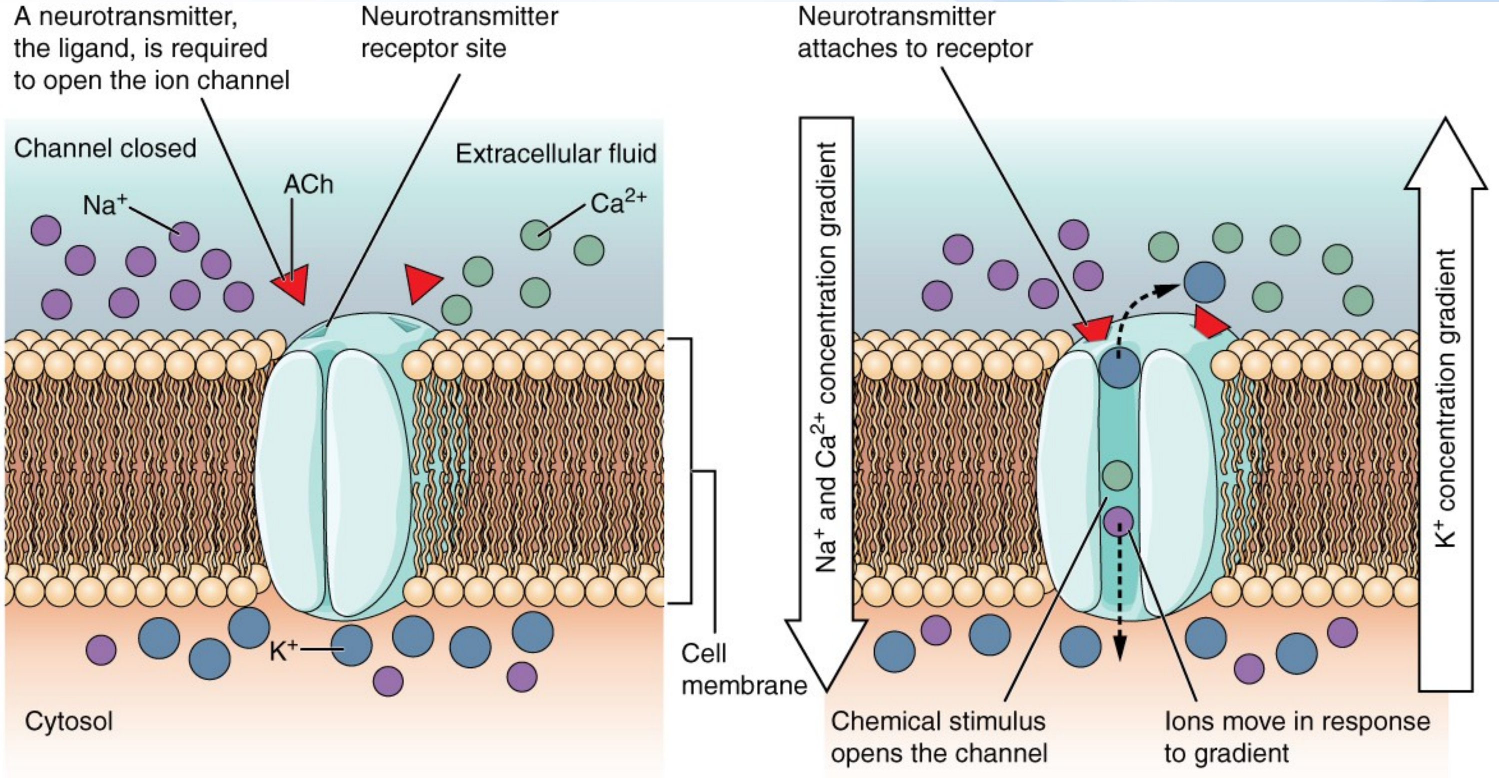


Various membrane channels - examples



Activation of AcChol receptors
