Parasympathetic Pharmacology

Prof Michael Veltman

Director of Anaesthesia
Joondalup Health Campus

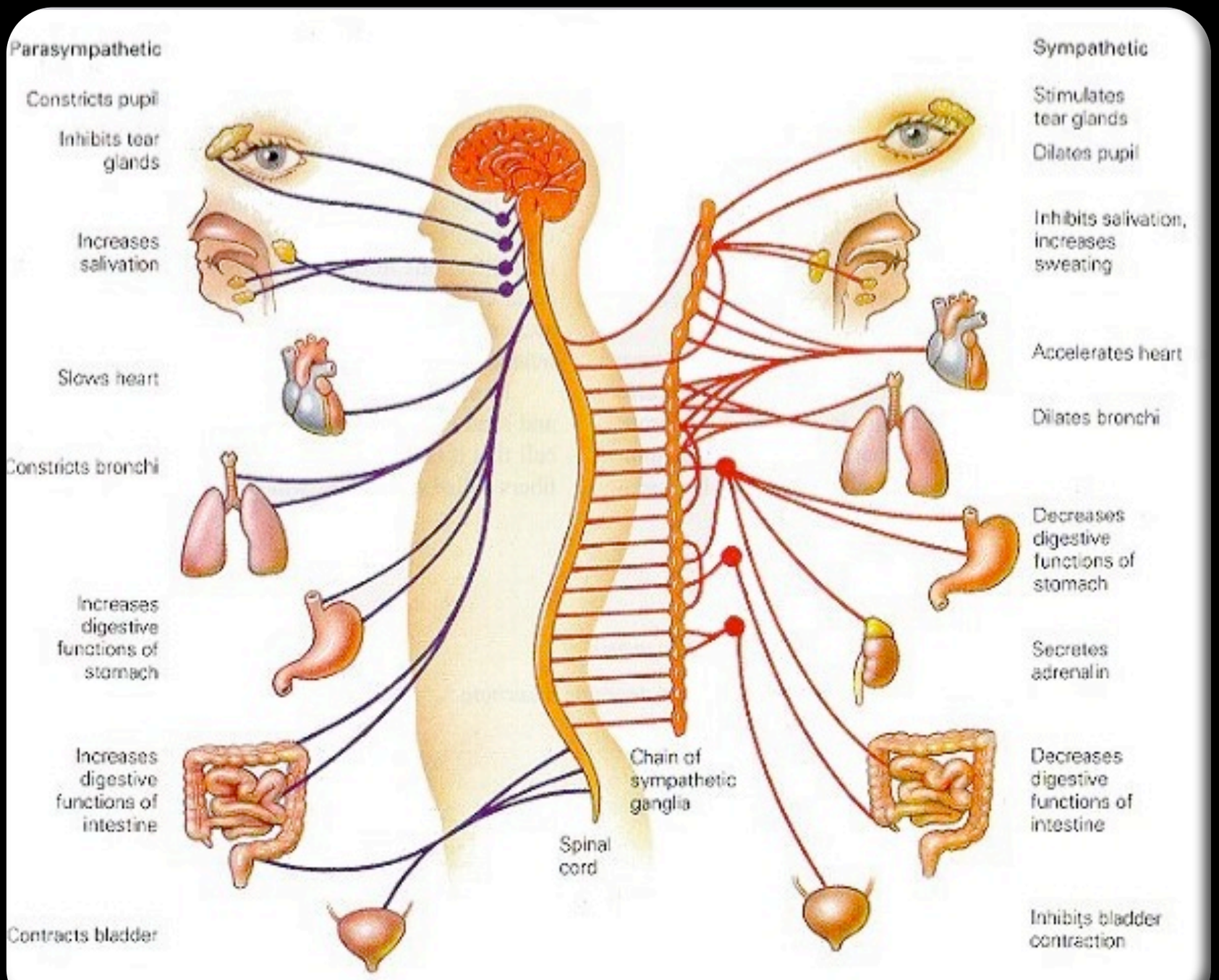
Staff Specialist Anaesthetist
RPH, SCGH

Outline

- Parasympthetic Nervous System
  - Review anatomy & physiology
  - Agonists & Antagonists
  - Cholinesterase inhibitors

Anatomy

Anatomy



- Craniosacral outflow
- Differenent from SNS
  - Finely controlled response
  - Different outflows

Efferent Fibres

- Origin in the sacral and cranial regions of the cord
- Long preganglionic and short post ganglionic fibres

Parasympathetic versus Sympathetic Innervation

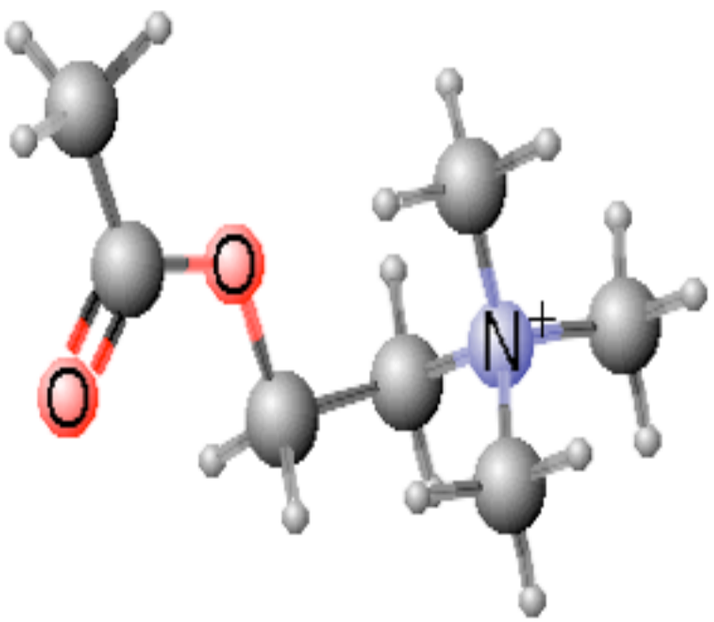
- Most organs have dual innervation
  - Generally reciprocal effects
  - Occasionally complimentary
    - Salivary Glands, Male sexual function
- Single innervation of some organs
  - PS: Lacrimal & GI glands
  - Sym: Adrenal medulla, visceral arterioles, sweat glands, spleen

