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Veterinary Bioscience: Cells to Systems

VETS30029 / VETS90121



Cholinergic Pharmacology

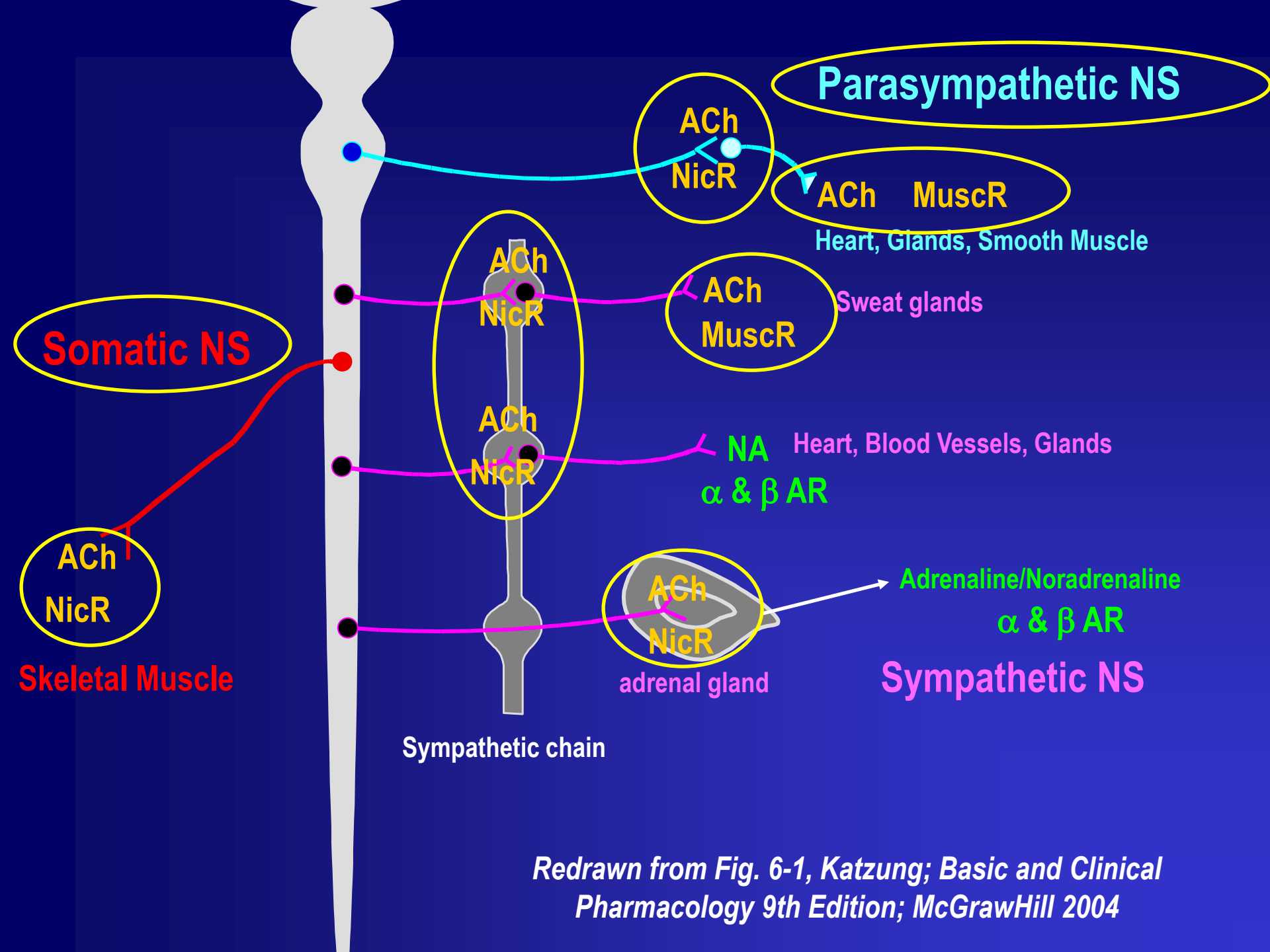
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Part 1 of 2

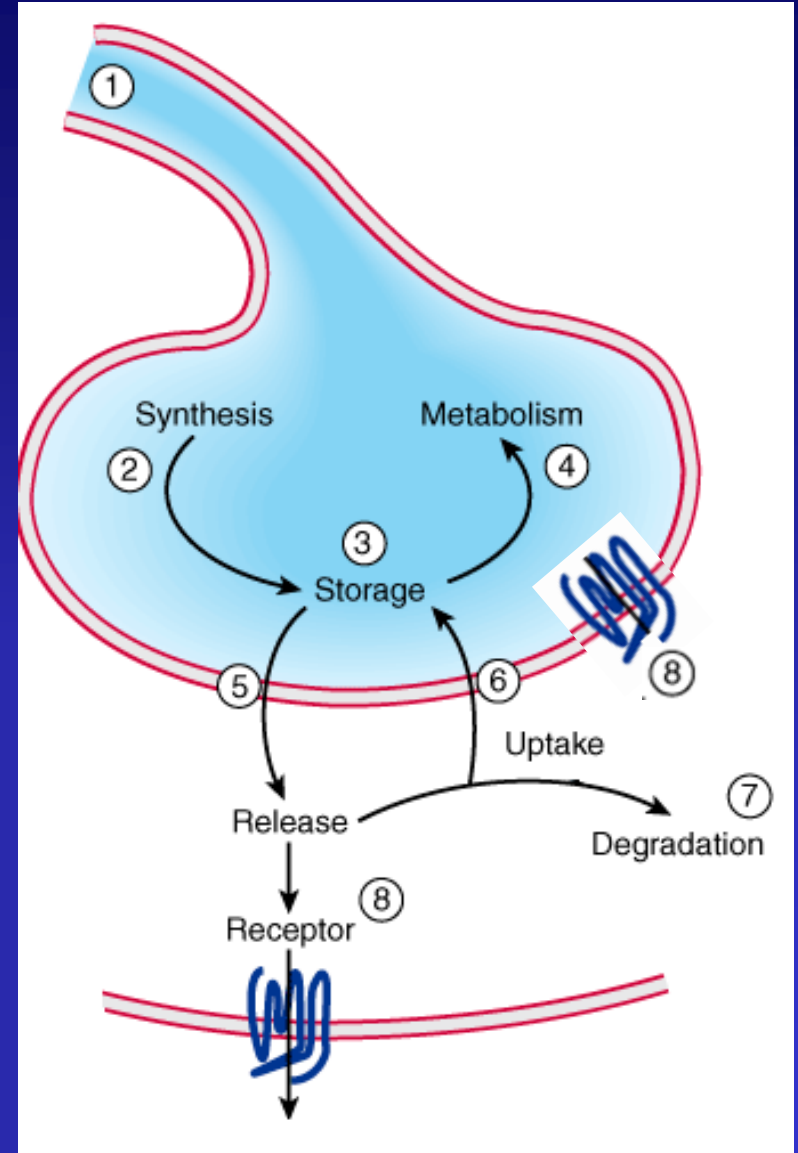
Structure of Lecture

- Neurotransmitter- ACh (*PART 1*)
 - Synthesis/Release/Inactivation
- Receptors (*PART 2*)
 - Muscarinic & Nicotinic
- Selective Drugs and their Uses (*PARTS 1&2*)
 - Modulators of the above processes/receptors