→ Disruption
of membrane gradients





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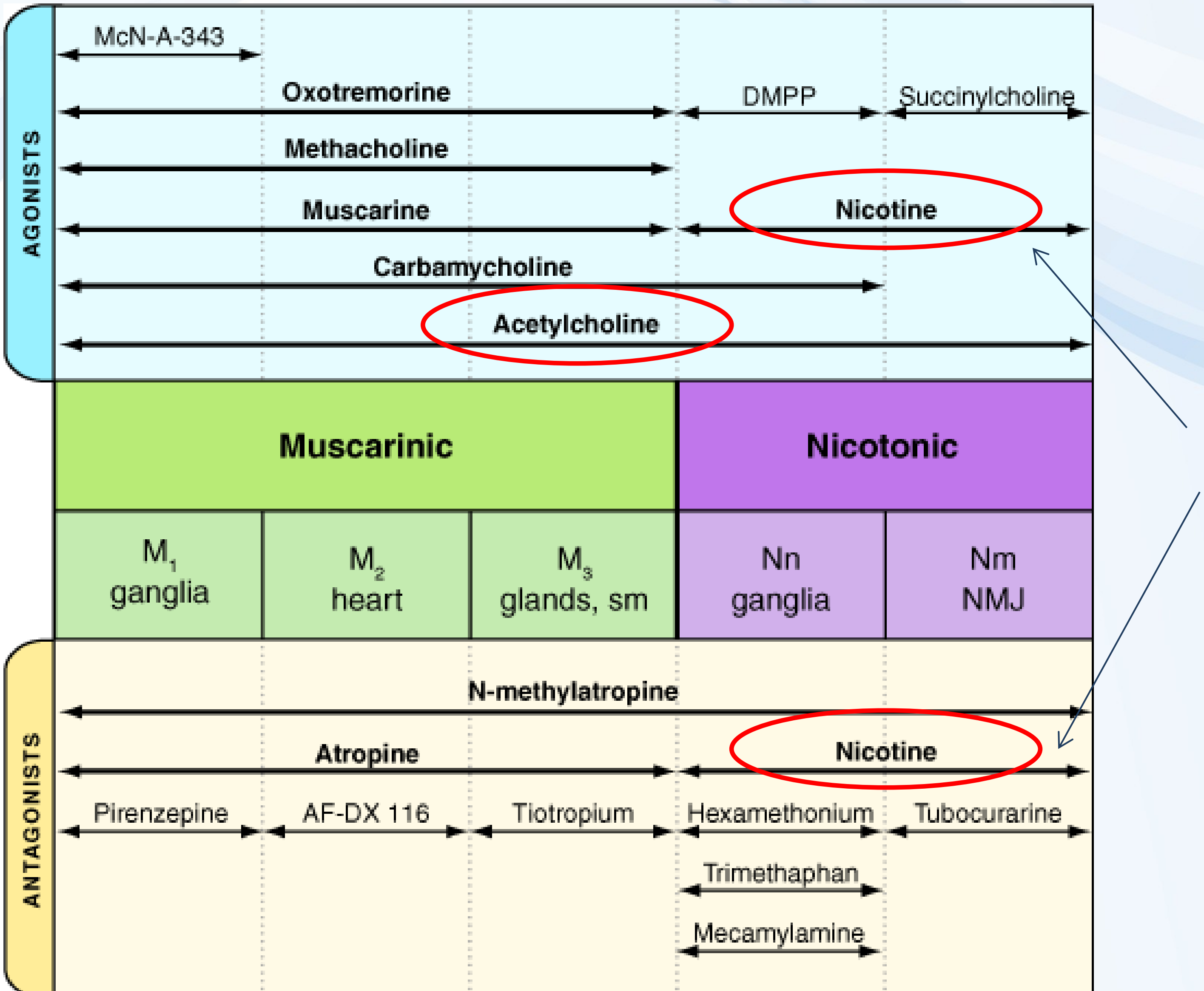
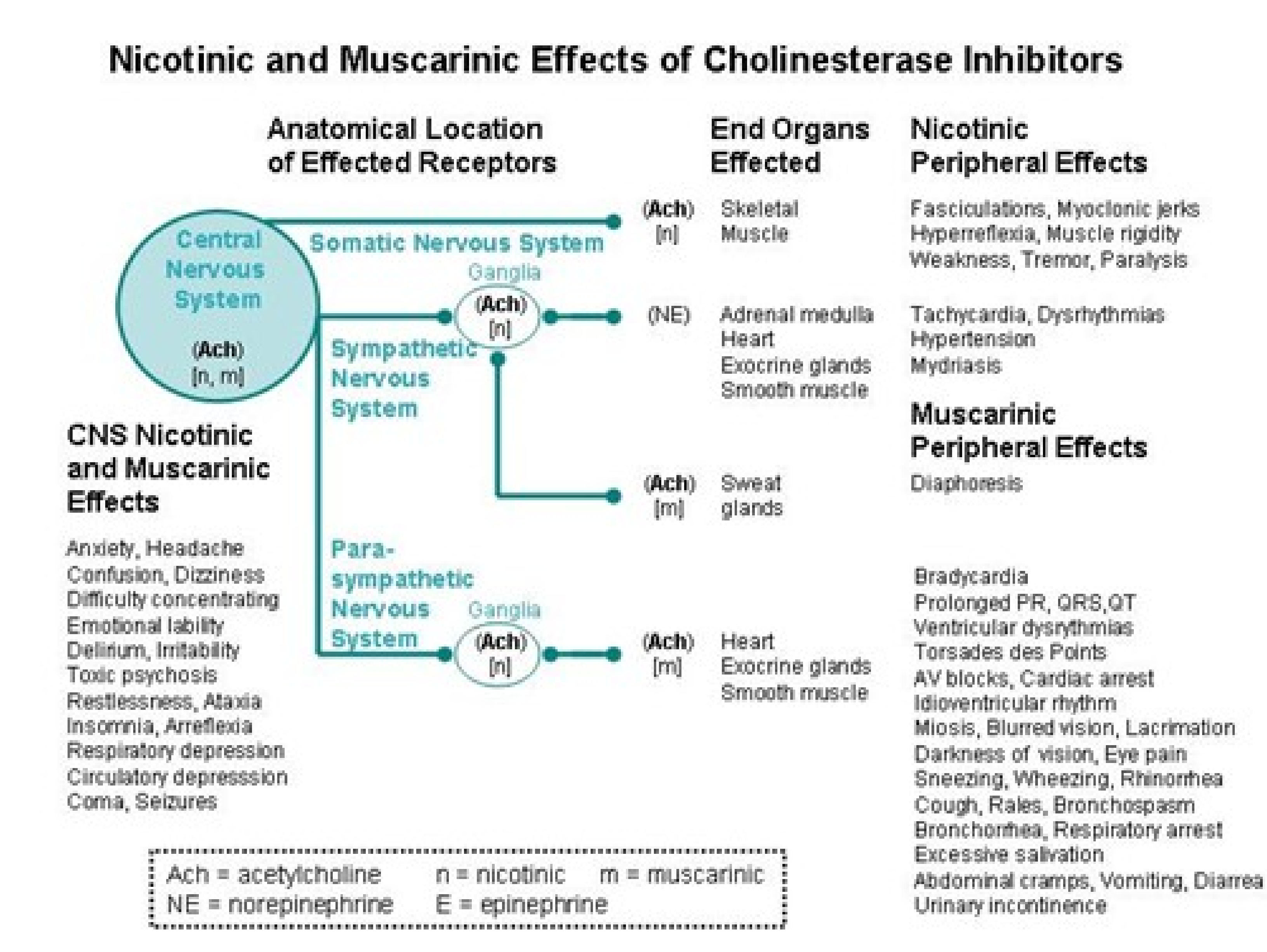
Activation / inhibition of ligand-gated channels



