Drugs affecting motor system

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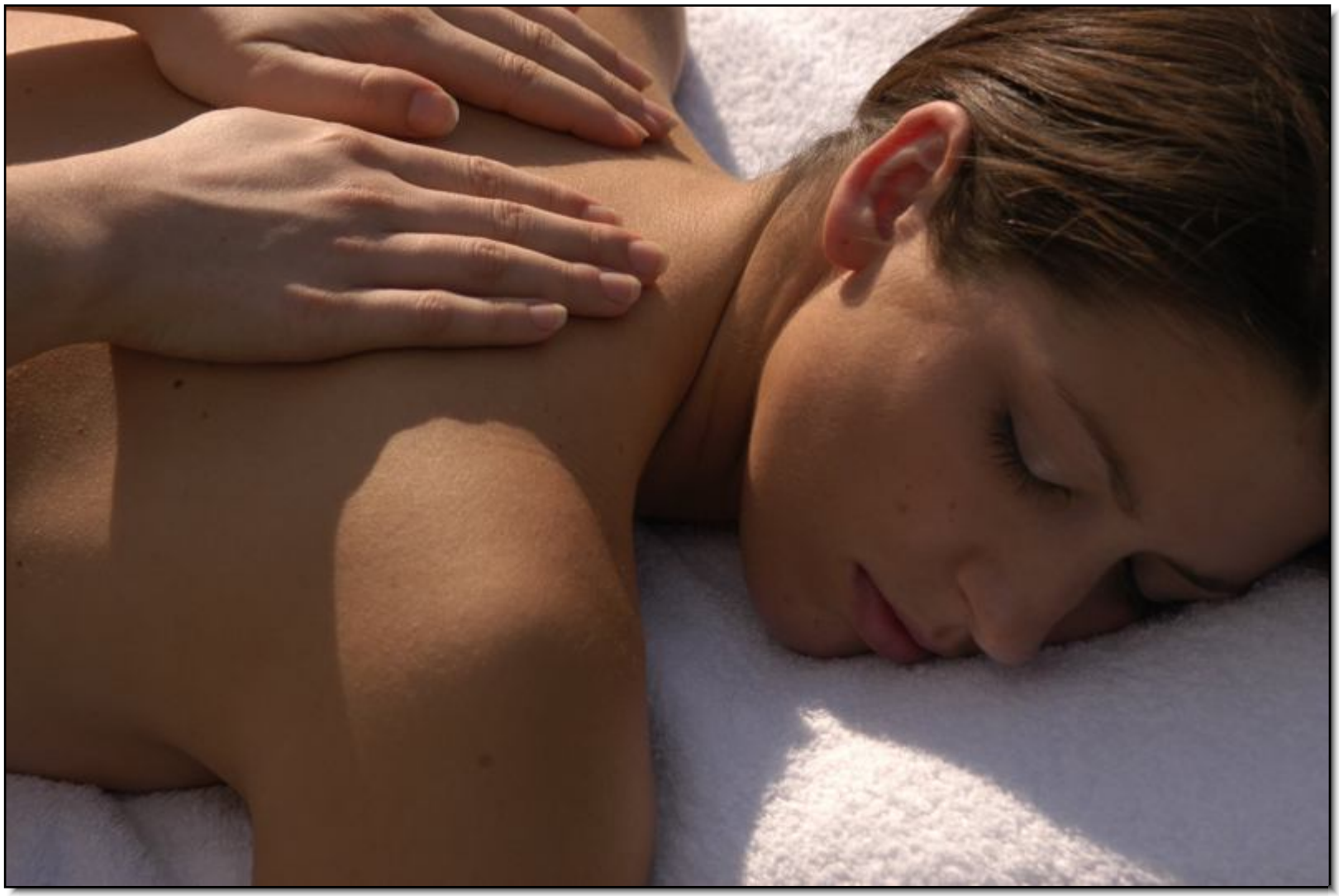
Outline