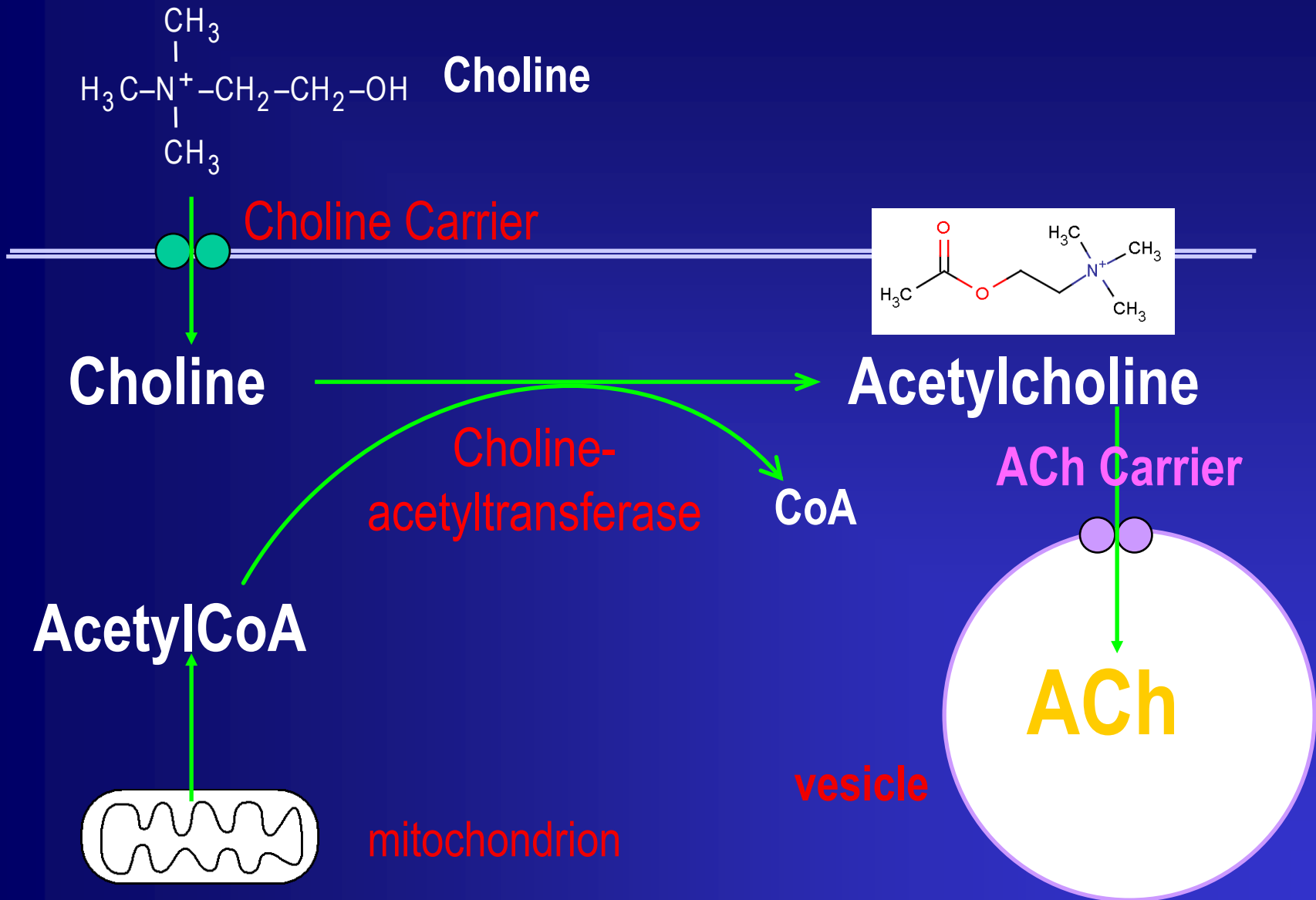
Redrawn from Fig. 6-1, Katzung; Basic and Clinical Pharmacology 9th Edition; McGrawHill 2004