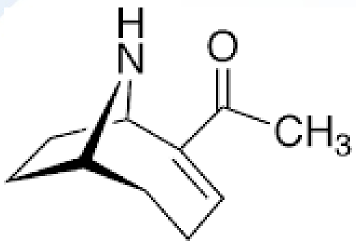
Concentration -dependent action

Activation / inhibition of ligand-gated channels

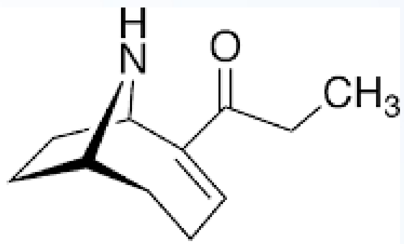


Environmentally relevant ion channel activators

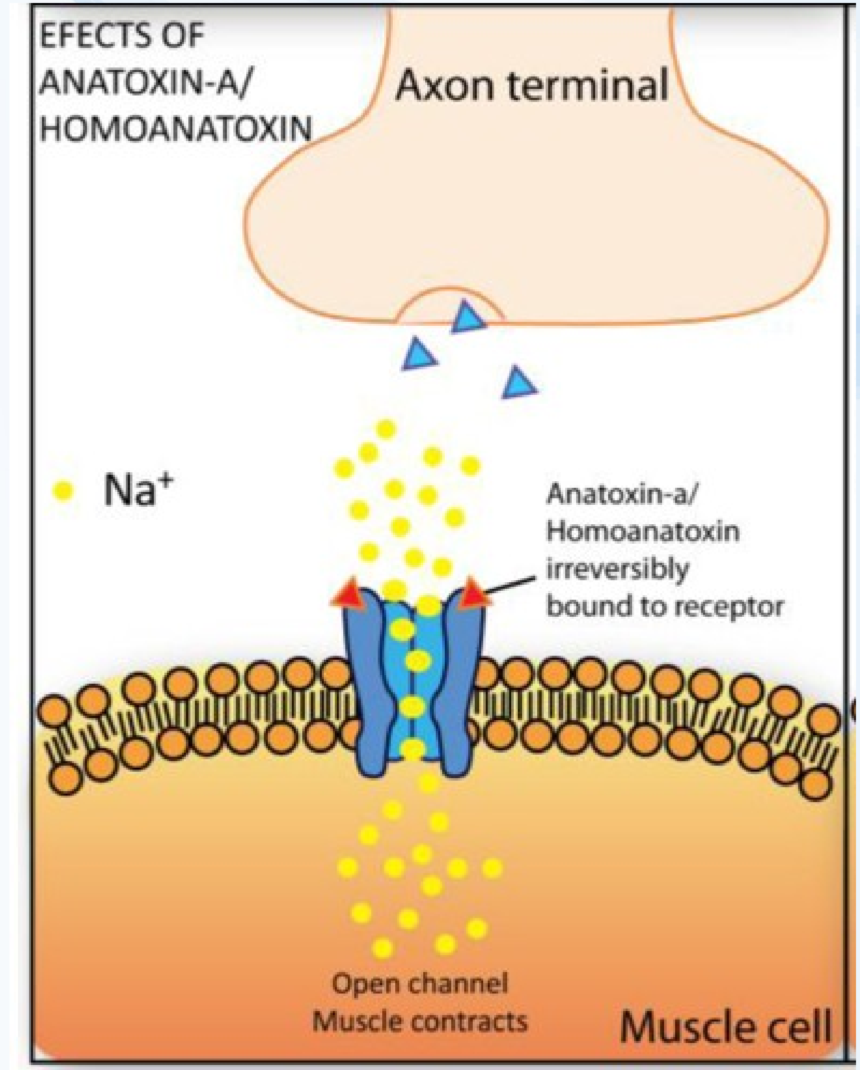
Neurotoxins (cyanobacterial)