Parasympathetic Nervous System

Physiology

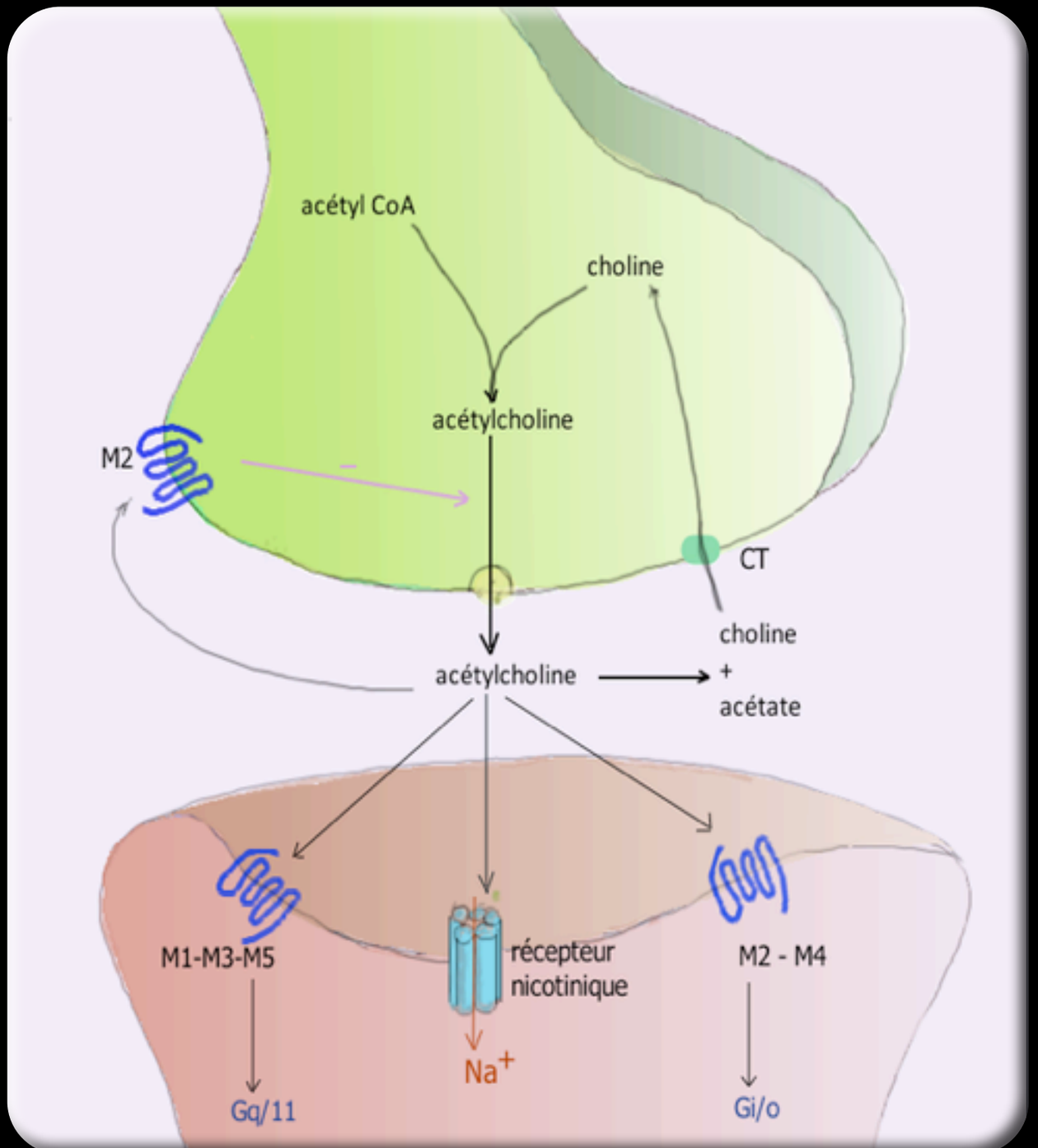
- Messengers
- Receptors
- Secondary messengers
- Effects