Muscle relaxation: mechanism of action

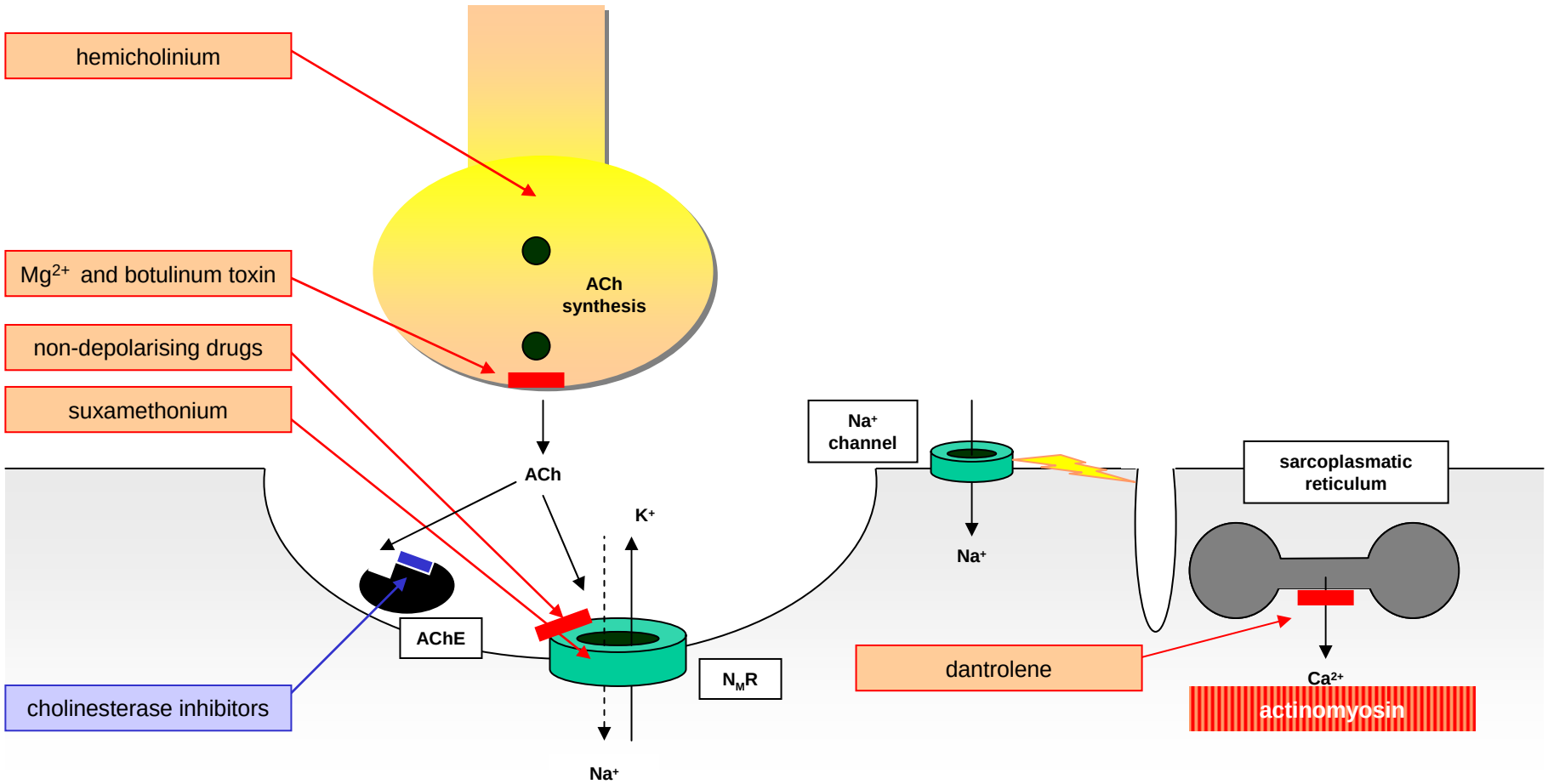


Muscle relaxation: mechanism of action

Indications and clinical use

- Muscle relaxing agents
  - intubation, surgery, bone reposition, intoxications, ventilation, electroconvulsions…
  - spasticity (MS, blepharospasms)
  - malignant hyperthermia, neuroleptic malignant sy
  - cosmetics (botulinum toxin)
- Drugs enhancing transmission
  - termination of relaxation
  - myastenia gravis
  - Lambert-Eaton syndrome