Anatoxin-a



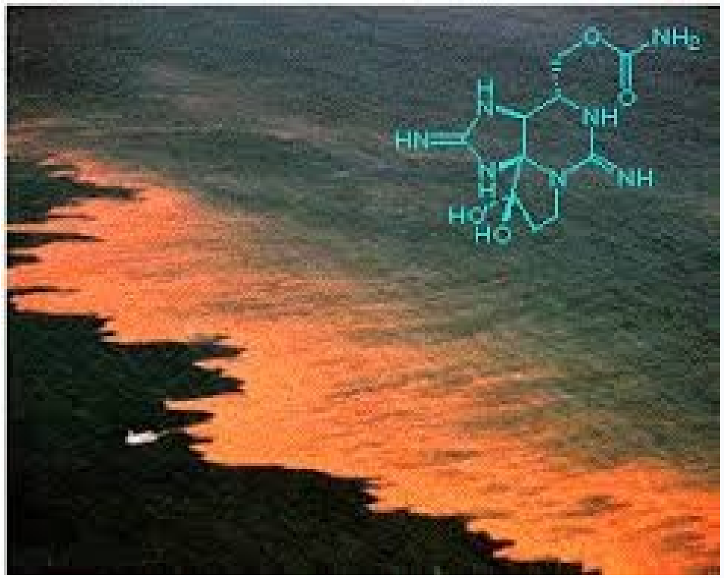
Homoanatoxin-a

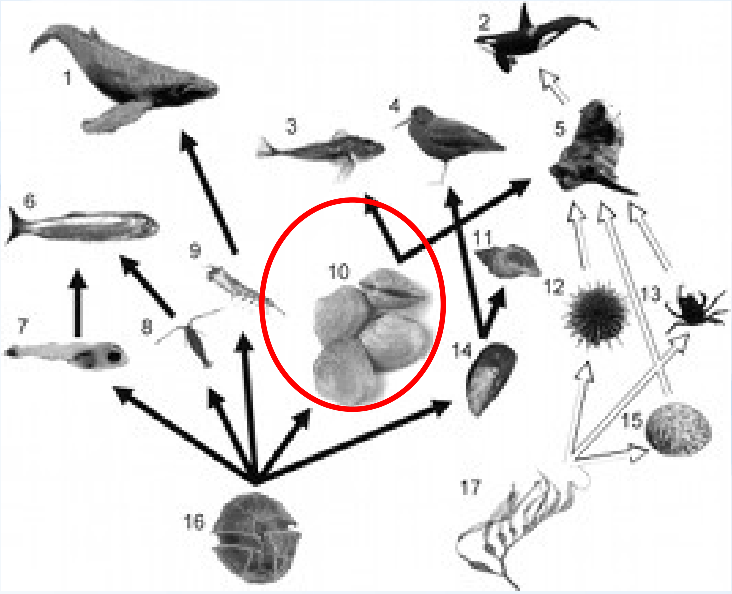


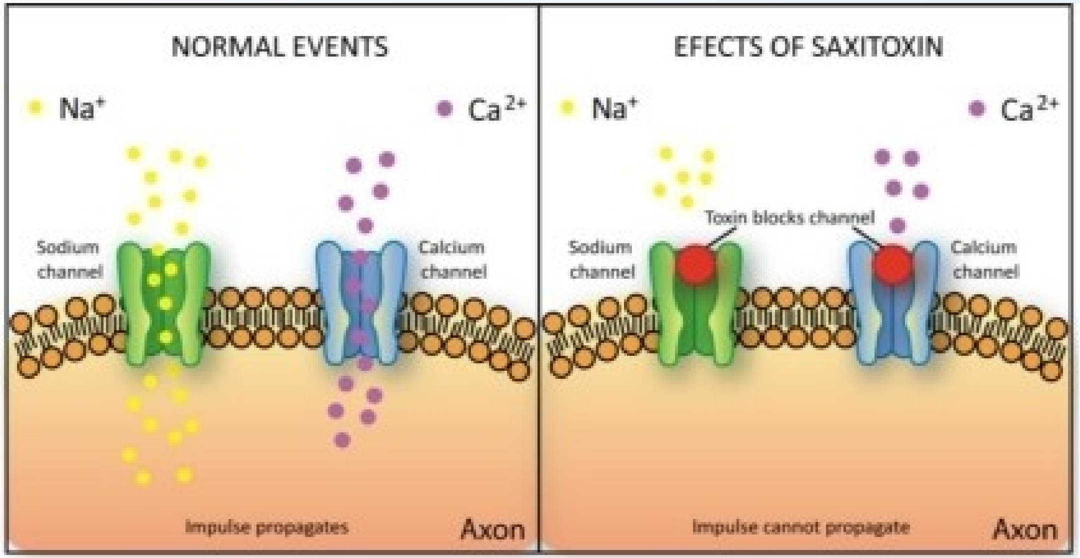
Environmentally relevant ion channel activators

