Veterinary Bioscience: Cells to Systems

VETS30029 / VETS90121

THE UNIVERSITY OF MELBOURNE

Nicotinic Receptors and the Neuromuscular Junction

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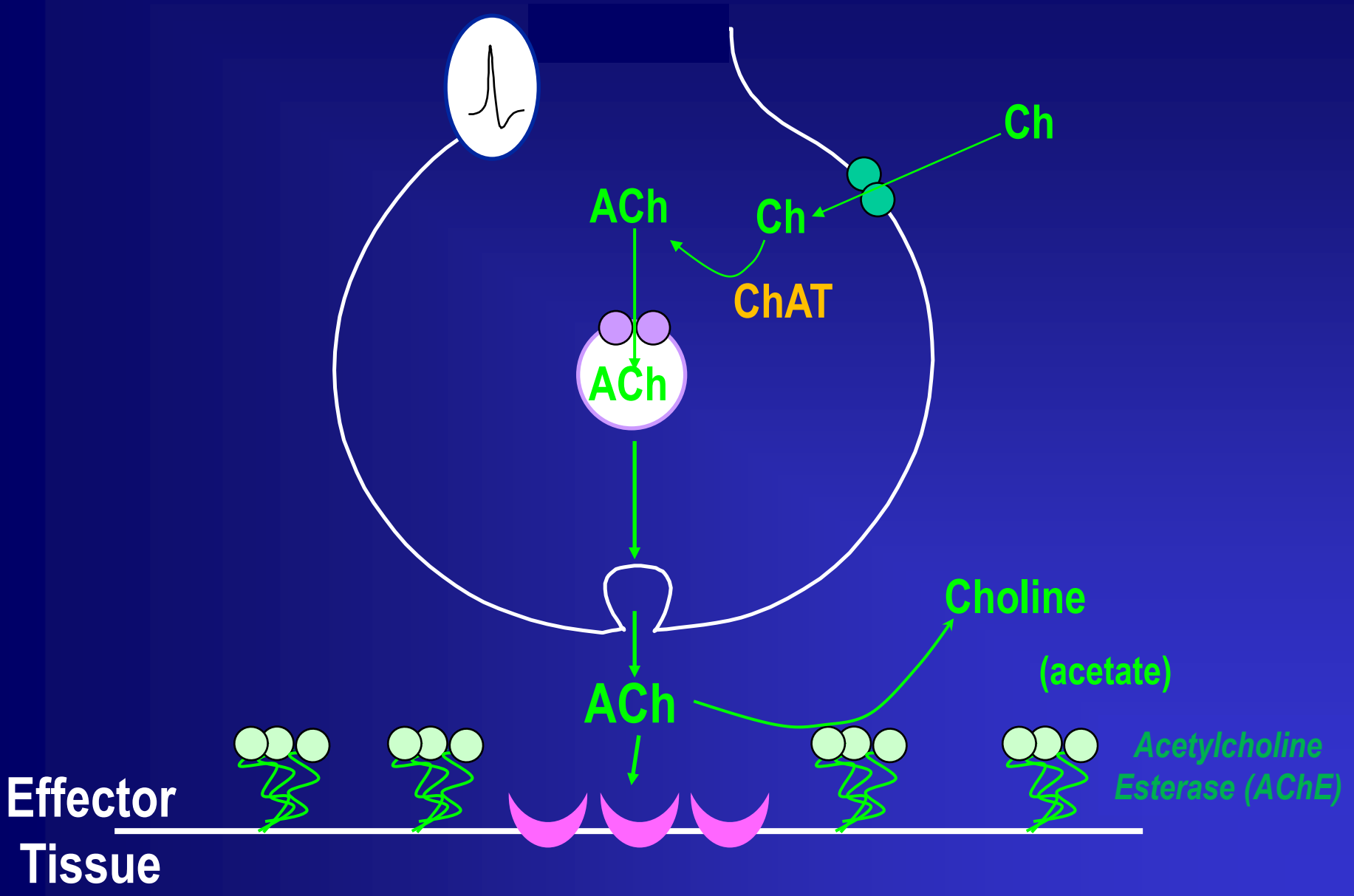
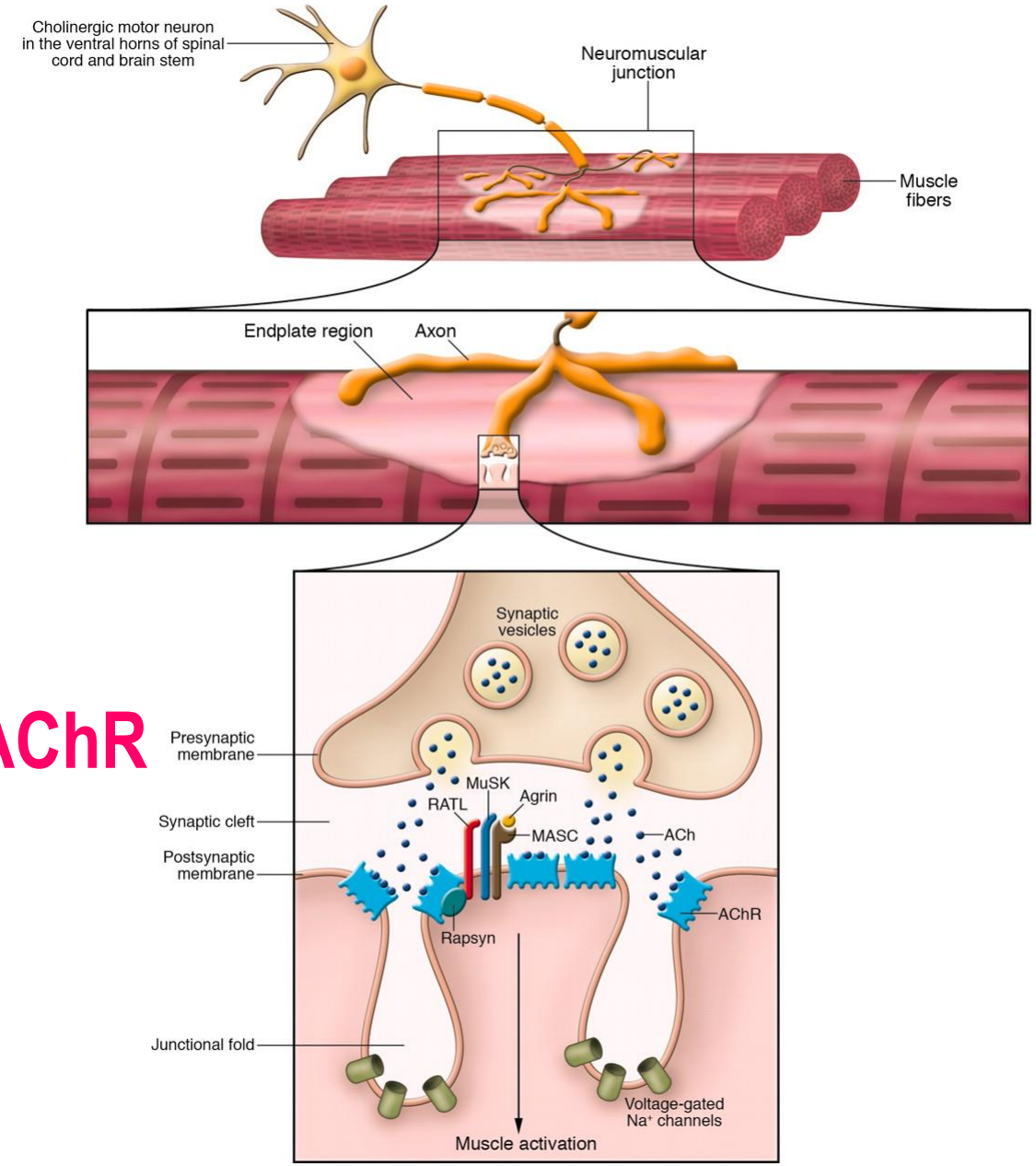
Cholinergic Nerves