Physiology



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Outline

Presynaptic modulation

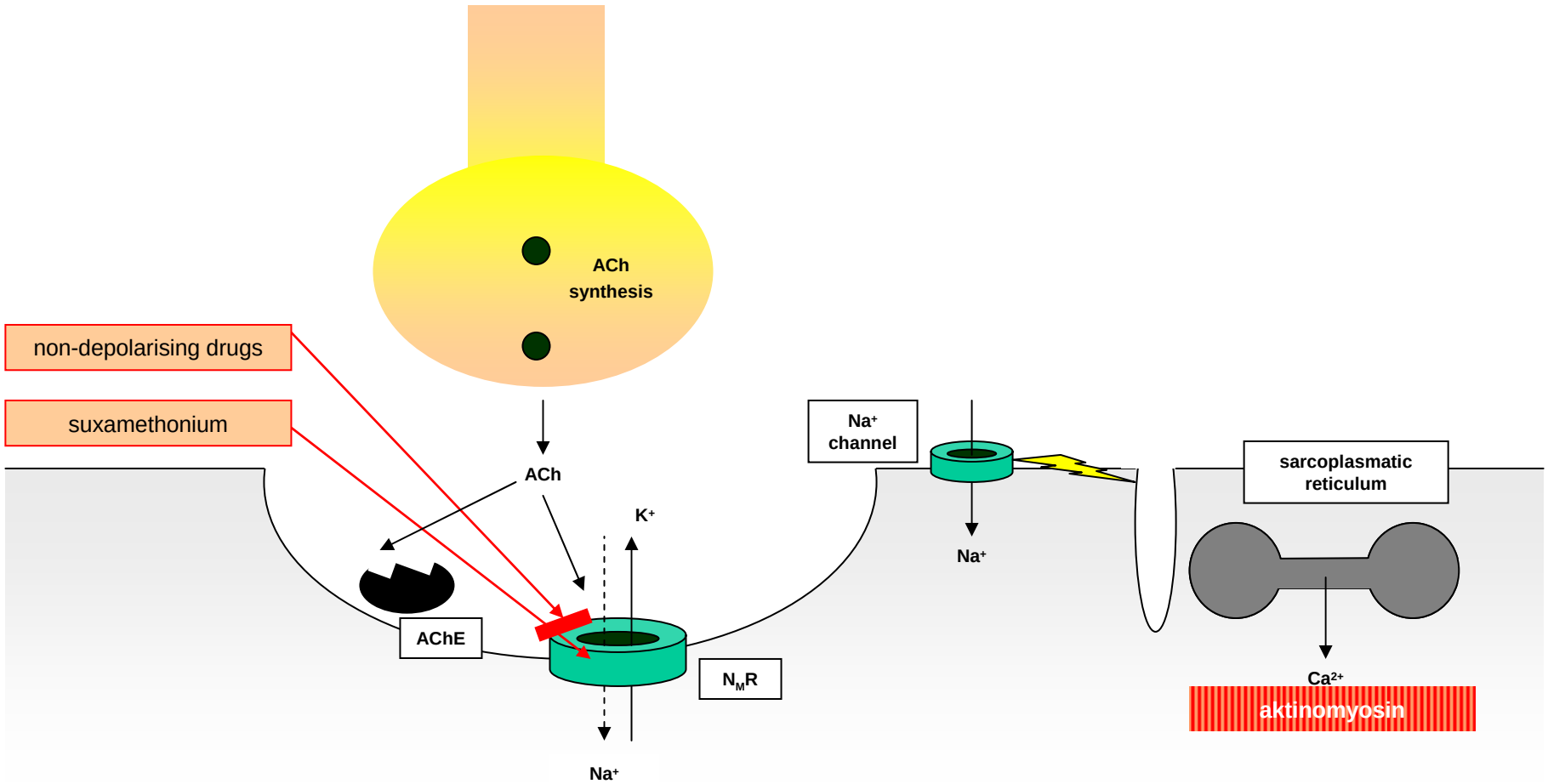
- Botulinum toxin
  - protein produced by Cl. botulinum
  - presynaptic blockade
  - blocks ACh release
  - inactivates SNAP 25
- β-bungarotoxin

Botulinum toxin: indications

- blepharospasm
  - spasm of m. orbicularis oculi
- local spasms
- cosmetics – wrinkles