Acetyl Choline



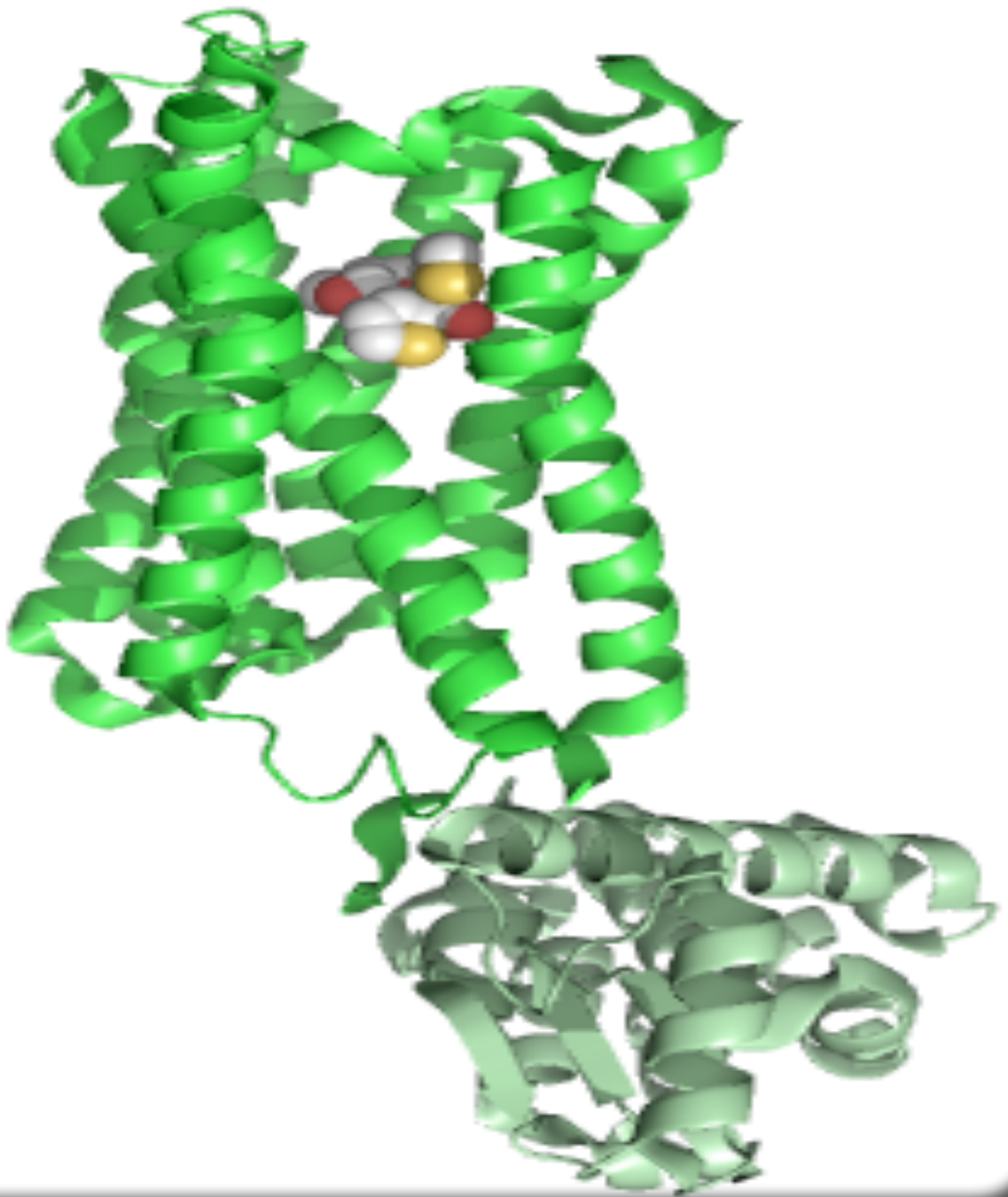
- Produced from
  - Choline
  - Acetyl CoA
    - Choline acetyl transferase
- Metabolised by
  - Acetylcholinesterase
    - Choline
    - Acetate

Acetyl Choline Receptors



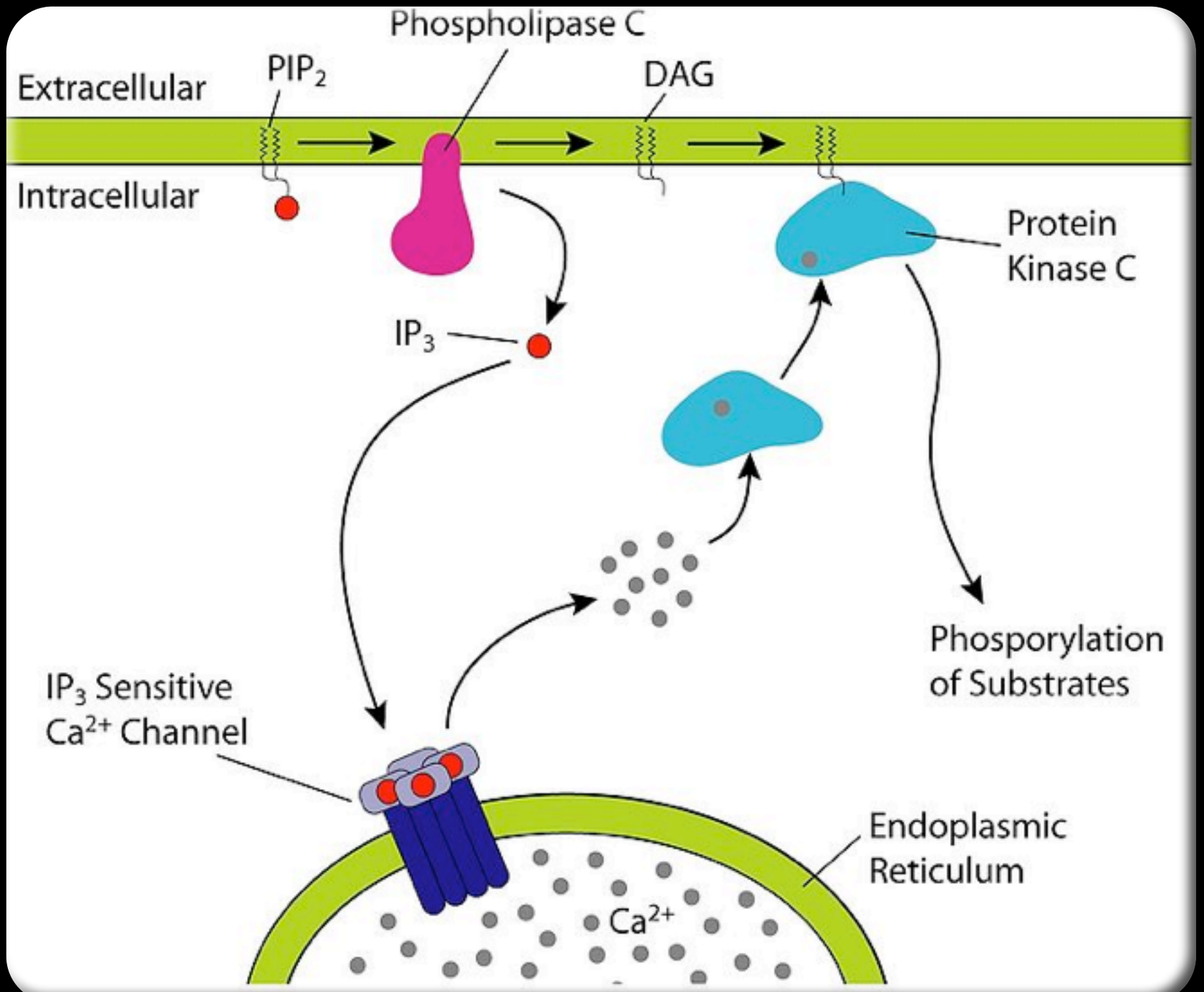
- Receptors
- Nicotinic
- Muscarinic
  - M1, M3, M5 (Gq)
  - M2, M4 (Gi)