Sites of Pharmacological Modulation at a Synapse

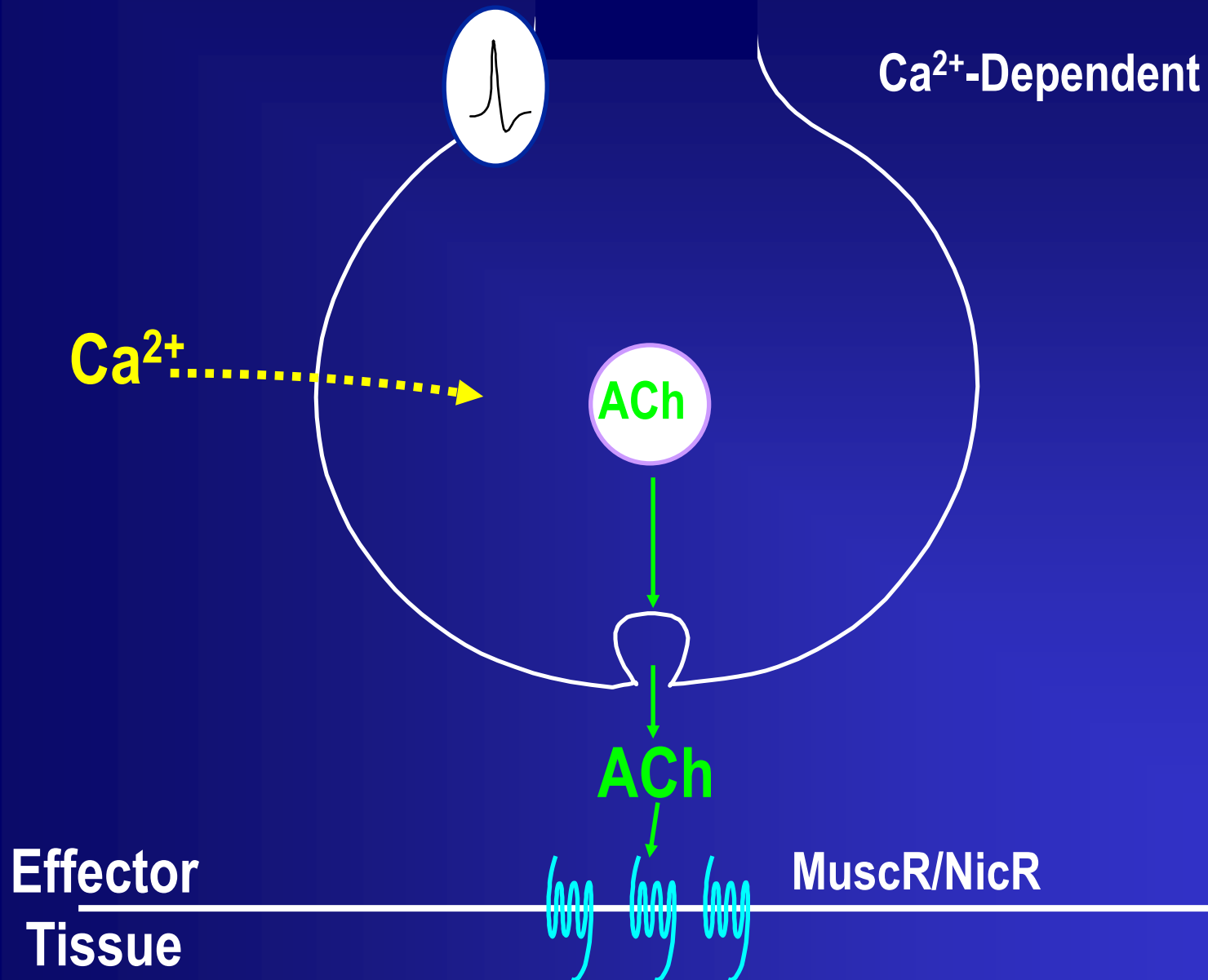


Katzung; 2009, 11th edition; Fig. 21-5

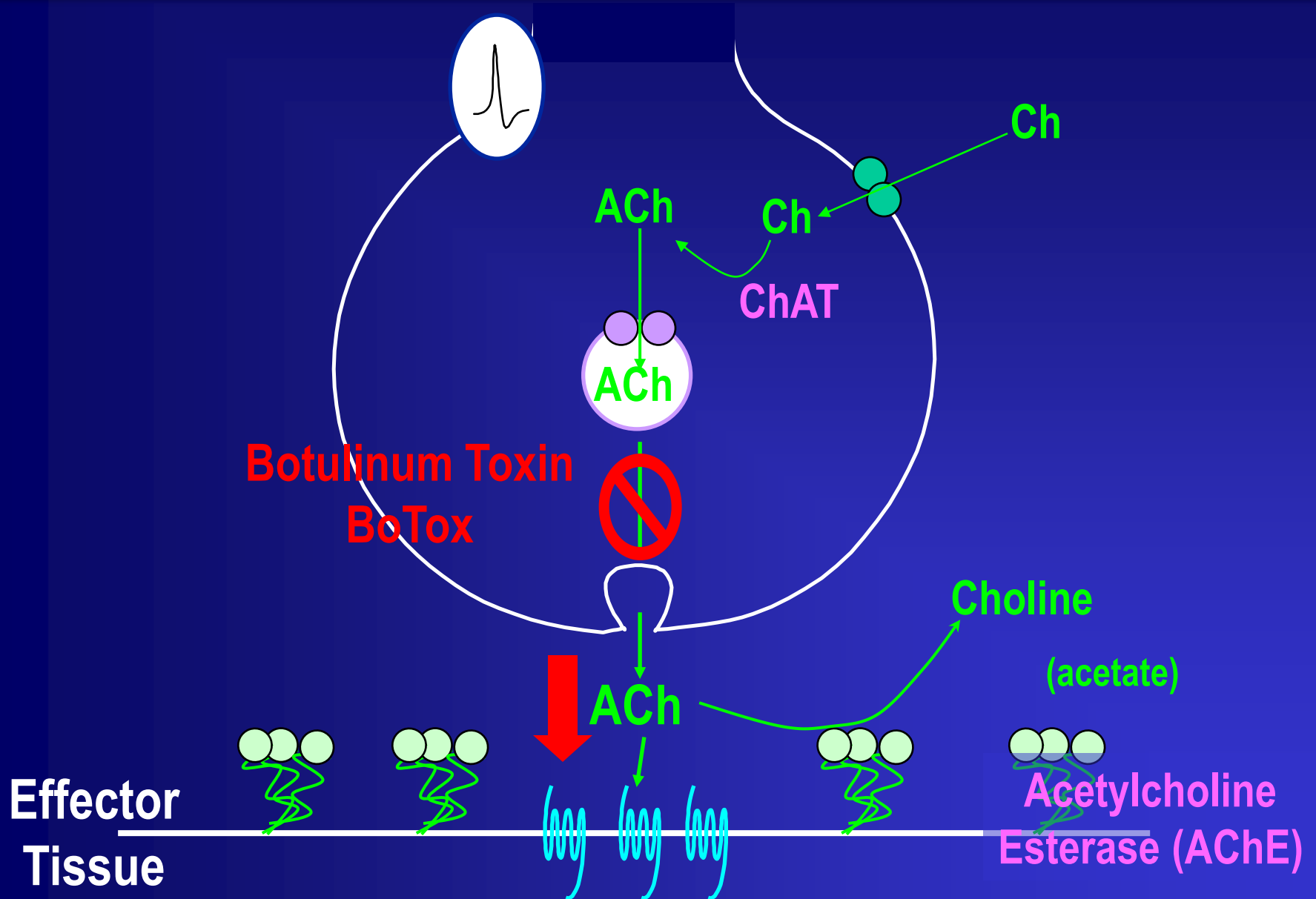
ACh Synthesis