Outline

Peripheral relaxants: physiology



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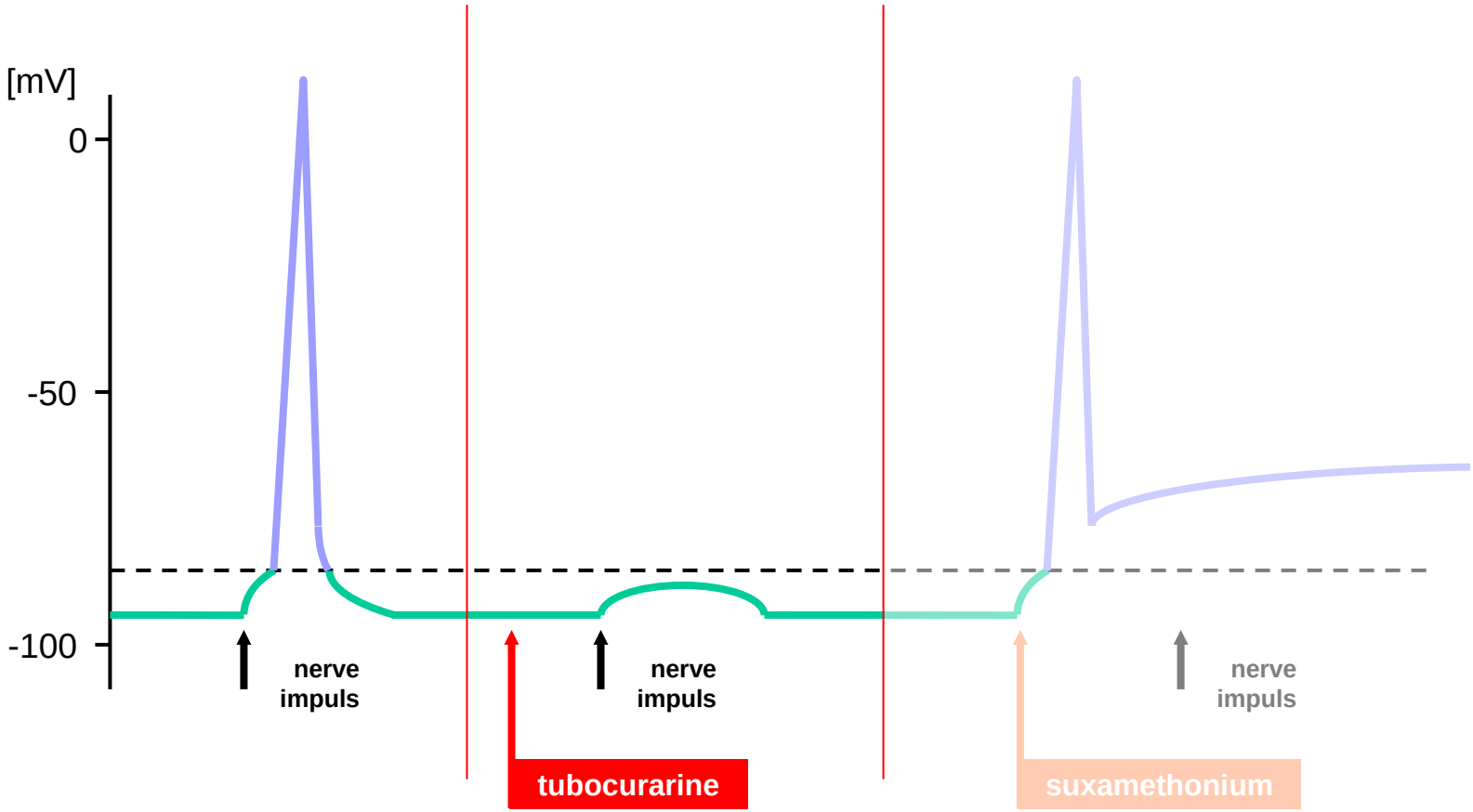
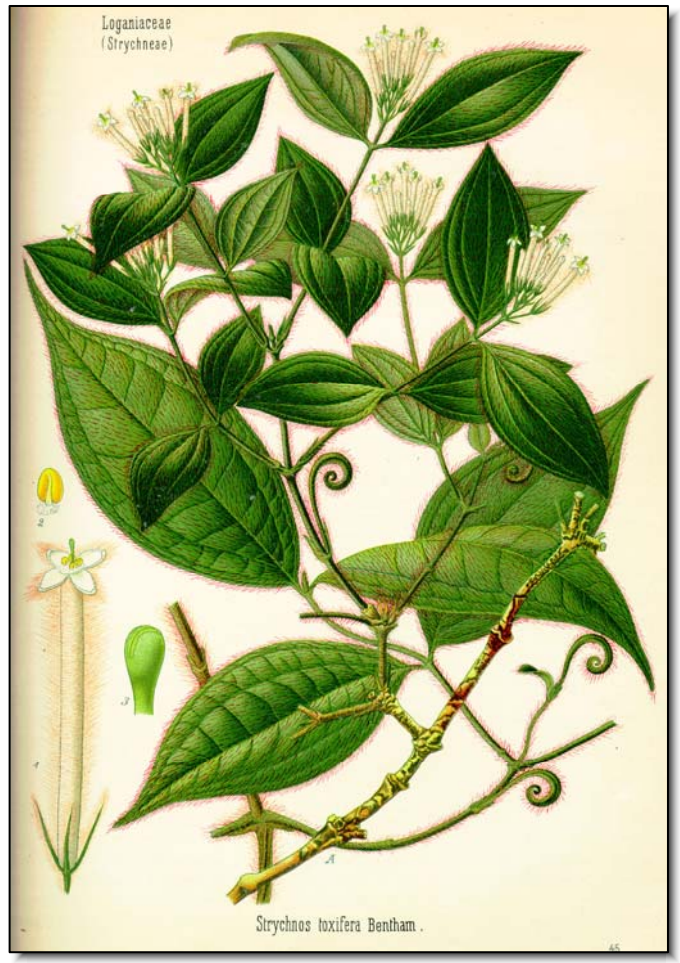
Peripheral relaxants: physiology

non-depolarising vs. depolarising



Non-depolarising drugs

- Drugs derived from plant alkaloids (Strychnos a Chondrodendron).
- First mentioned in 15th century, arrow poison used by South American Indians.
- Curaré = “poison” & “bird”