The Neuromuscular Junction

Transmitter- ACh

Receptor- Nicotinic AChR



Conti-Fine et al, 2006.
JCI 116;2843

Nicotinic ACh Receptor

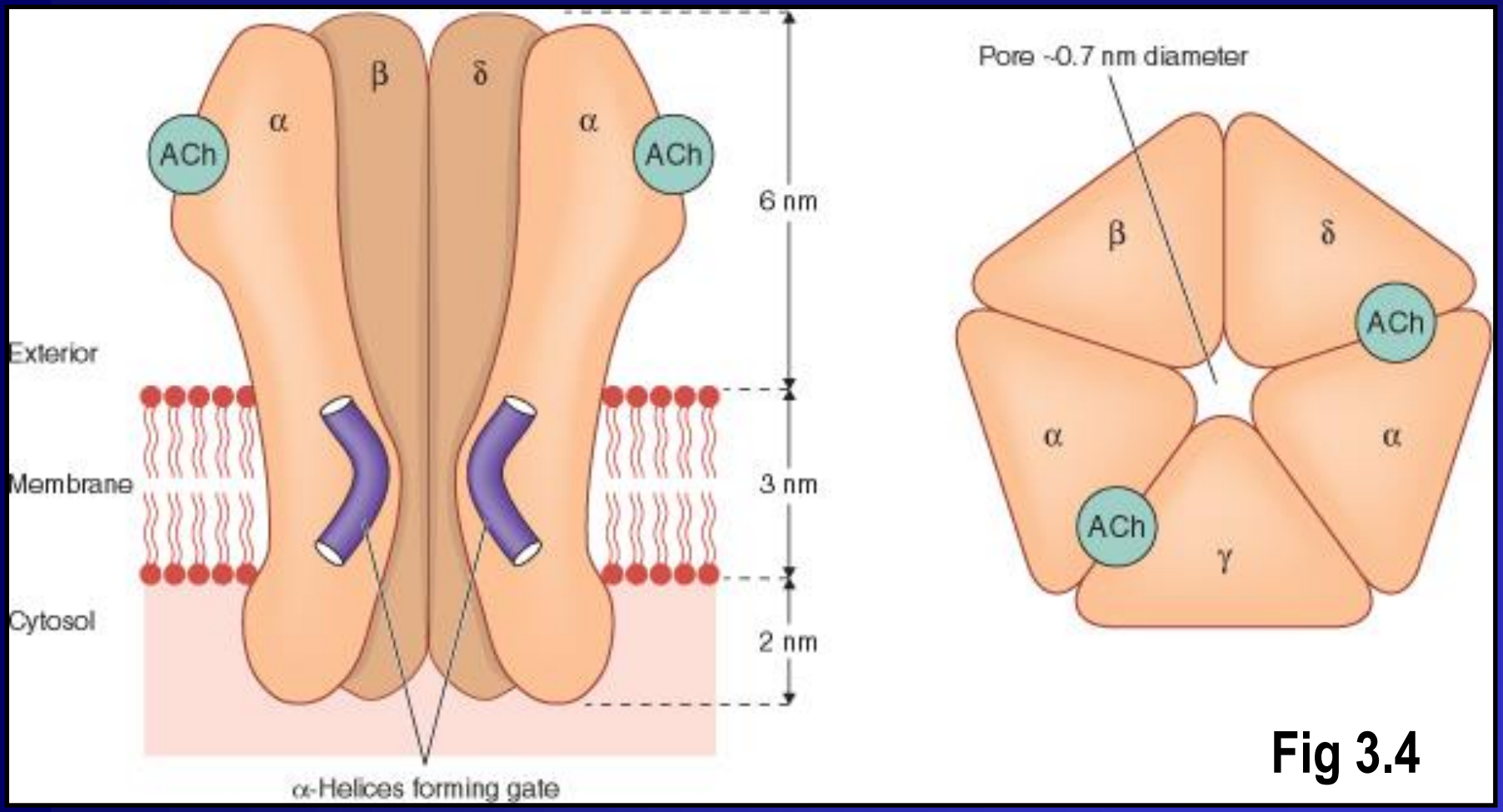
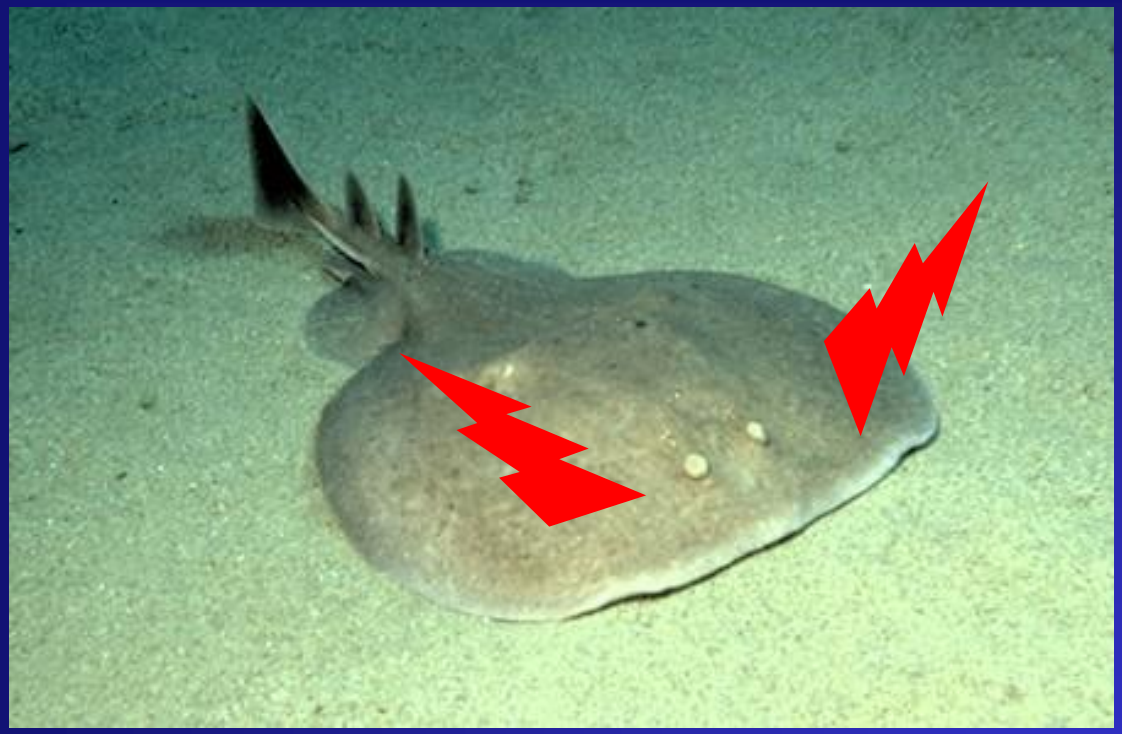


Fig 3.4

Rang et al; Pharmacology 6th Edition; Churchill Livingstone, 2007

The Nicotinic ACh Receptor



Torpedo marmorata

The Nicotinic ACh Receptor

Miyazawa et al, 2003. Nature 423;949.