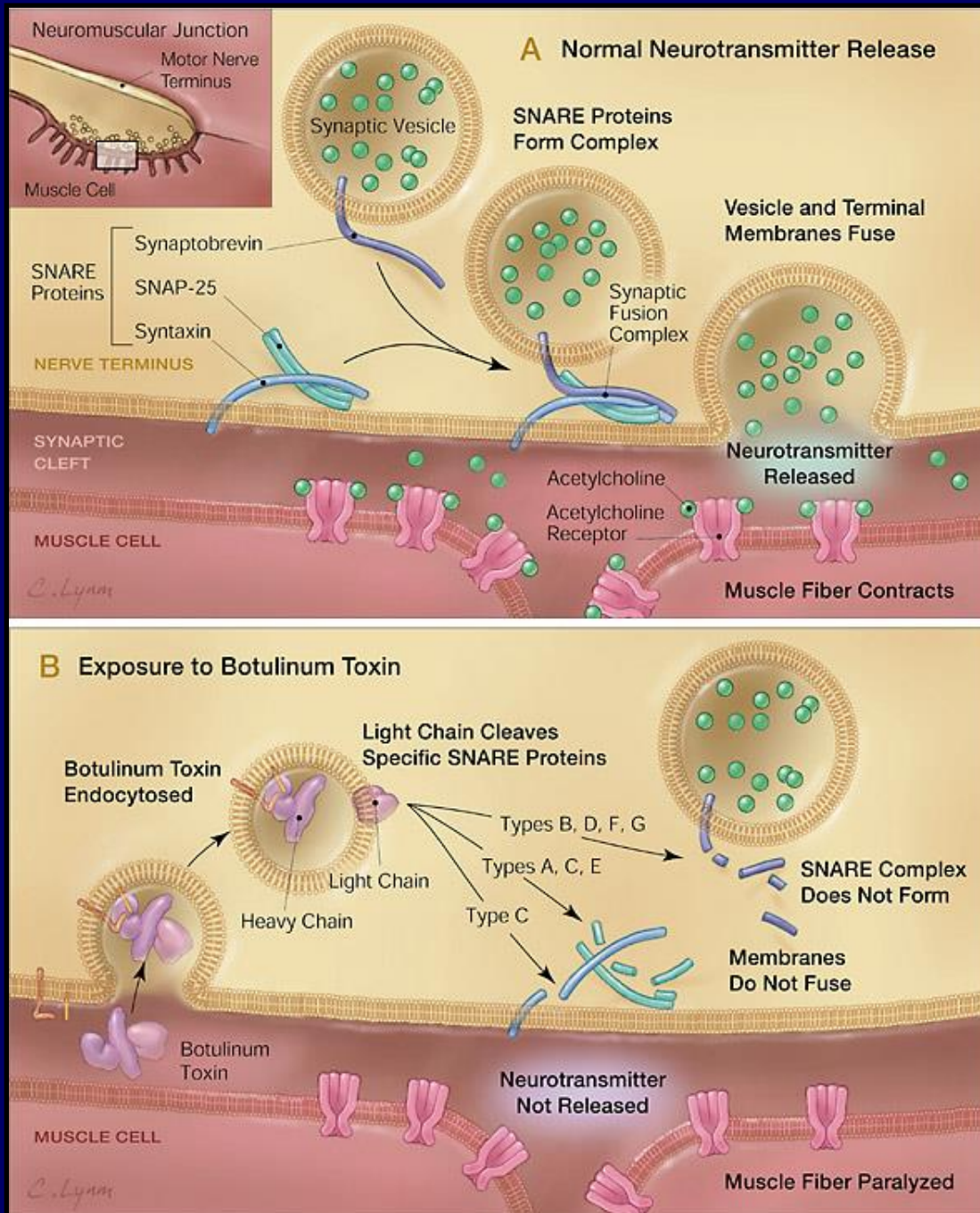
ACh Release



ACh Release- Pharmacological Modulation



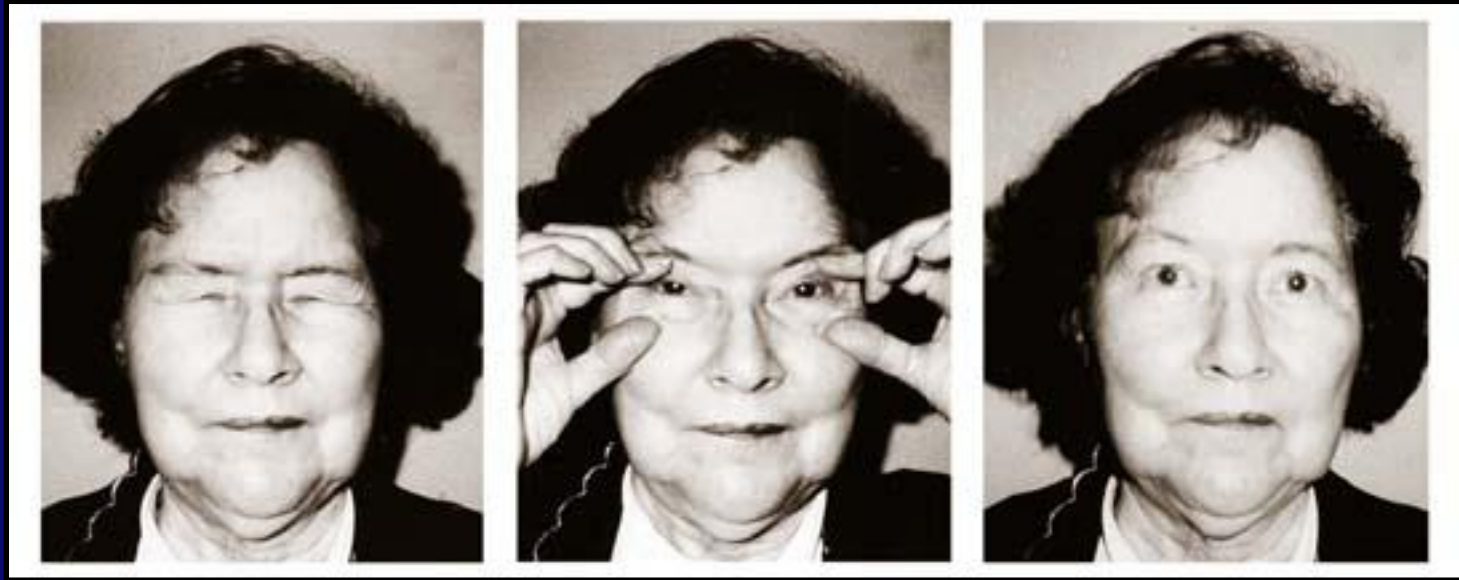
Effects of Botulinum Toxin on ACh Vesicle Exocytosis