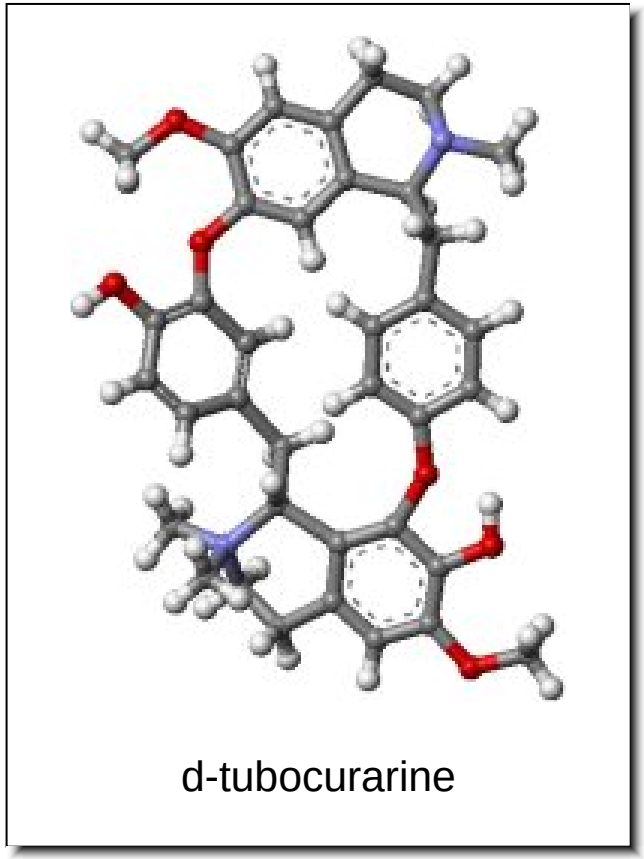


Non-depolarising drugs: history

- 15th century - Sir Walter Raleigh
  - described the use of curare by Indians
- 1803 - Alexander von Humboldt
  - brought curare to Europe
- 1825 - Charles Waterton
  - experiments on donkeys
- 1850 - Claude Bernard
  - experiments on frogs, mechanism of action
- 1912 - Rudolf Böhm and Arthur Läwen
  - "Über die Verbindung der Lokalanästhesie mit der Narkose, über hohe Extraduralanästhesie und epidurale Injektion anästhesierender Lösungen bei tabischen Magenkrisen"
- 1935 - Harold King
  - structure of d-tubocurarine
- 1957 - Daniel Bovet
  - Nobel Prize

Non-depolarising drugs: curare

- a mixture
  - main active substance
    d-tubocurarine and toxiferin
- tubocurare, kalabashcurare
- no absorption
  - quaternary ammonium
  - no IA
- fast acting



d-tubocurarine

Non-depolarising drugs

- mechanism: ACh-R blockage
- different susceptibility
  - intercostal muscles last
- no BBB crossing
  - no influence on consciousness
  - anesthesia then relaxation!
- direct histamine liberators, hypotension

Non-depolarising drugs

- pancuronium
  - 5× more potent than tubocurarine, faster
  - lasts for about 1 hour, excreted by kidneys
- vecuronium
  - the same, faster, shorter
- rocuronium
  - extremely fast, medium acting
- atracurium
  - Hoffman elimination kinetics, fast
- mivacurium
  - suitable for long term relaxation (ventilation)
- *BW 785 U*
  - *fast and short*

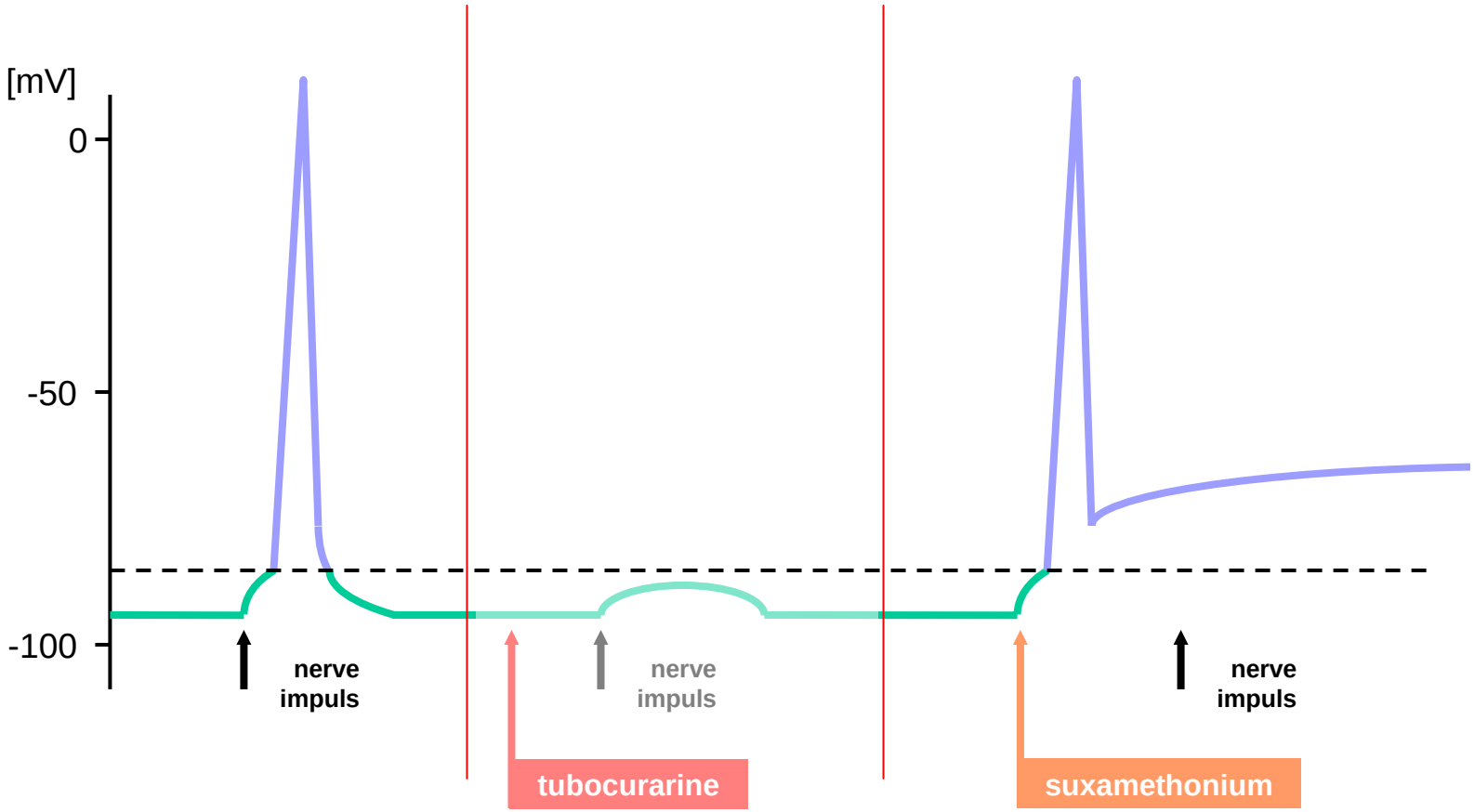
"Breathe deeply and count to three."