SAXITOXINS

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







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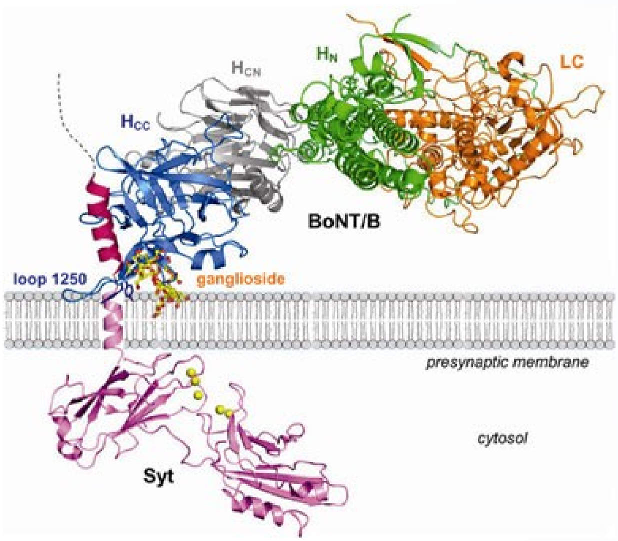
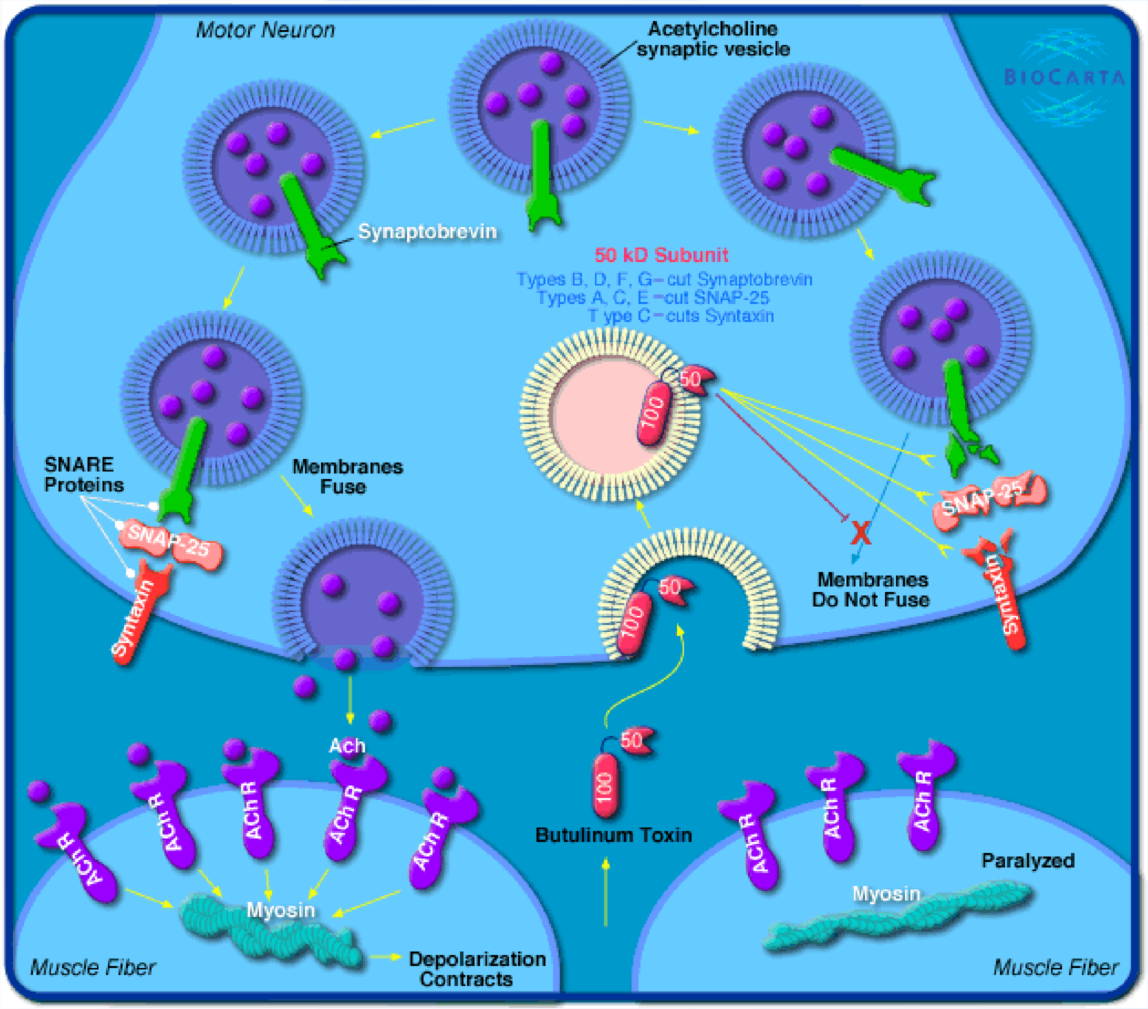
Botulinum and Tetanus toxins