From- Botulinum Toxin
as a biological weapon.
Arnon SS *et al*

JAMA, 2001, 285, 1059.

Botulinum Toxin (Type A)



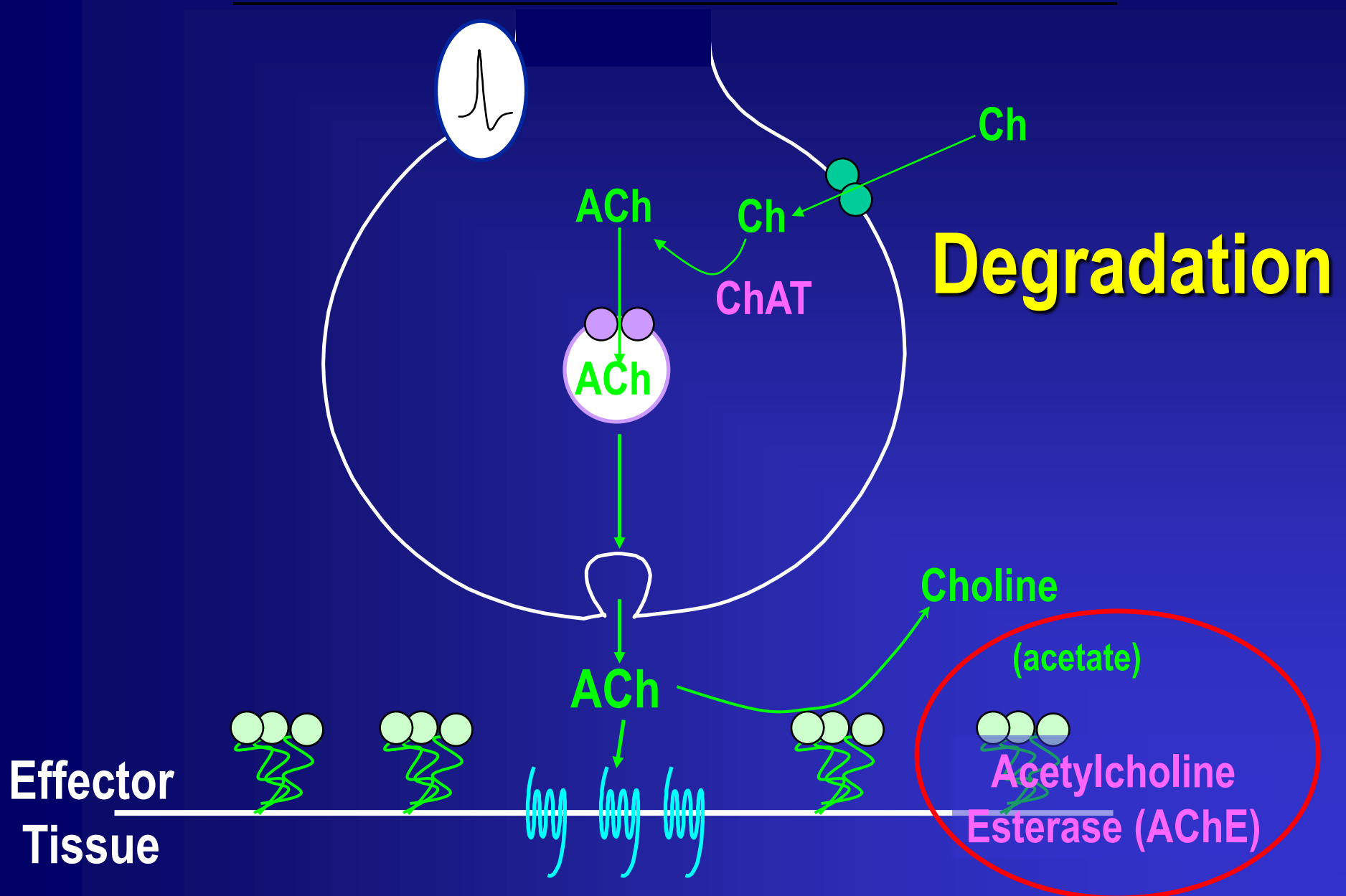
Before

After

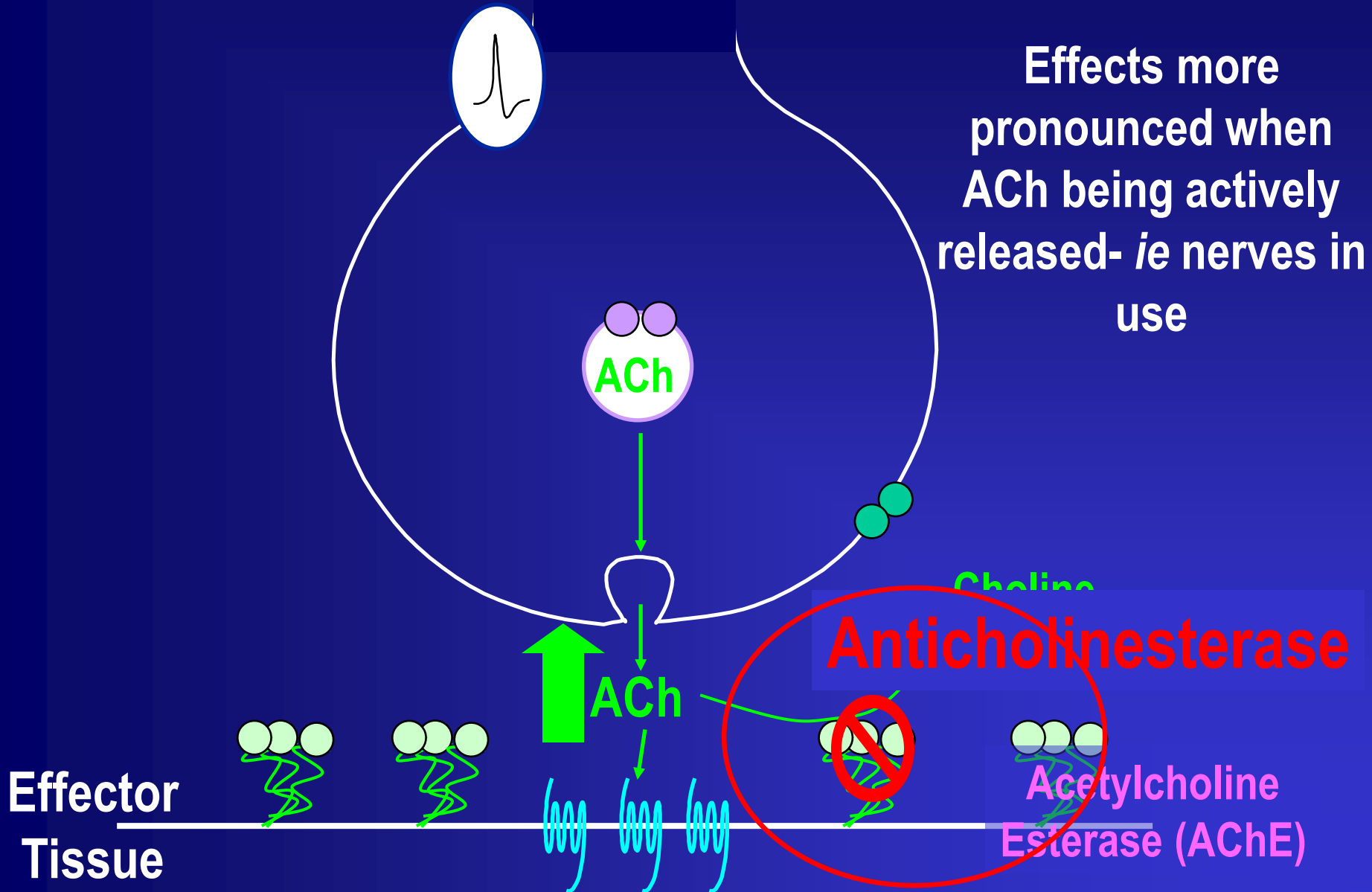
Blepharospasm

Image courtesy of the FDA and Joseph Jankovic, M.D., professor of neurology, Baylor College of Medicine, Houston, Texas.

ACh Inactivation



Anticholinesterase drugs



Therapeutic Uses of Anticholinesterases

- **Physostigmine (*and others*)**
 - More activity at parasympathetic NS
 - Used to treat glaucoma
- **Neostigmine (*and others*)**
 - More activity at NMJ
 - Used to reverse effect of non-depolarising neuromuscular blockers (see later)
 - Used to treat myasthenia gravis (dogs)(see later)

Irreversible Anticholinesterases

Organophosphates



Insecticides

Learning Outcomes

- **After studying this topic you should be able to:**
 - Describe the synthesis, storage, release and inactivation of acetylcholine (ACh).
 - Describe how certain drugs/agents are able to modulate cholinergic nervous system activity through alteration of the above processes and any clinical/other uses that they might have.