Non-depolarising drugs: side effects

- Death
  - therapeutic use of lethal doses
- Histamine liberation
- Hypotension
  - esp. patients treated for hypertension
- Ganglion blockade

Peripheral relaxants: physiology

non-depolarising vs. **depolarising**



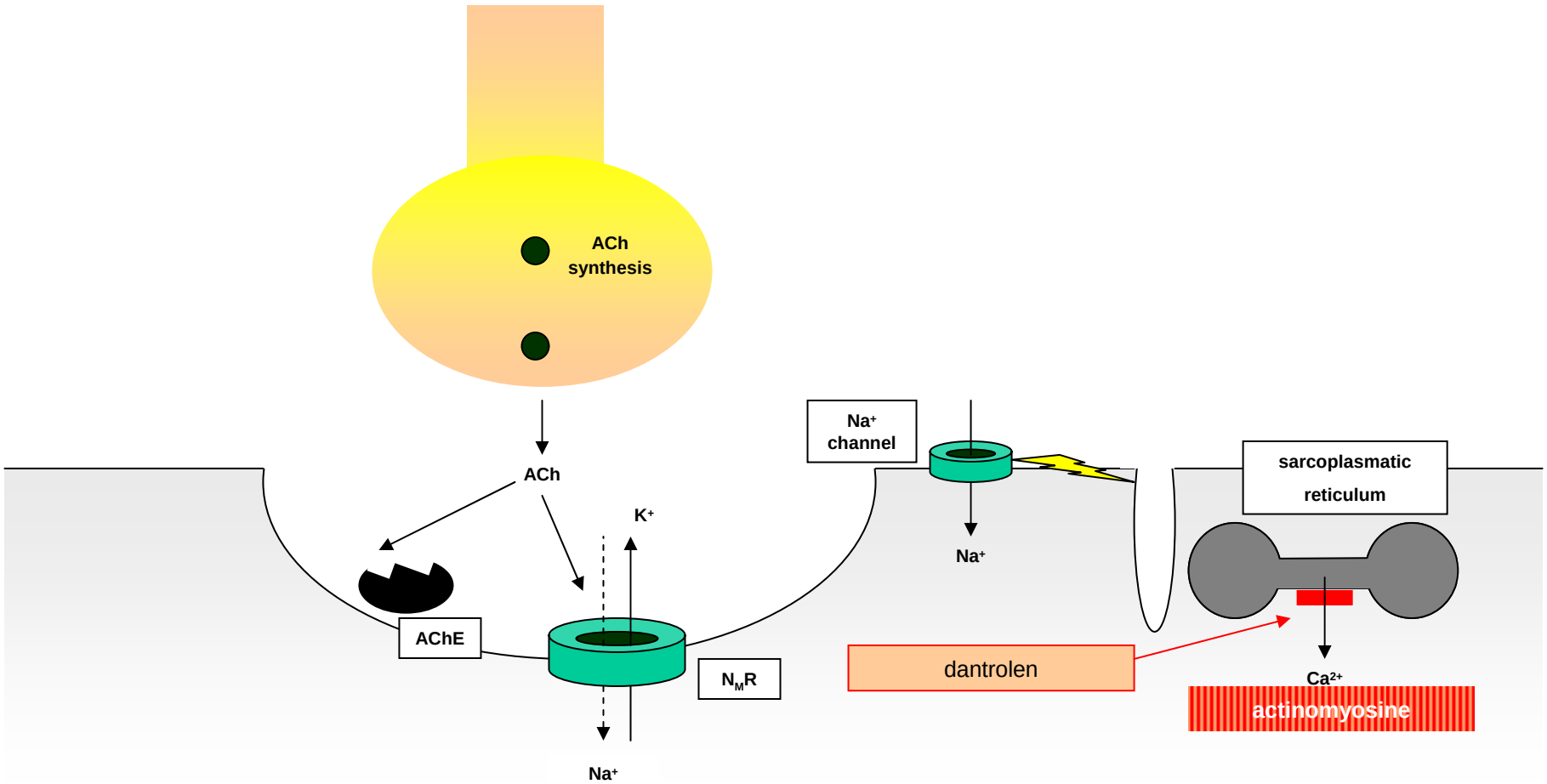
Peripheral relaxants: depolarising

- Both affinity *and* IA
- Suxamethonium
  - two ACh molecules linked
  - slow degradation = long depolarisation
- Use: short term relaxation
  - less used today