Receptor Types



- G-Protein
  - 7 segments
  - Secondary messenger systems
- Gs (Raises cAMP)
- Gi (Lowers cAMP)

Secondary Messengers



- IP3
  - Insitol Triphospate
- Mediates calcium levels

Cardiovascular System

- Vasodilation
  - Pulmonary
  - Cardiac
  - Everywhere
- Mediated by M3 receptor
  - Release of EDRF (NO)

Cardiac effects

- Negative chronotrophic effect
- Negative inotrophic effect
- Negative lucitrophic effect
- Negative dromotrophic effect

GIT Effects

- Increase in motility:
  - Tone
  - Amplitude of contractions
  - Peristaltic activity
- Sphincter relaxation

GIT Effects

- Secretory activity increased
  - Gastric secretions (Acid)
  - Salivation
- Liver: Glycogen Synthesis

Urogenital Effects

- Motility increased
- Ureters
- Detrusor contraction
- Decreased bladder capacity
- Increased bladder voiding pressures

Occular Effects

- Miosis
- Lacrimation
- Reduced IOP

Glandular effects

- Adrenal medulla (Increased Adrenaline & Noradrenaline)
- Sweat glands (Increased secretion)
- Exocrine glands (increased secretion)

Other Effects

- Stimulation of secretion by all glands that receive parasympathetic innervation
  - Lacrimal, tracheo-bronchial, salivary, digestive, and exocrine sweat glands
- Respiratory system
  - ↑ Tracheobronchial secretion
  - Bronchoconstriction

Summary

- Messengers
- Receptors
- Secondary messengers
- Effects

Parasympathomimetics

Cholinomimetics Outline

- Muscarinic Agnoists
  - Structure & Analogs
  - Mechanism of action
  - Pharmacodynamics
  - Uses
  - Side Effects & Toxicity

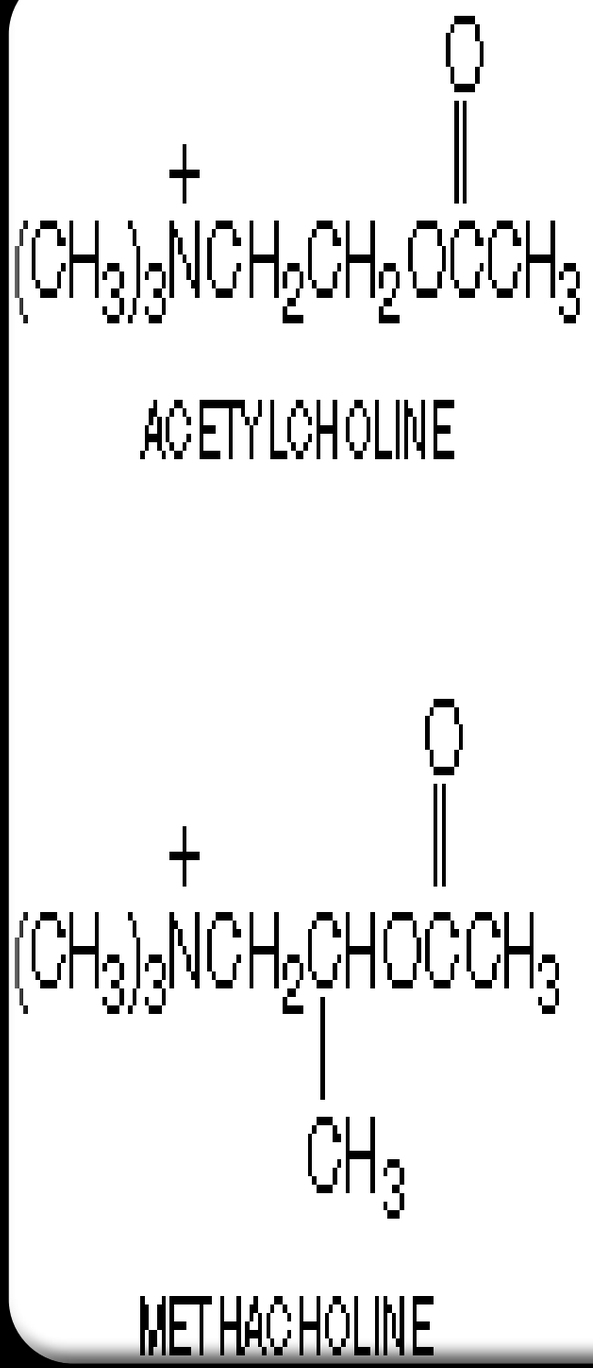
Choline Esters

- Acetylcholine
- Methacholine
- Carbachol
- Bethanechol

Structure Activity

- ACh is the acetyl ester of choline
- A quaternary ammonium compound
- Cationic (positively charged) head
- Joined by a two carbon chain
- Ester grouping tail

Muscarinic Agonists



	A	M	C	B
AchE	+++	+	-	-
CVS	++	+++	+	±
GIT	++	++	+++	+++
GUS	+	+	++	++
Block	+++	+++	+	+++
Nicotinic	++	+	+++	-