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Cholinergic Pharmacology

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Part 2 of 2

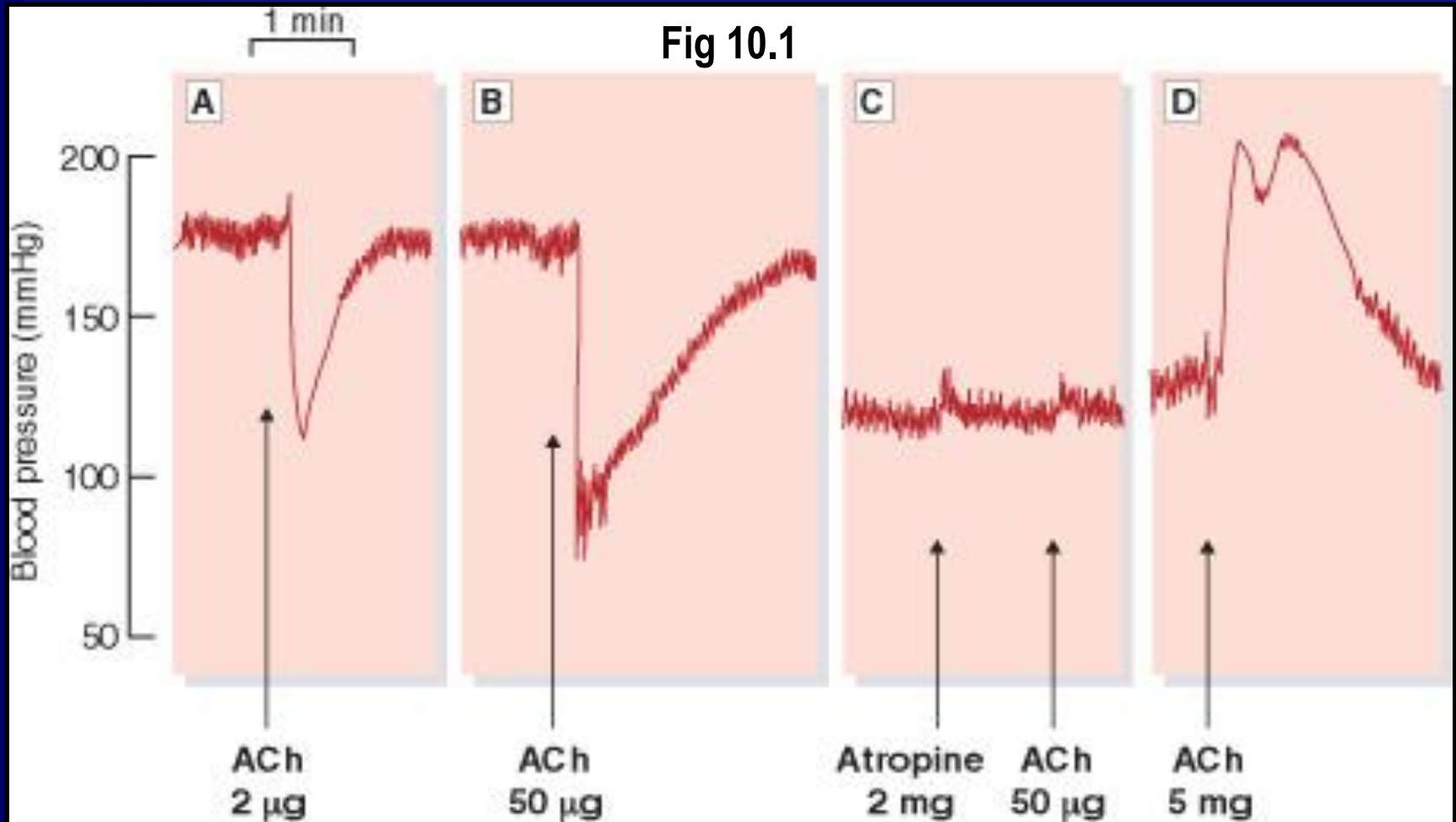
ACh Receptors

Muscarinic

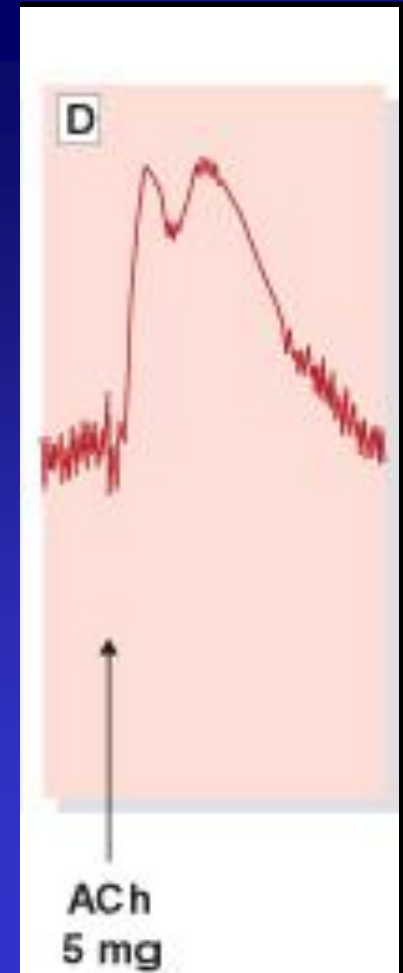
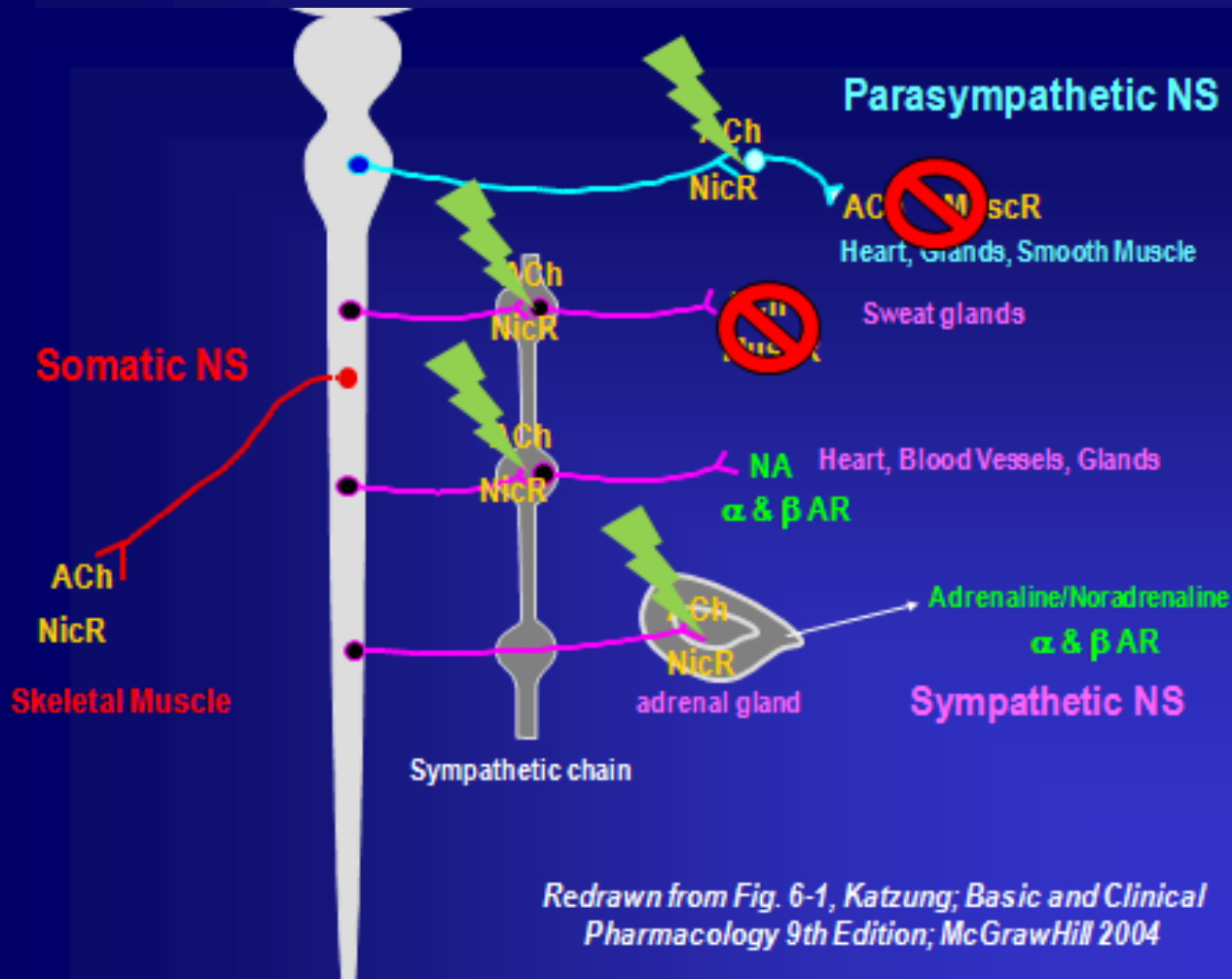
Nicotinic

Muscarinic and Nicotinic Effects of ACh; Cat Blood Pressure Model

Fig 10.1



Muscarinic and Nicotinic Effects of ACh; Cat Blood Pressure Model



Cholinoceptor Agonists

Nicotiana tabacum

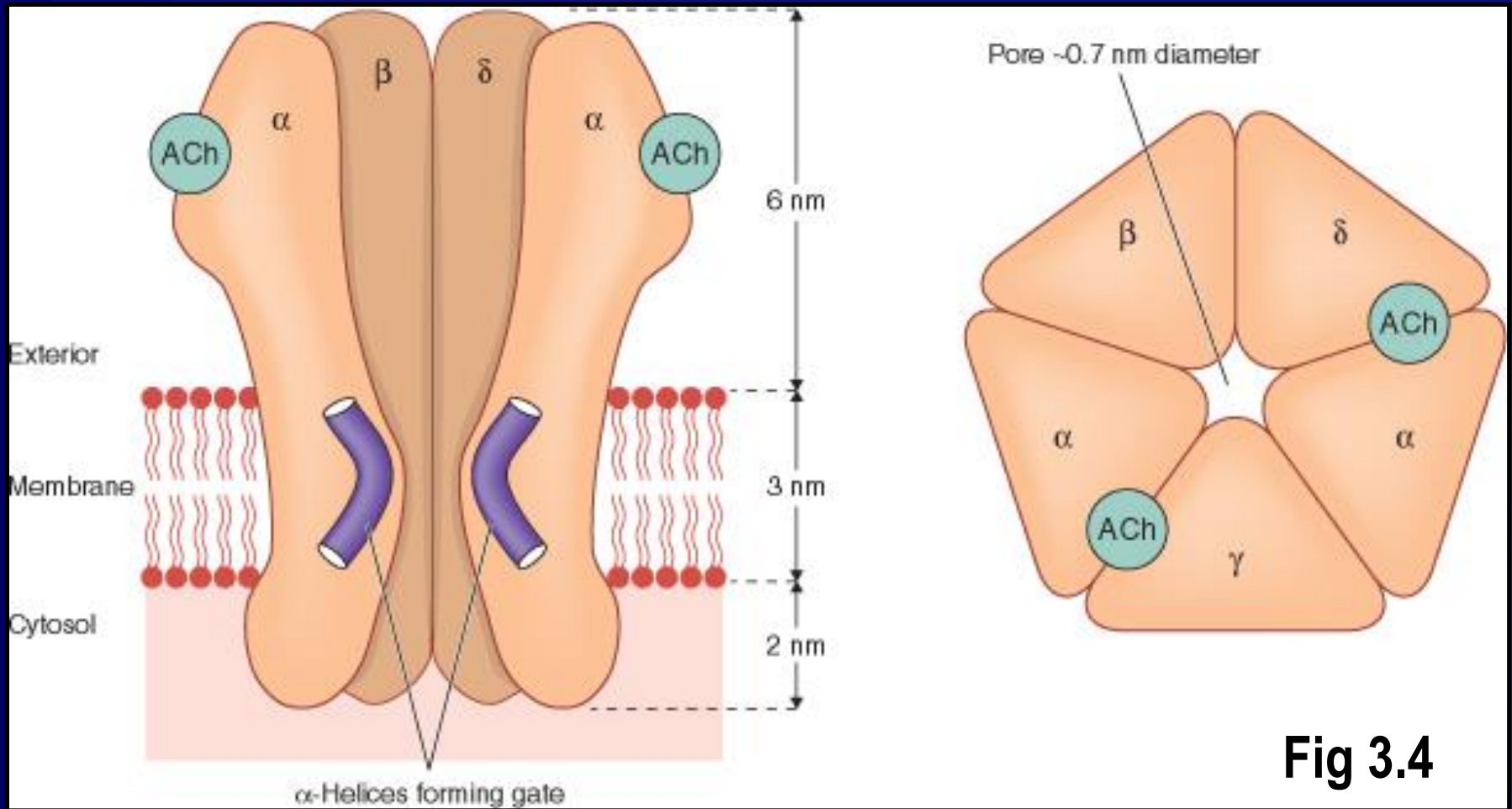


Amanita muscaria



Picture from: <http://www.sporeworks.com>

Nicotinic ACh Receptor



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

Nicotinic Receptor Signalling



Very Fast Response (ms)