Peripheral relaxants: suxamethonium

- Side effects:
  - muscle pain
  - effect on ganglia, vegetative symptoms
  - hyperkalemia
  - increased intraocular pressure
  - dangerous in combinations (halothane)
    - malignant hyperthermia

Peripheral relaxants: direct relaxants



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Peripheral relaxants: direct relaxants

- Dantrolene
  - blocks Ca release from sarcoplasmic reticulum
  - decreases strength of contraction
  - used in spastic states - MS, cerebral or spinal trauma
  - treatment of malignant hyperthermia

Peripheral relaxants: malignant hyperthermia

Malignant hyperthemia

Peripheral relaxants: malignant hyperthermia

Peripheral relaxants: malignant hyperthermia

Peripheral relaxants: malignant hyperthermia

Peripheral relaxants: malignant hyperthermia

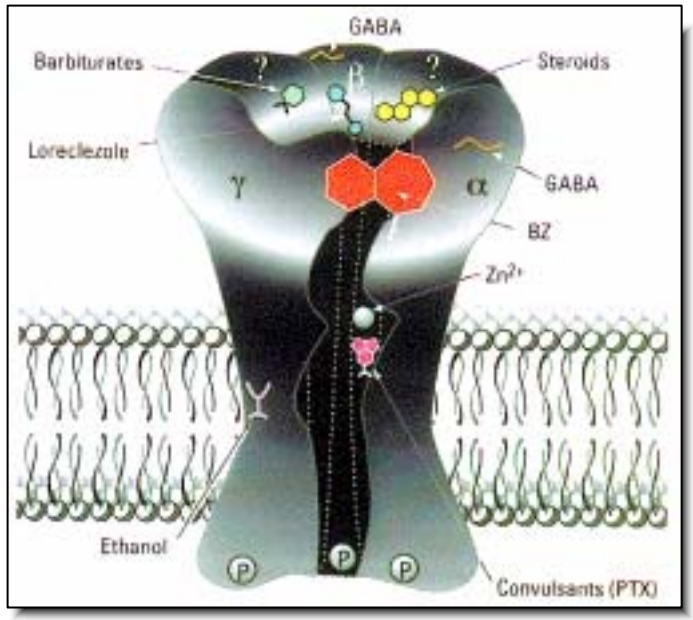
Peripheral relaxants: malignant hyperthermia

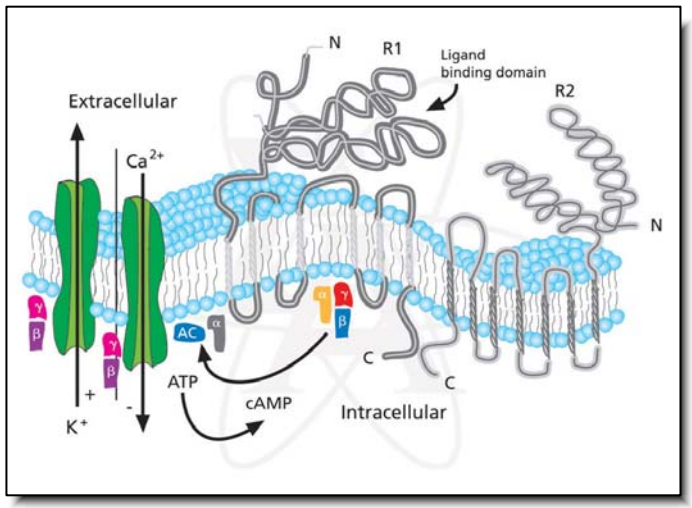
Outline

Central relaxants: mechanism of action

- Spinal cord
- GABA agonists

  (gama aminobutyric acid)
- $GABA_{A/B}$ receptors



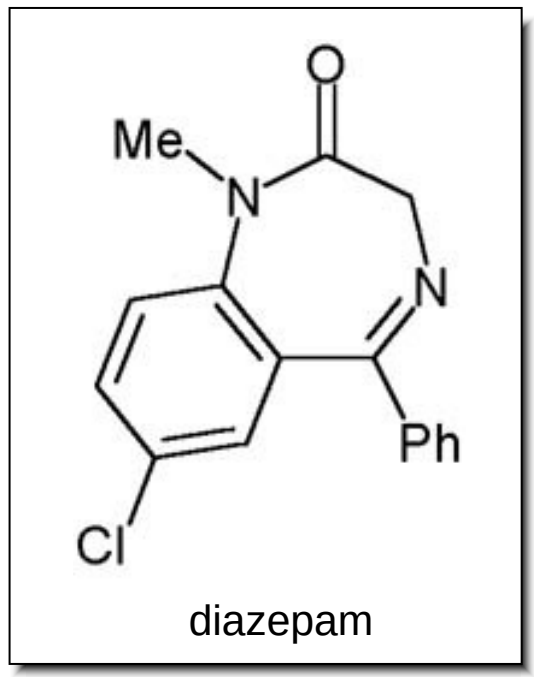


Central relaxants: indications

- central spasticity
  - multiple sclerosis
  - cerebrospinal trauma
  - paralysis
  - arthritis spasticity
  - chronic back pain