Choline Esters

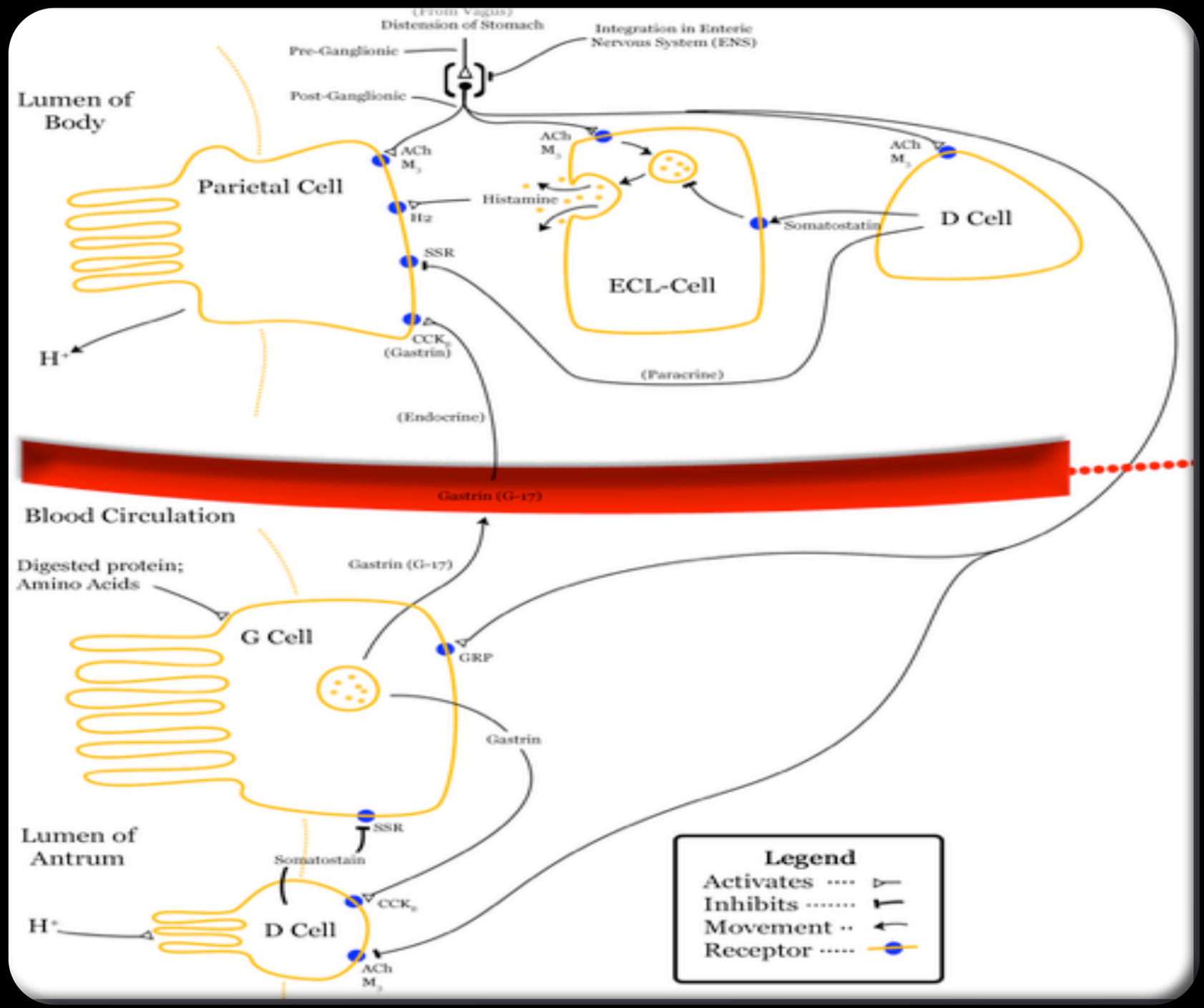
	A	M	C	B
AchE	+++	+	-	-
CVS	++	+++	+	±
GIT	++	++	+++	+++
GUS	+	+	++	++
Block	+++	+++	+	+++
Nicotinic	++	+	+++	-

- AcH not used much
  - Hydrolysed too rapidly
- Related agents differ in
  - Nicotinic versus muscarinic activvity
  - Kinetics (Resistance to hydrolysis)

Side Effects & Toxicity

- Bronchoconstriction
- Hypotension
- Gastric acid secretion
- Flushing
- Sweating
- Abdominal Cramps

Contraindications



- Asthma
- Myocardial ischaemia
- Peptic ulceration
- Hyperthyroidism

Cholinomimetics Summary

- Muscarinic Agnoists
  - Structure & Analogs
  - Mechanism of action
  - Pharmacodynamics
  - Uses
  - Side Effects & Toxicity

Anticholinesterases

Outline

- Mechanism of action
- Classification
- Indications
- Contraindications
- Side Effects
- Toxicity

Mechanism of Action

- Bind to and inactivate the cholinesterase enzyme

Mechanism of Action

- Inactivation of acetylcholinesterase:
  - Higher levels of AcH
  - Longer duration of action

- Both water-soluble and lipid soluble inhibitors bind acetylcholinesterase and block its active site.

Lipid Soluability

- Water-soluble inhibitors are hydrolyzed within 2-8 hours.
- Lipid-soluble inhibitors form stable complex with enzyme and are released over periods of days to weeks.

Classification

- Carbamates (reversible & water soluable)
  - Physostigmine
  - Neostigmine
  - Pyridostigmine, Edrophonium
- Centrally Acting Agents
  - Donepezil

Classification

- Organophosphates (irreversible & lipid soluable)
  - Isoflurophate (Pralidoxime antidote)
  - Echothiophate
- Insecticides: Malathion, Parathion
- Nerve Gases: Sarin, Tabun

Indications

- Reversal of neuromuscular blockade
- Myasthenia Gravis

Muscarinic Effects

- "Amplify" endogenous acetylcholine.
  - Eye (Miosis)
  - Resp (Bronchoconstriction)
  - CVS (Hypotension, bradycardia)
  - Urological (Urination)

Muscarinic Effects

- GI effects
  - Diarrhoea
  - Vomiting & Salivation
- CNS effects
  - Tremor & Anxiety
  - Convulsions & Coma

Nicotinic Effects

- Skeletal muscle
  - Fasiculations

Side Effects

- Can be predicted from the physiology of acetyl choline
  - Muscarinic
  - Nicotinic
- DUMBELS
  - Diarrhea, Urination, Miosis, Bronchoconstriction, Excitation (of skeletal muscle & CNS), Lacrimation, and Salivation and Sweating

Toxicity

- Seen with clinical overdosage, pesticide poisoning and chemical warfare (Sarin, Soman)
- ANTI-MUSCARINIC - Atropine
  - Reduces the effects of ACh at muscarinic sites
- CHOLINESTERASE REACTIVATOR