Depolarisation

*(action potential also requires
activation of voltage-gated Na⁺
channels)*

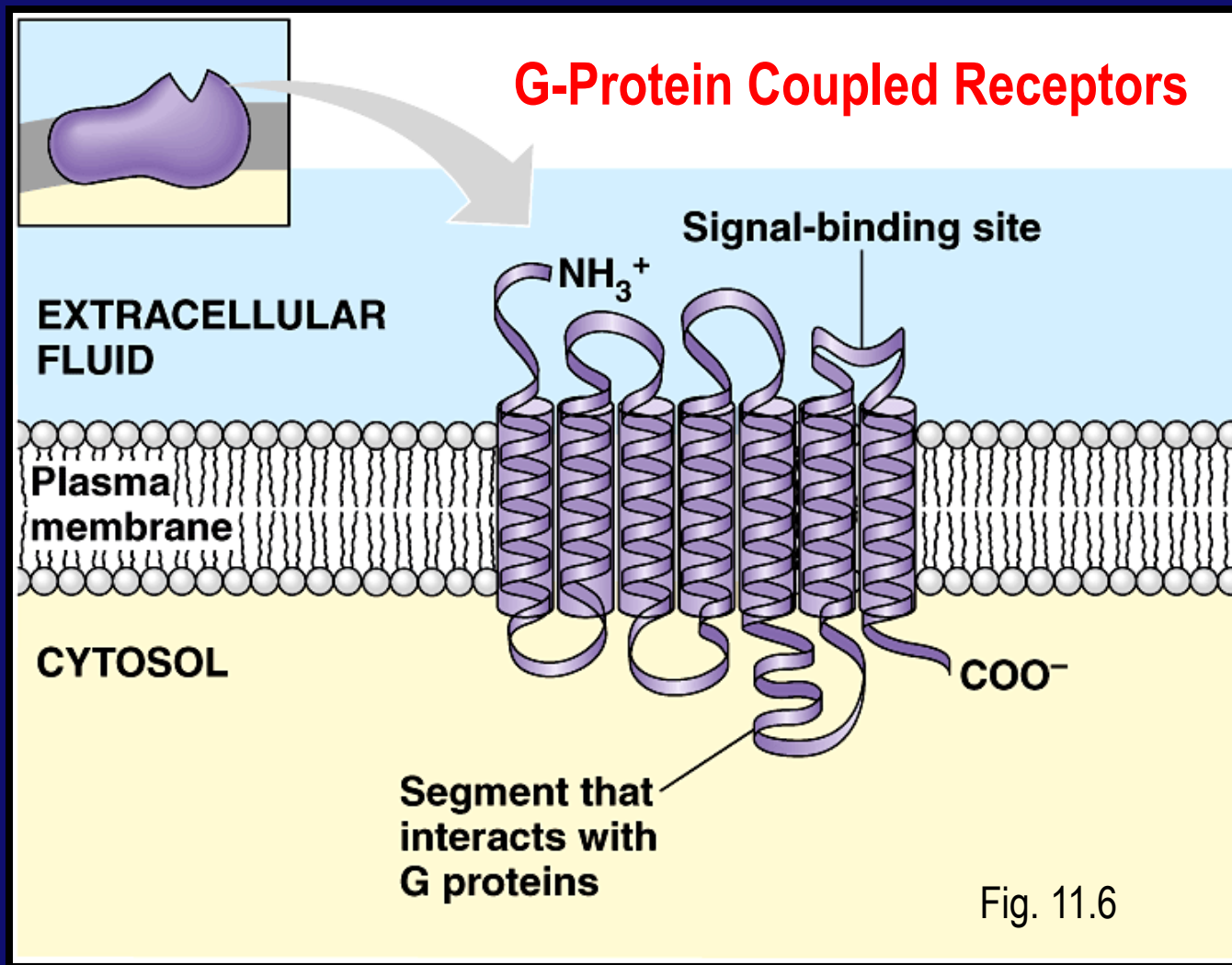
Skeletal muscle contraction (NMJ) (Nm)

Action potential initiation (Ganglia) (Nn)

Nicotinic ACh Receptors

- A number of different NicR exist
- For simplicity these separated into:
 - **Neural** (N_n found at ganglia)
 - **Muscle** (N_m found on skeletal muscle at the NMJ)
- Differences in these receptors underlie differences observed in drug selectivity (NMJ vs ganglia).

Muscarinic ACh Receptors

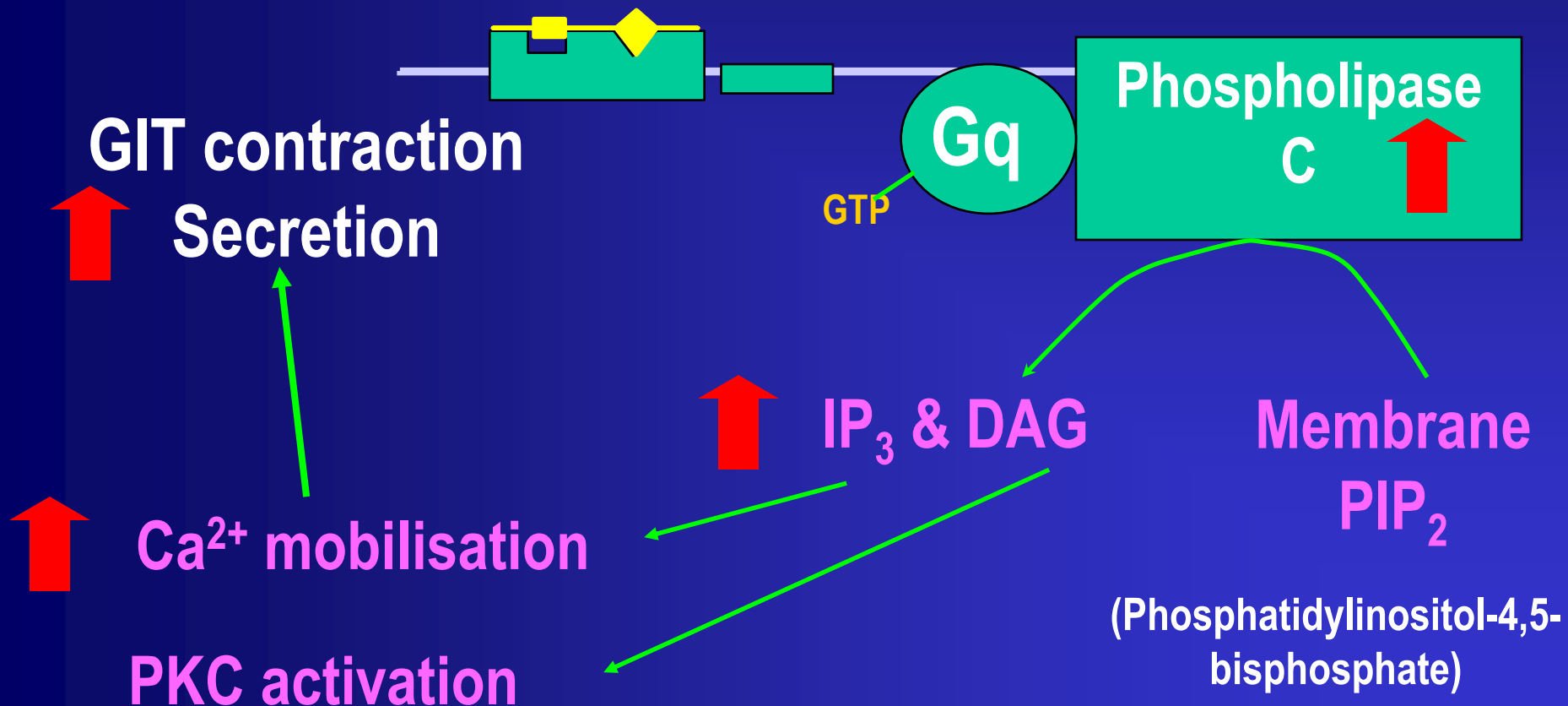


Muscarinic ACh Receptors

- 5 different types of MuscR identified and well characterised- all GPCRs
- Agents that selectively act at these receptors developed.
- **M₃- 'smooth muscle/glandular'**
 - Stimulatory- generates IP₃
- **M₂- 'cardiac'**
 - Inhibitory- inhibition of cAMP production
 - Increased K⁺ channel opening