Central relaxants: benzodiazepines

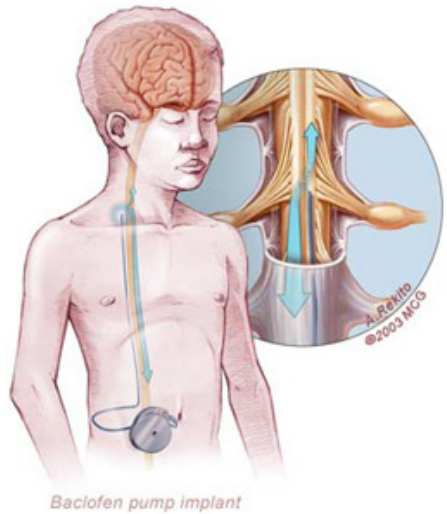
- covered already in psychopharmacology
- allosteric effect on $GABA_A$-R
- main agents:
  - diazepam
  - tetrazepam



diazepam

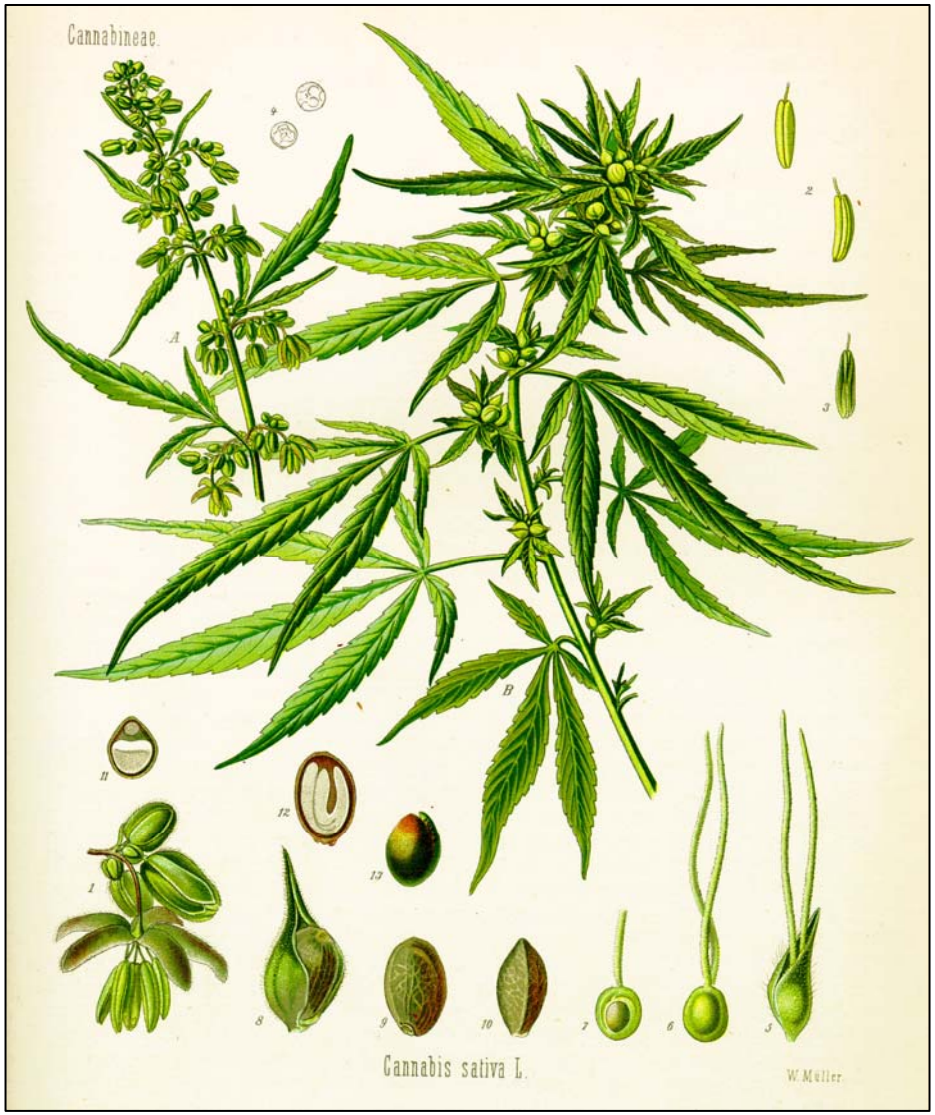
Central relaxants: tizanidine, baclofen and others

- tizanidine (*Sirdalud*®)
  - mechanism not clear yet
- baclofen (*Lioresal*®)
  - beta-(p-chlorphenyl)-gamma-aminobutyric acid
  - direct agonist at $GABA_B$
- mephenoxalone (*Dorsiflex*®)
- guaifenesin (*Guajacuran*®)



Baclofen pump implant

Other drugs



Outline

Acetylcholinesterase inhibitors

- covered in Parasympathetic system
- syntostigmine, physostigmine, neostigmine, …
  - termination of relaxation
    - combination with atropine
  - Myastenia gravis treatment
    - decrease in ACh-R numbers
  - Lambert-Eaton syndrome

thank you for your attention