Toxicity

- Pralidoxime (2-PAM)
  - N+ interacts with the anionic site
  - Donates the proton from the NOH group to the phosphorylated enzyme
  - Dephosphorylation of the enzyme

Outline

- Mechanism of action
- Classification
- Indications
- Contraindications
- Side Effects
- Toxicity

Anticholinergic agents

Anticholinergics

- Chemistry
- Mechanism of action
- Classification & Pharmacology
- Indications
- Side effects
- Toxicity

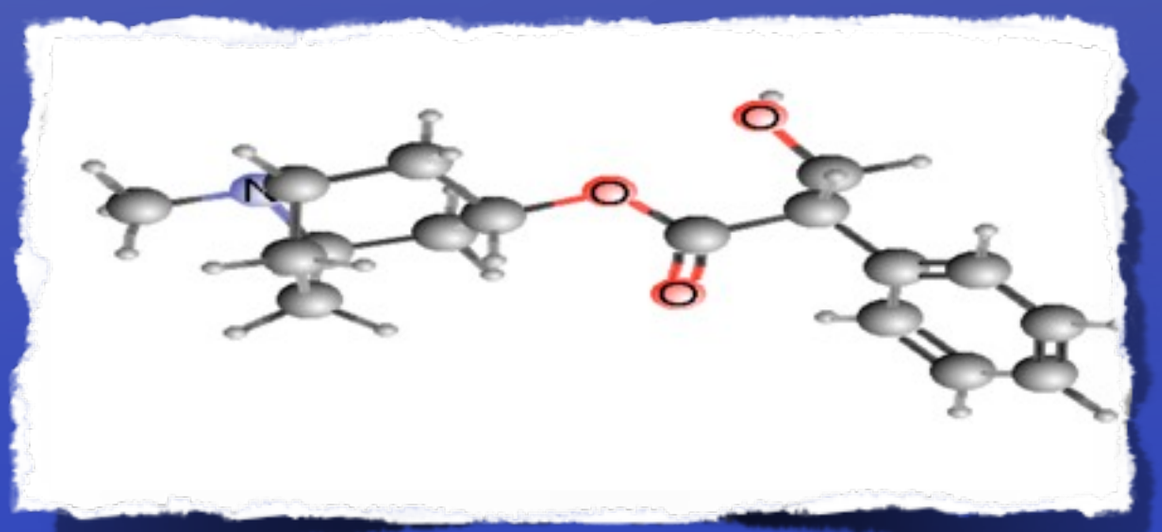
Chemistry

- Widely found in nature
- Atropine
  - Deadly nightshade (Atropa Belladonna)
  - Datura Stramonium (Jamestown Weed)
- Scopolamine
  - Hyoscyamus niger, henbane

Atropine

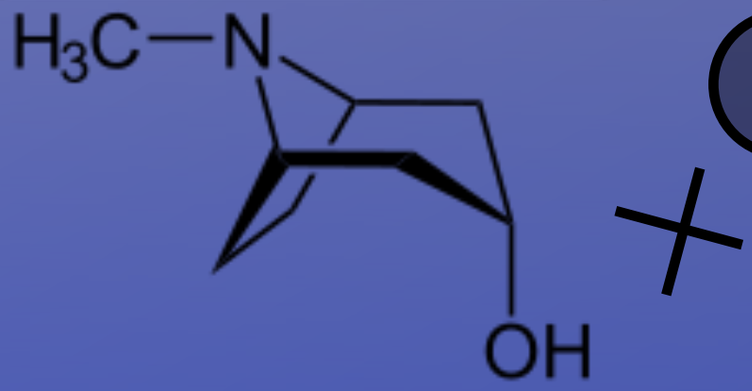
- Atropine is the ester of the organic base tropine and tropic acid
- It is a nonselective competitive antagonist
  - M1 & M2 receptors
- Negligible effects at nicotinic receptors