(Clostridium botulinum, Clostridium tetani)

Toxins = enzymes - <u>proteases</u> (!)
- direct cleavage of proteins involved in vesicle formation
- selective inhibition of neutrotransmitter release

BOTULINISM
→ neurotoxicity (paralysis)





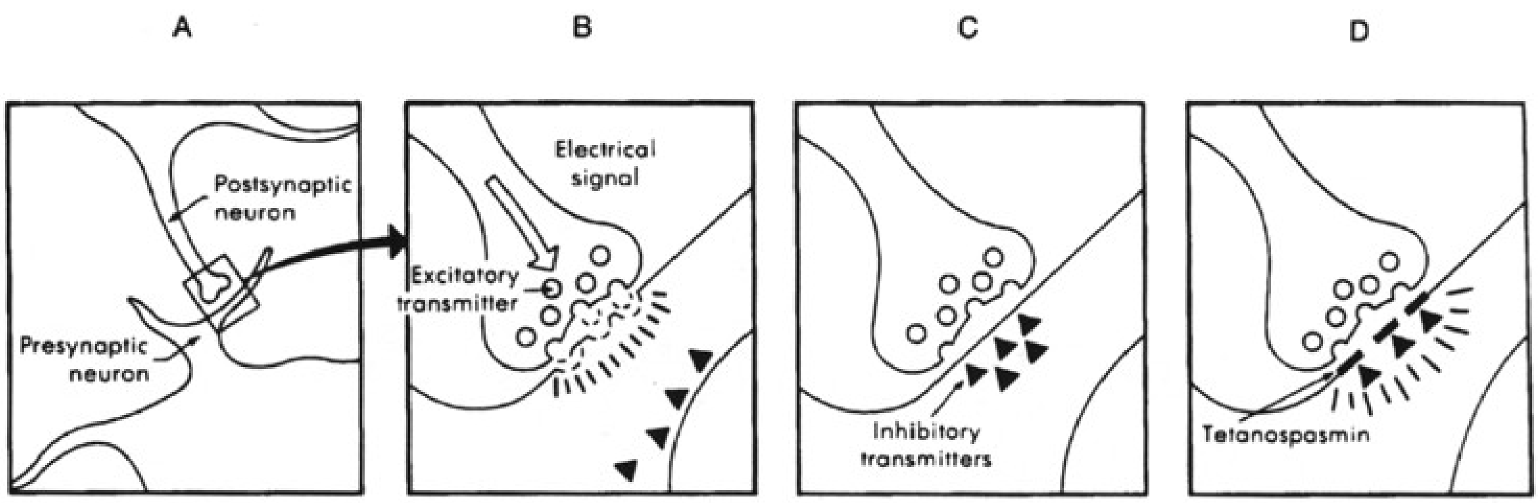
Botulinum and Tetanus toxins

(Clostridium botulinum, Clostridium tetani)