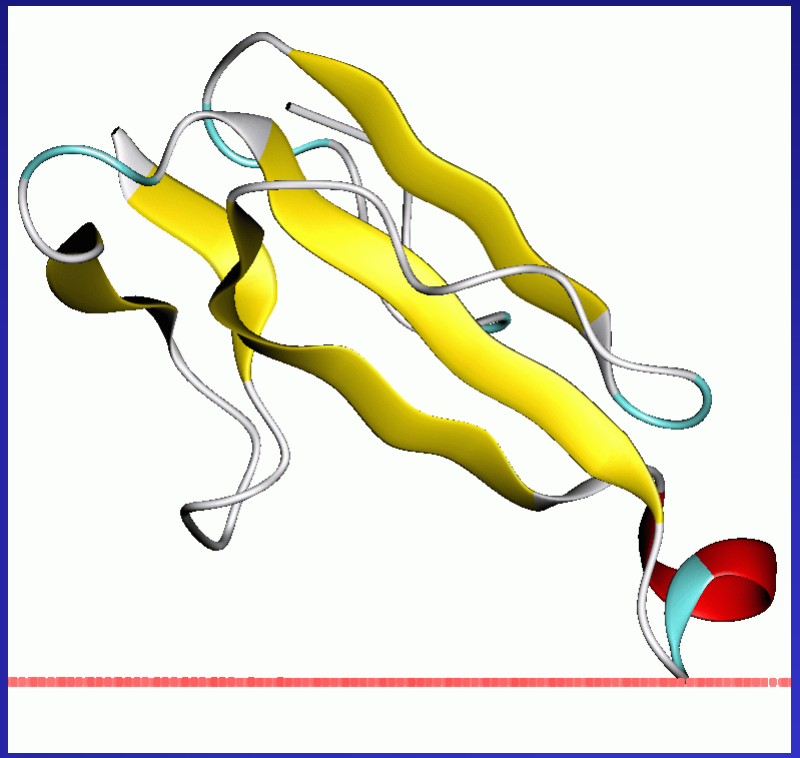
The Nicotinic ACh Receptor

Bungarus multicinctus

Taiwanese banded krait

α-Bungarotoxin

Binds with high affinity and blocks NicR

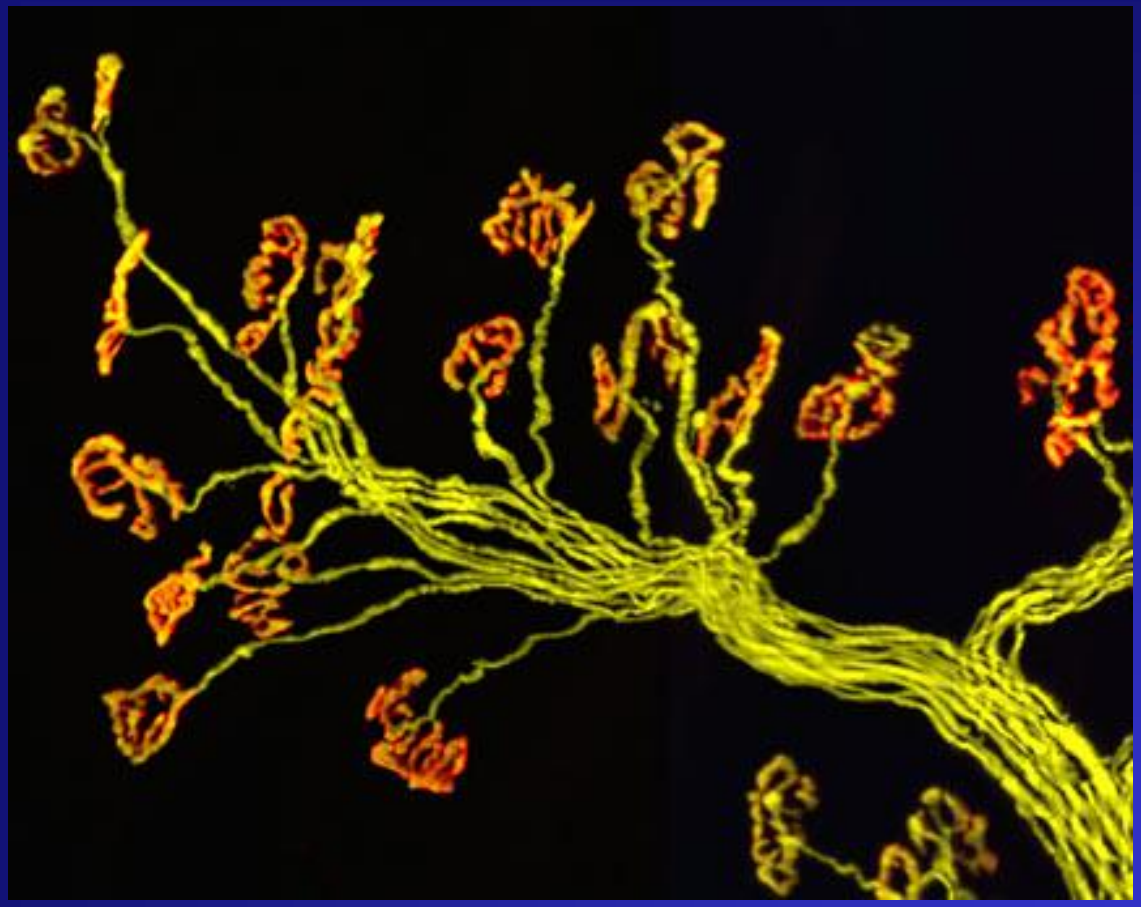


http://opm.phar.umich.edu/protein.php?pdbid=1hc9

α-Bungarotoxin