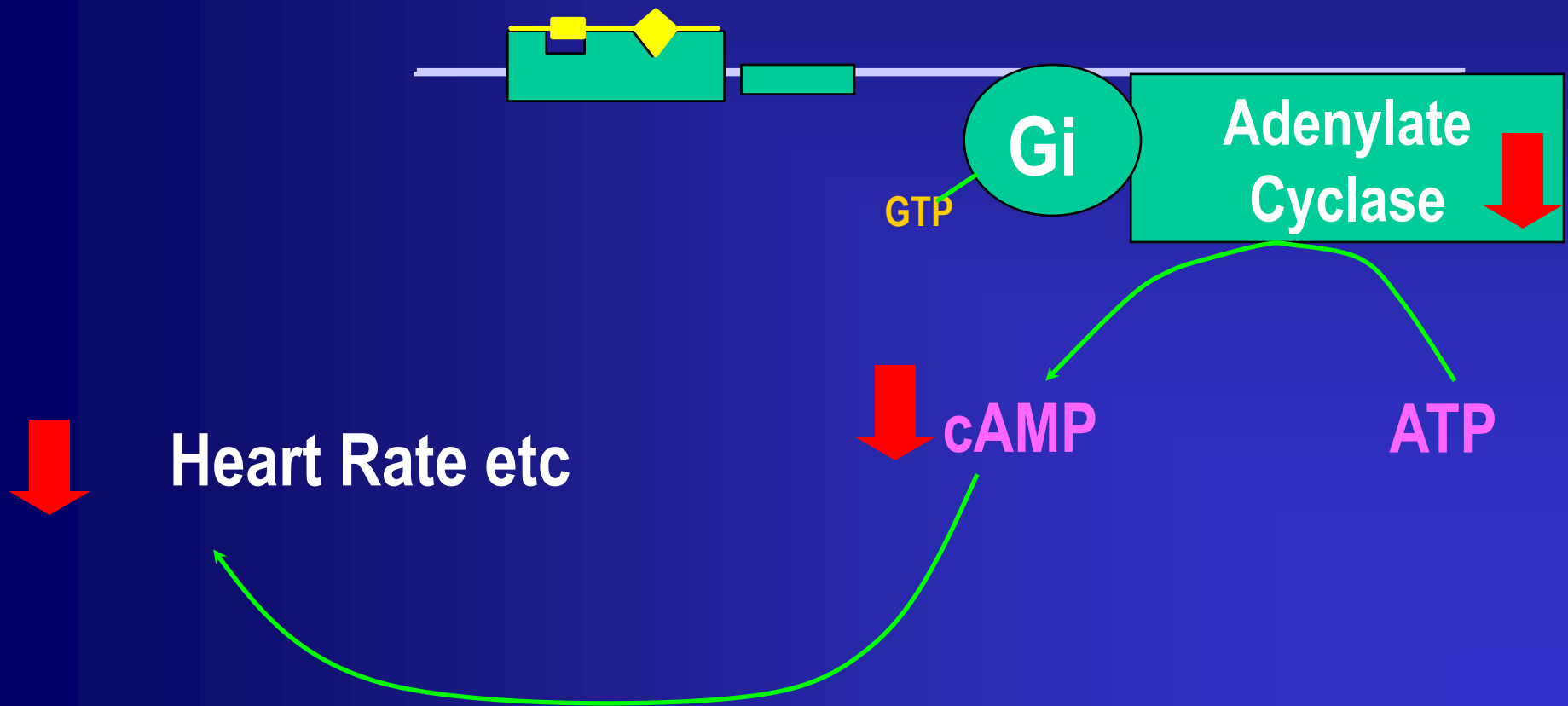
Signal Transduction Through Muscarinic Receptors

M₃ (smooth muscle, glands)



Signal Transduction Through Muscarinic Receptors

M_2 (Cardiac)



Muscarinic Receptor Actions

When activated will cause:

- **SLUD**
 - **S**alivation
 - **L**acrimation
 - **U**rination
 - **D**efecation
- Sweating
- Slowing of Heart
- Bronchoconstriction
- Vasodilatation (NB:non-neural effect)

Some Clinical Uses of Cholinoceptor Agonists

All selective Muscarinic receptor agonists

pilocarpine Glaucoma (in dogs)
(*cf. neostigmine*)

carbachol GIT and bladder paralysis

bethanecol (*care required re: obstruction*)

Cholinoceptor Antagonists

- **Muscarinic Antagonists**

- Blockade of the Parasympathetic NS (parasympatholytics)

- **Nicotinic Antagonists**

- Neuromuscular blocking drugs
 - Non-depolarising
 - Depolarising
- Ganglion blocking drugs

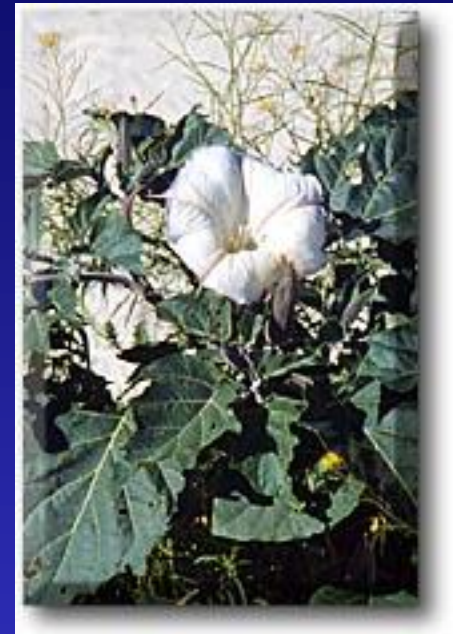
Cholinoceptor Antagonists



Muscarinic Antagonists

Atropa belladonna
Deadly Nightshade

Mainly Atropine
(some Hyoscine)



Datura stramonium
Angels Trumpet/Thorn apple

Mainly Hyoscine
(some Atropine)

Effects of Atropine etc

- Anti-SLUD
- Ocular: dilated iris and loss of accommodation
- Tachycardia
- CNS effects (depending on dose)
 - agitation, restlessness, disorientation, coma

Some Clinical Uses of Anti-Muscarinics

- **General**
 - Anti-spasmodics (gut/airway smooth muscle)
 - Ophthalmological use- dilation of pupil permits examination of eye
- **atropine /(glycopyrrolate)**
 - Reduce secretions and produce bronchodilation (pre-anaesthetic)
 - AChE-inhibitor poisoning
 - Bradycardia
- **hyoscine**
 - Motion sickness
- **Ipratropium (and others) (inhaled)**
 - Chronic obstructive pulmonary disease (COPD)/asthma

Cholinoceptor Antagonists

Nicotinic Antagonists



Curare
(d-tubocurarine)



http://ucjeps.berkeley.edu/hebe/hebe_darts

Neuromuscular blocking agents

- d-tubocurarine
 - Pre-operative muscle relaxation (artificial ventilation required)
 - Replaced clinically by 'better' agents- e.g. **rocuronium** etc
- **Competitive reversible antagonist/ 'non-depolarising' blocker**
 - Block reversed with *neostigmine*
- Less effective at autonomic ganglia- but can block at high concentrations
- (also 'depolarising' blockers- (suxamethonium)- *see Twitch Prac!*)

Toxicology

- Many of the agents active on cholinergic NS are natural products or have agricultural uses (*insecticides etc*)
- Danger of poisoning through feedstuff or exposure.

Cholinergic Receptors- Summary

Tissues with
parasympathetic nerves
(& sweat glands)

Muscarinic

Activated by:
ACh, pilocarpine

Blocked by:
atropine

Autonomic ganglia &
skeletal muscle

Nicotinic

Activated by:
ACh, nicotine

Blocked by:
hexamethonium (ganglia)
d-tubocurarine (NMJ)

Learning Outcomes

- **After studying this topic you should be able to:**
 - Describe how **ACh receptors** are divided into subtypes and the pharmacological basis for this division.
 - Describe the basic signal transduction mechanisms that ACh receptors employ to produce their functional effects.
 - Describe the **ACh receptors** responsible for the major physiological roles of ACh within the parasympathetic and somatic NS and at autonomic ganglia.
 - Give examples of **agonists and antagonists** that have selective activity at ACh receptors.
 - Describe the major **pharmacological effects** and **therapeutic uses** of the above agonists and antagonists.

Suggested Readings

➤ Rang & Dale's Pharmacology

9th edition, 2020, Elsevier, Churchill Livingstone, **Chapters 13,14**

<https://www-clinicalkey-com-au.ezp.lib.unimelb.edu.au/#!/browse/book/3-s2.0-C2016004202X>

Veterinary Pharmacology and Therapeutics,

by Riviere JE and Papich MG (eds) 9th edition, 2009, Wiley-Blackwell

Chapters 5 & 7

Handbook of Veterinary Pharmacology

Hsu WH (2008). 1st edition. Blackwell.

Chapter 2