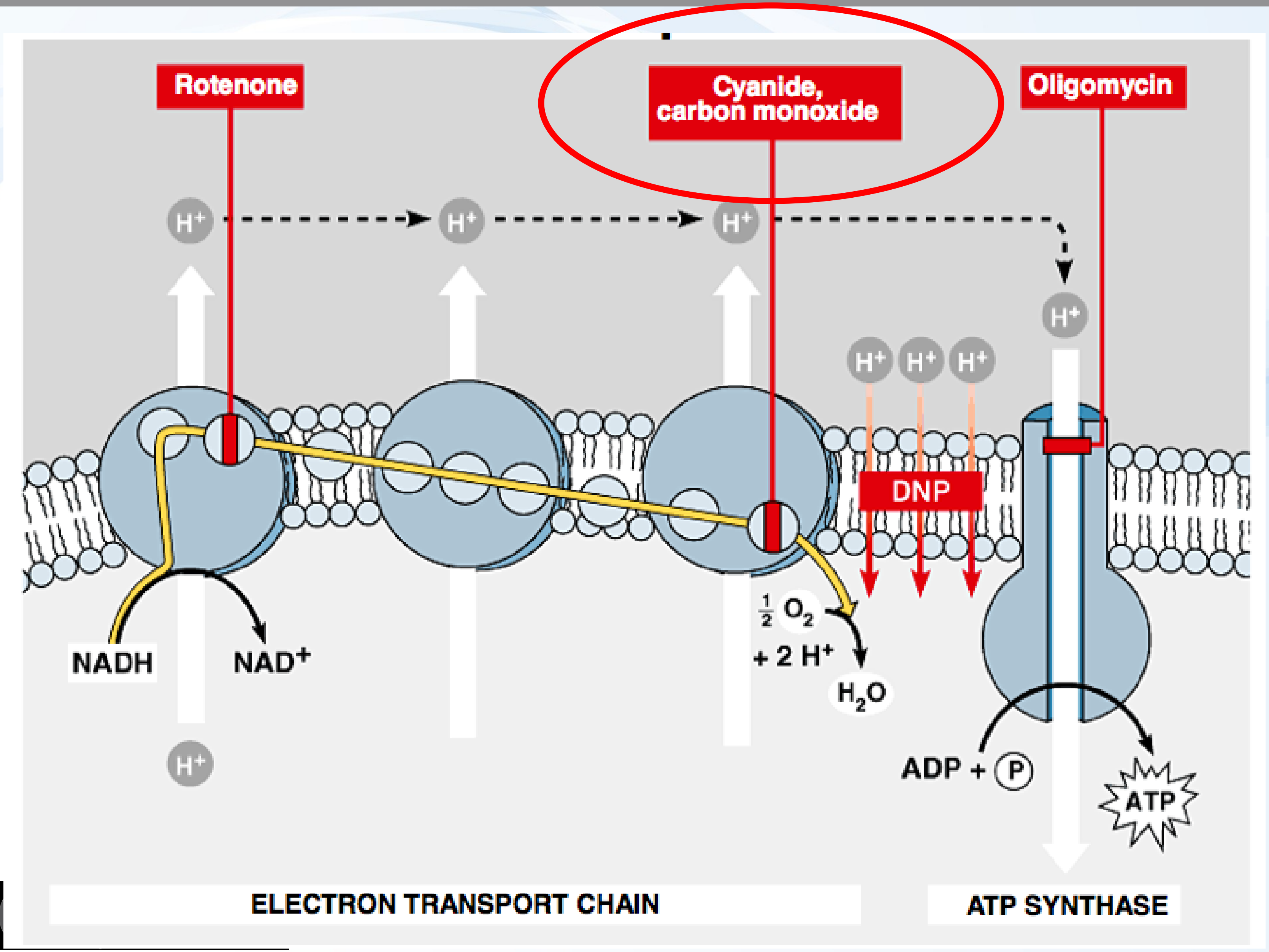
TETANUS TOXIN (tetanospasmin)

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

→ neurotoxicity – permanent contraction

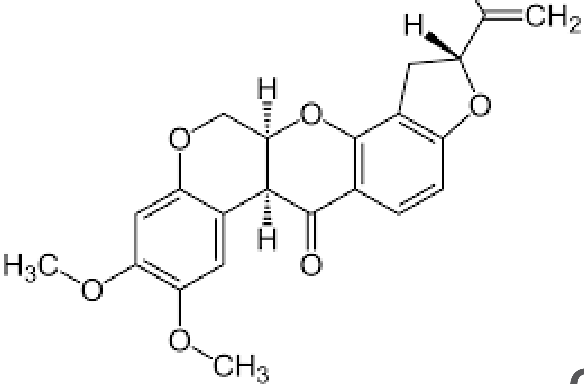


Gradient of H+ → ATP generation & its disruption

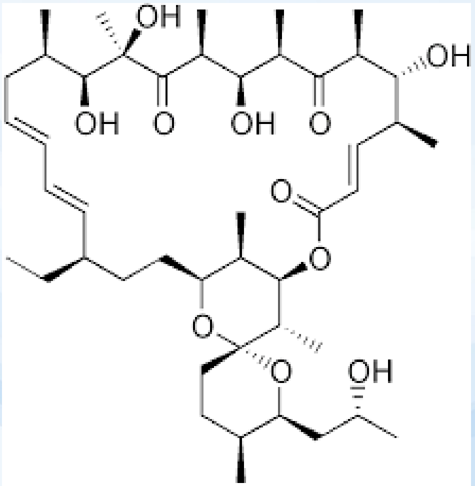


Gradient of H+ → ATP generation & its disruption

Rotenone



Oligomycin



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