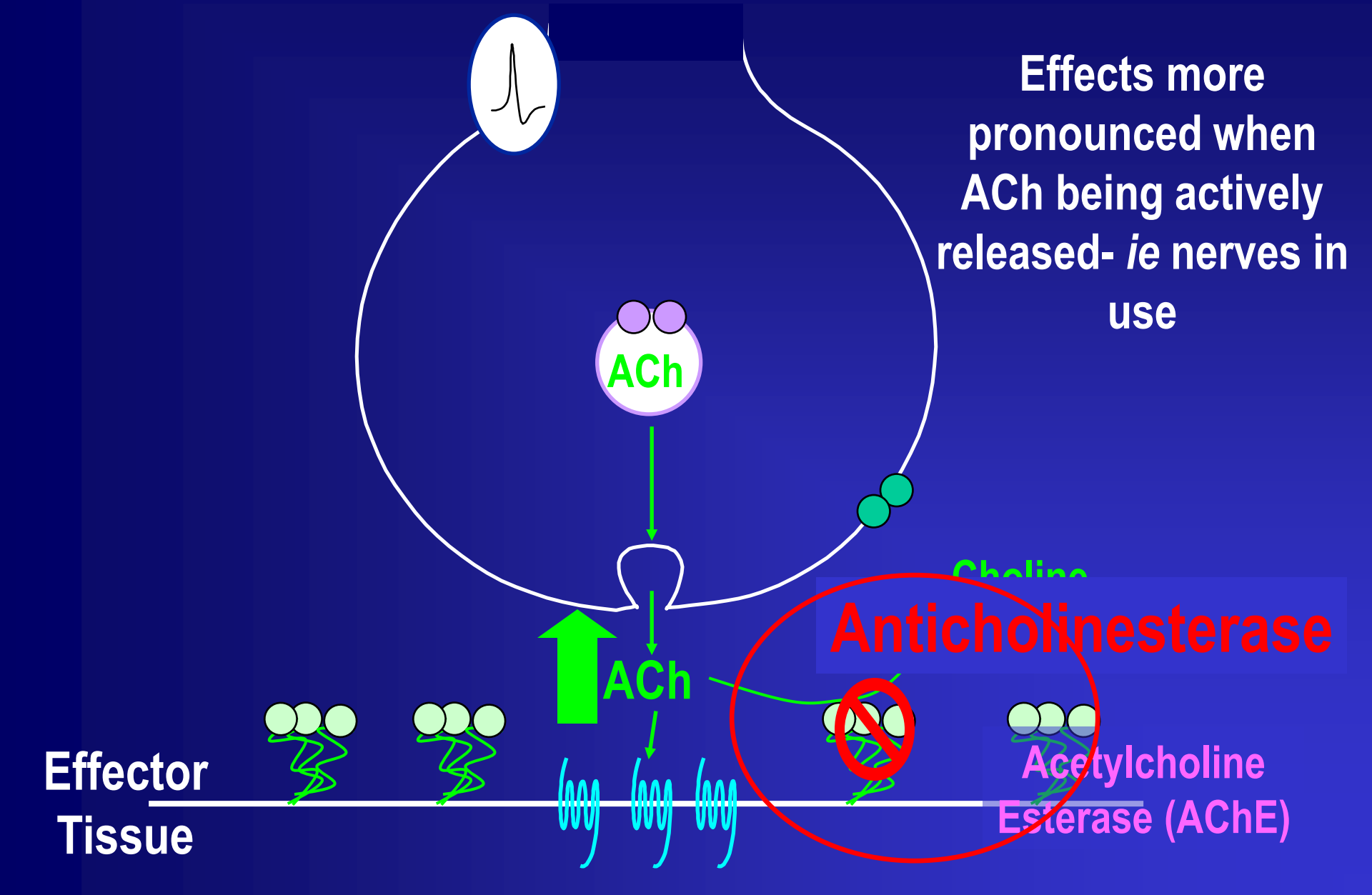
- A tool for purifying NicR
  - Permitted structural analysis
  - Permitted protein isolation, that led to sequencing and gene cloning
- A tool for visualising/understanding the NMJ and NicR
- A diagnostic tool- *myasthenia gravis*