Synthesis of Atropine

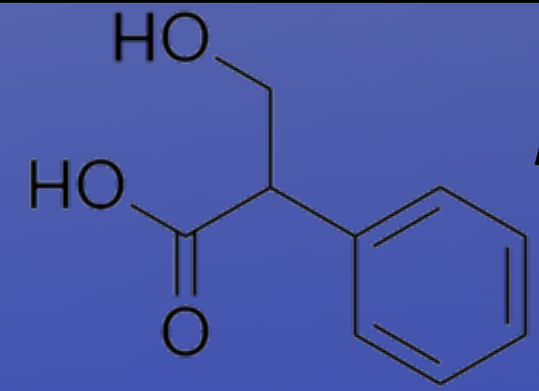


Synthesis of Atropine

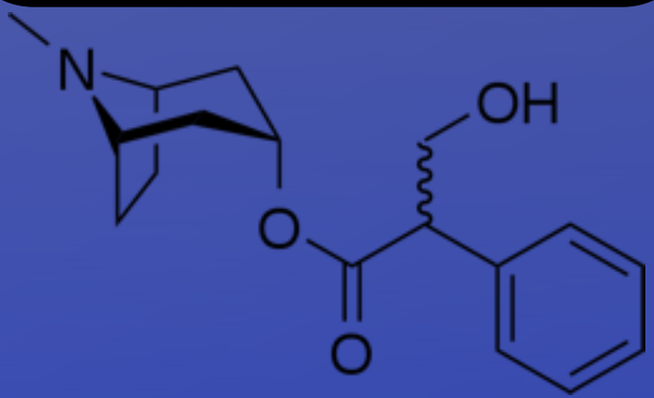
Trophine

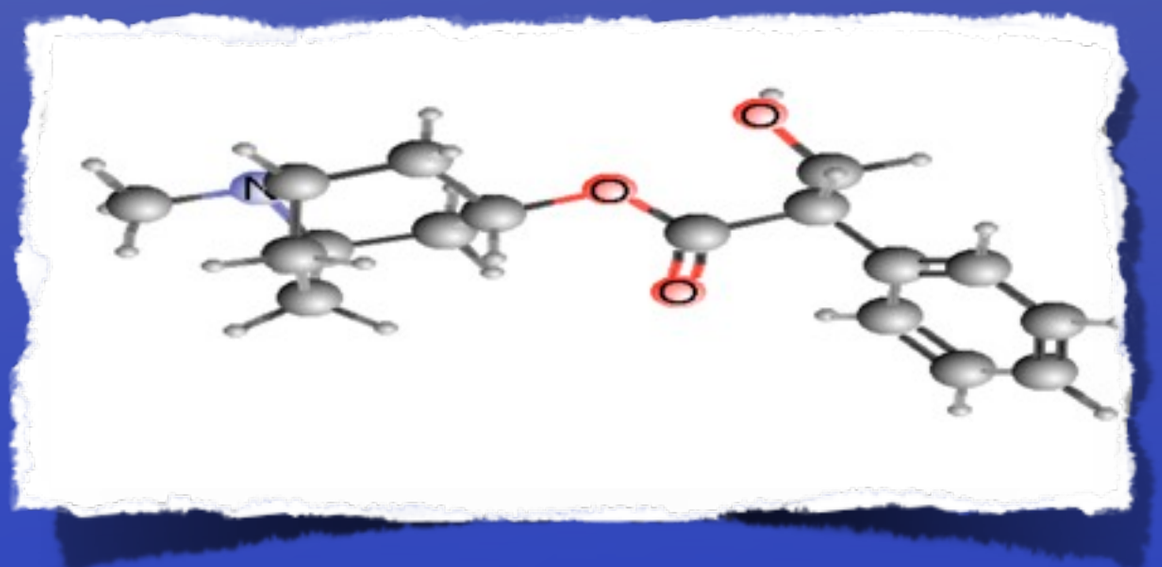


Trophic Acid



Atropine

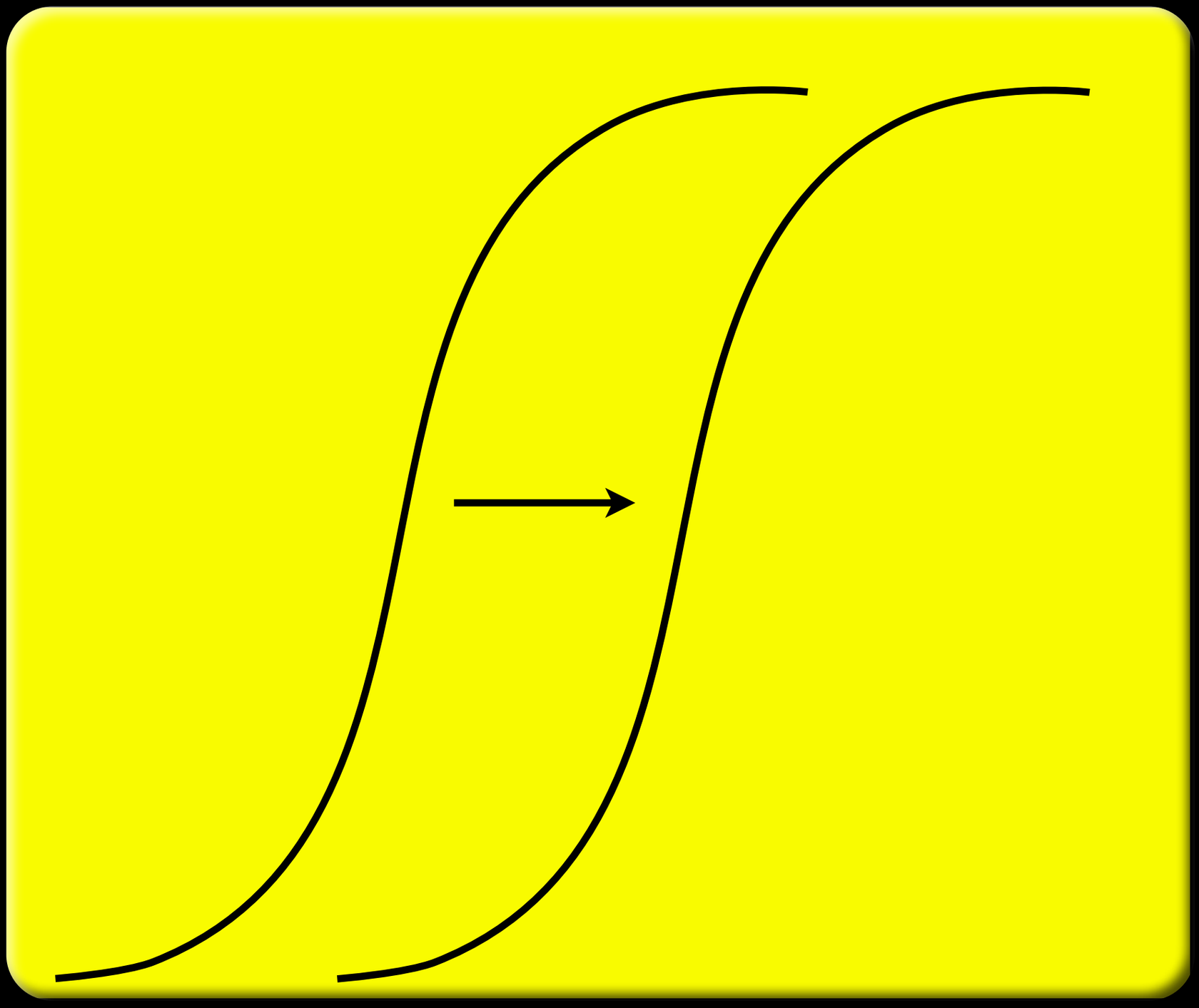




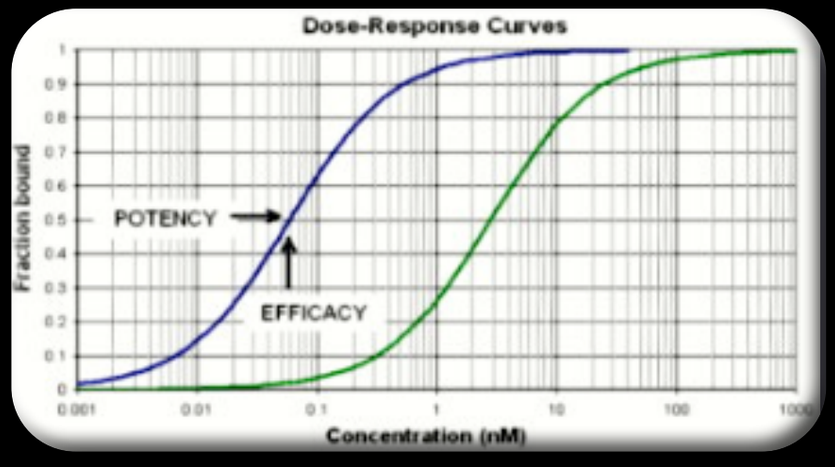
Structure Activity Isomerism

- Asymmetrical carbon atom in the acid portion of the ester conveys optical activity.
  - Scopolamine is l-hyoscine and is far more potent than the d-isomer
  - Atropine is a racaemic mixture of d & l-hyoscyamine but the antimuscarinic activity is almost entirely due to the l-isomer

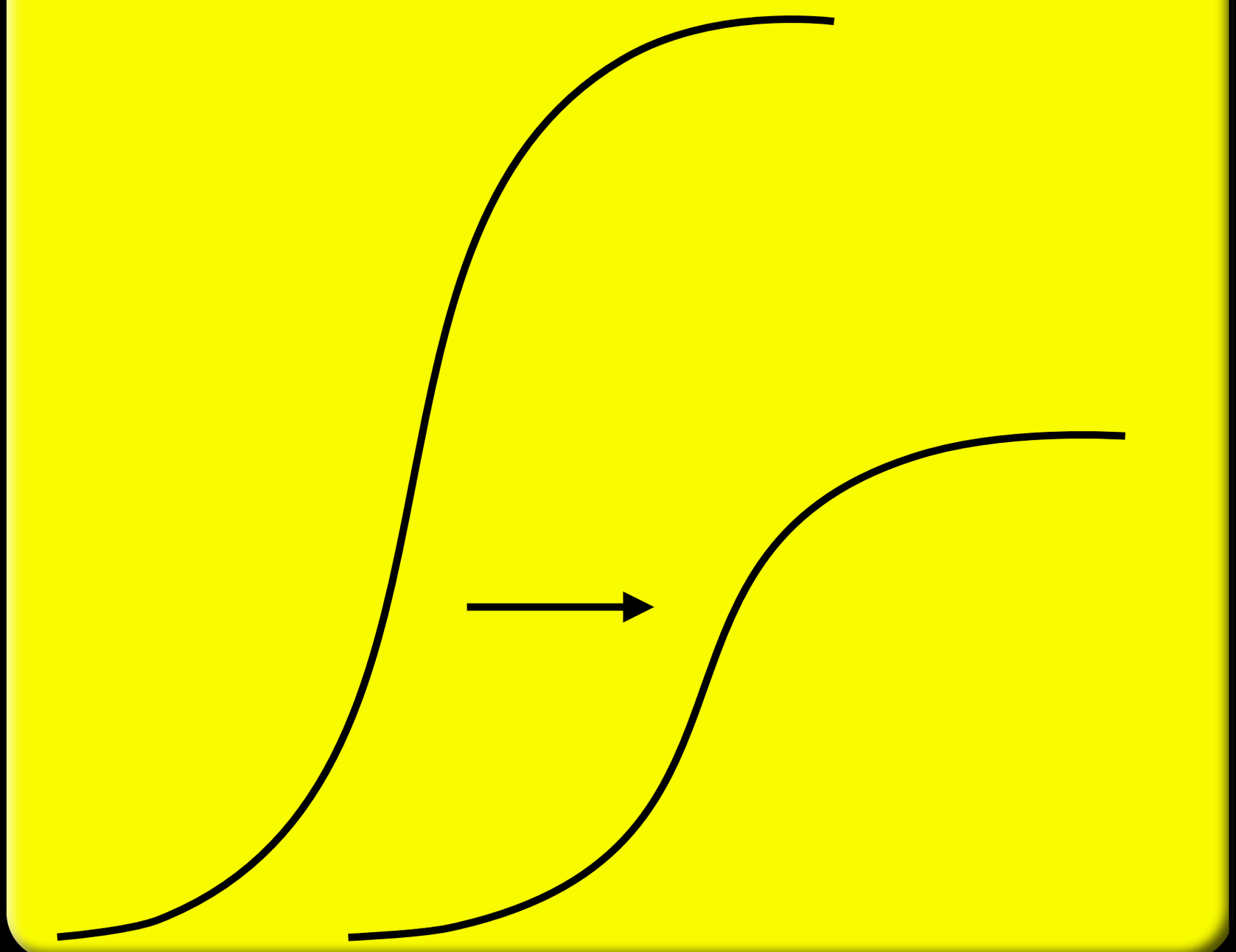
Antagonists Competitive



- Competitive antagonists of ACh
- Bind to the same site on the M receptor



Antagonists
Non - Competitive



- Non competitive antagonist
- Bind differently

Atropine: Indications

- Cardiovascular
- Respiratory / Secretory
- Acid suppression (Obsolete)
- Sedation
- In reversal of blockade

Atropine: Dosage

- 5-10 mcg/kg (0.3-0.6 mg)
- Larger doses used
  - In reversal of blockade
  - In myasthenic syndromes
  - With organophosphate toxicity
  - In severe bradycardias

Glycopyrrolate

- Originally used in the treatment of peptic ulcer disease
- Anaesthetic premedicant
- Antisialogogue action
  - long duration
  - potency relative to atropine ~ 2:1

Ipratropium

- Anticholinergic that is poorly absorbed
- Useful topically
  - Asthma

Toxicity

- Cardiovascular
- CNS
- GIT
- Urogenital

Anticholinergics

- Chemistry
- Mechanism of action
- Classification & Pharmacology
- Indications
- Side effects
- Toxicity