α-Bungarotoxin



www.mcb.harvard.edu/Faculty/Gallery/Lichtman2.jpg

Anticholinesterase drugs

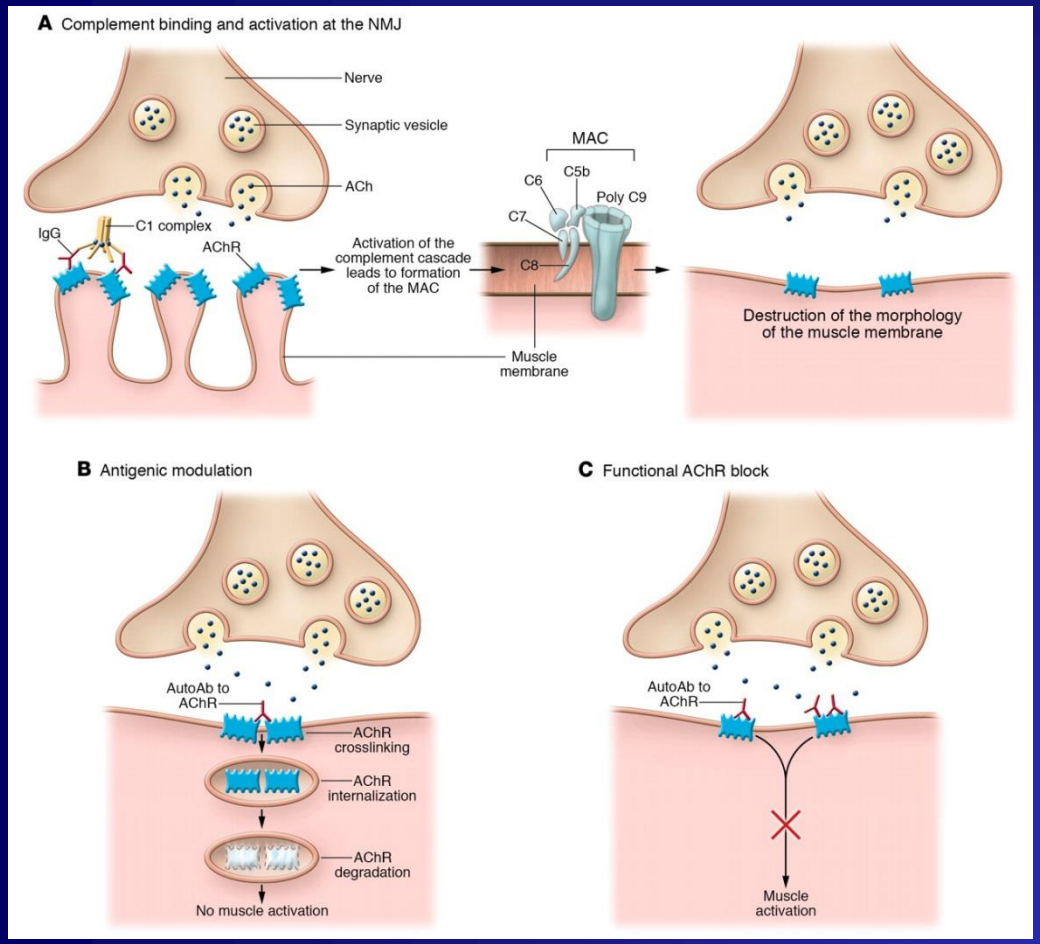


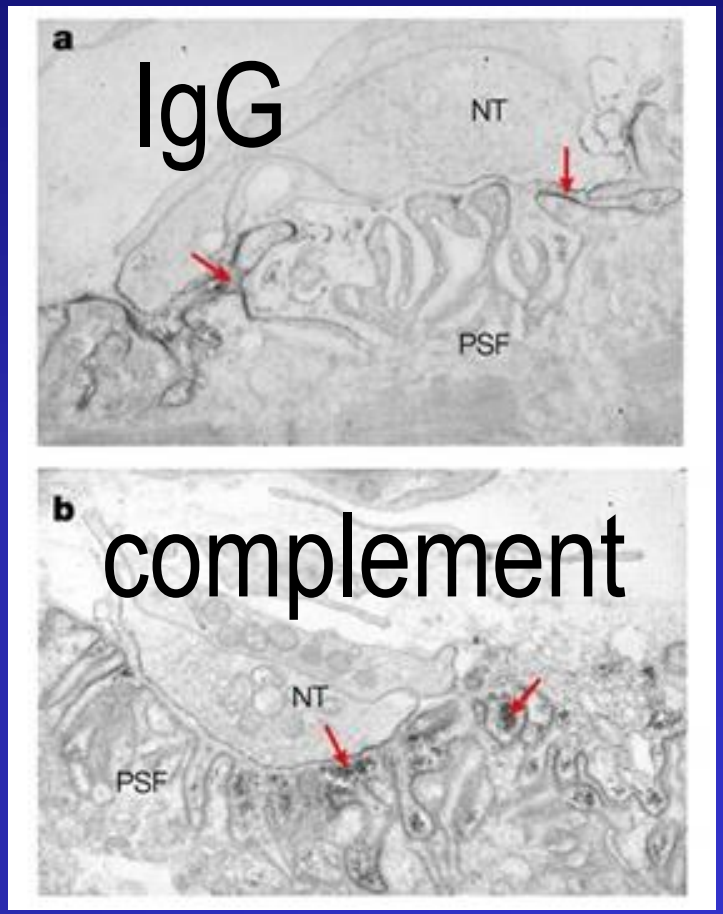
Effects more pronounced when ACh being actively released- *ie* nerves in use

Anticholinesterases

- **Drugs in this category have:**
- **Variable selectivity**
  - between NMJ and postganglionic parasympathetic junctions
- **Variable CNS access**
- **Variable duration of action**
  - Short-Acting; Medium-Duration; Irreversible

What is Myasthenia Gravis?

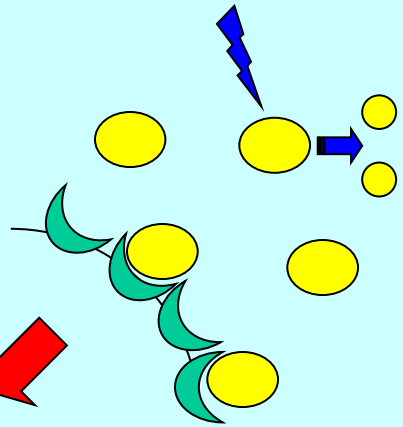




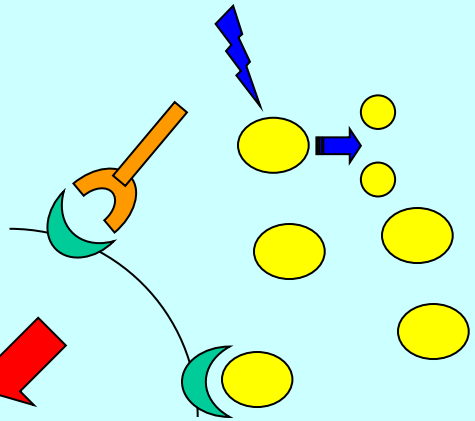
Conti-Fine et al, 2006. JCI 116;2843

Vincent, 2002. Nat Rev Immunol 2;797

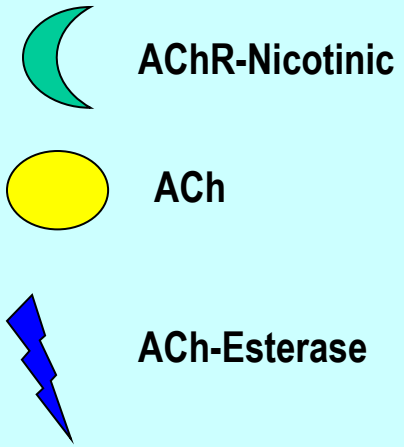
Treatment of Myasthenia Gravis with Anti-AChE

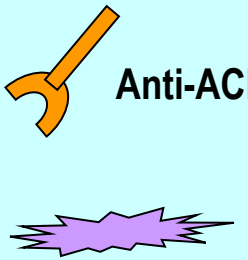


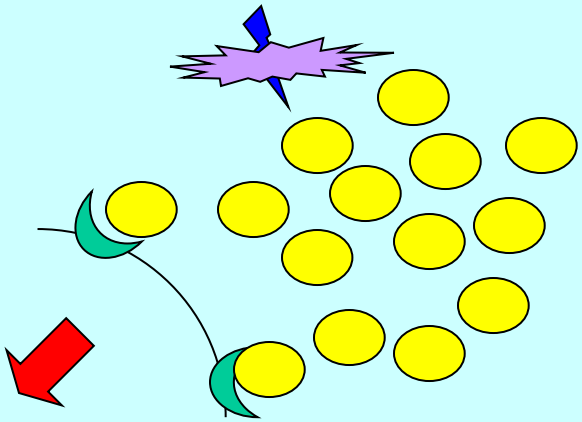
Normal Contraction of Skeletal Muscle



Reduced Contraction of Skeletal Muscle- Paralysis







Restored Normal Contraction of Skeletal Muscle

Myasthenia Gravis- “Tensilon” Test

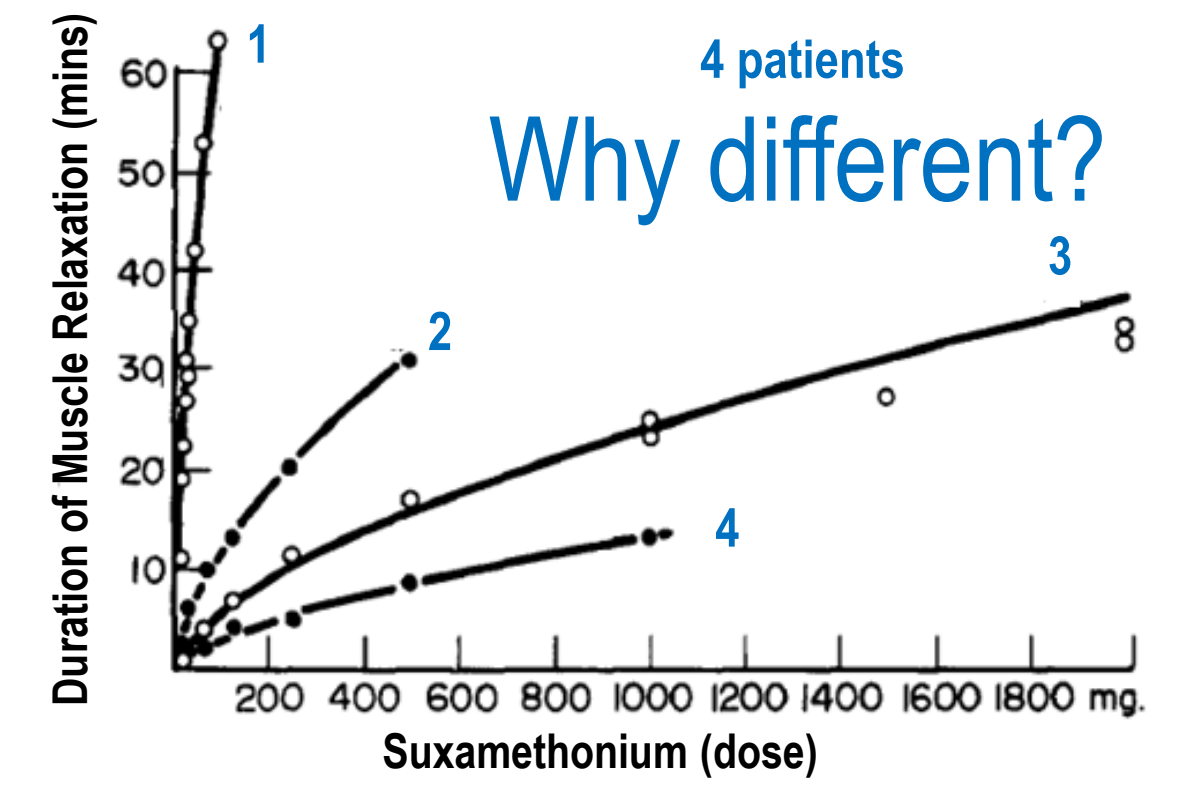
Tensilon = edrophonium
(short-acting anti-cholinesterase)

http://www.youtube.com/watch?v=k7YX9kuWrxA

Skeletal muscle relaxant-suxamethonium

- ‘Depolarising’ muscle relaxant
  - Agonist at NicR (?)
  - (cw mechanism of action of d-tubocurarine)
- Short-lived actions (mostly!)
  - Useful for ‘quick’ surgical procedures

Skeletal muscle relaxant-suxamethonium



Modified from: Lockeridge, Pharmac Ther; 1990; 47; 35-60

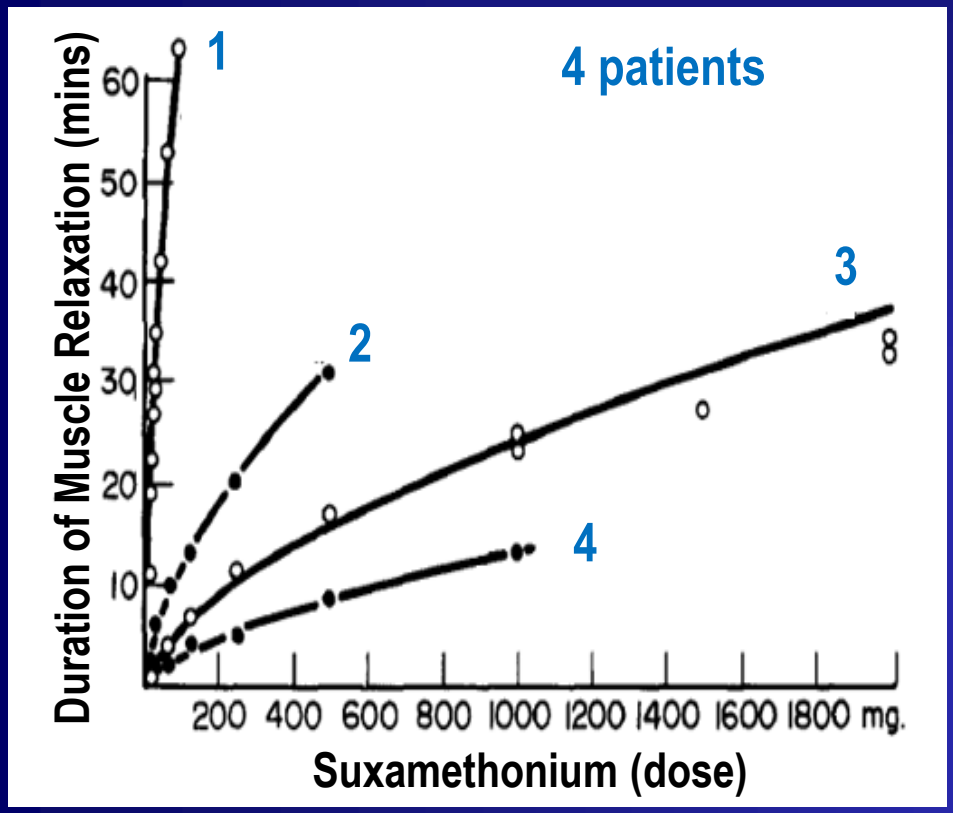
Skeletal muscle relaxant- suxamethonium

Suxamethonium
(active)

Plasma (psuedo/butyryl)
cholinesterase

inactive

Skeletal muscle relaxant-suxamethonium



Polymorphic forms of plasma cholinesterase

Alters enzyme expression/activity

Pharmacogenomics/ Pharmacogenetics

Modified from: Lockeridge, Pharmac Ther; 1990; 47; 35-60

Intro to CAL

Using drugs as tools to understand neurotransmission

Intro to CAL- ‘Virtual Twitch’

- The preparation
- Using the Software
  - Drug additions
  - Washing
  - New Rat
- Measuring responses
- Non-cumulative vs cumulative concentration response
- Play around with it! Try things and see what happens!