Autonomic Nervous System 3/3

DRUGS ACTING ON CHOLINERGIC TRANSMISSION

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SUMMARY

- General features of cholinergic transmission
- Actions of Ach and its destruction
- Cholinomimetics
- Muscarinic antagonists
- Cholinesterase inhibitors
- Principles of treating pesticide poisoning
- Next lecture: drugs acting on the NMJ

ANATOMICAL LAYOUT

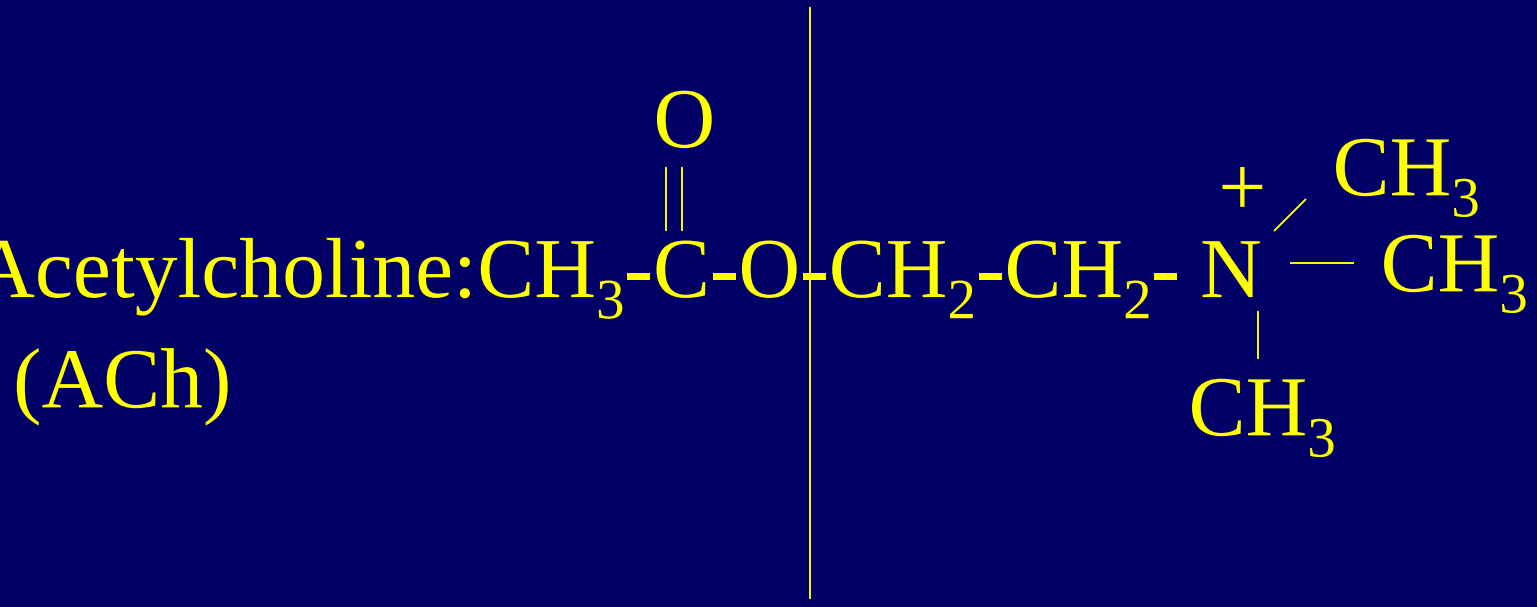
Parasympathetic Nervous System (PsNS)

- Preganglionic cell body
  cranio (III, VII, IX, X) & sacral (S1-4) CNS
- Long preganglionic nerve to wall of end-organ
- Short intramural postganglionic fibre

SITES OF ACTION

- All preganglionic fibres are cholinergic (ACh), both SNS & PsNS
- PsNS postganglionic neurones are also cholinergic (ACh)
- Most SNS postganglionic neurones are adrenergic (NA rather than Adr)
  - Except sweat glands, piloerector muscles & a few blood vessels which are cholinergic

TRANSMITTER

- Acetylcholine: 

(ACh)

An ester

TRANSMISSION

- Transmitters are preformed and stored in the vesicles in the nerve endings
- With depolarisation, vesicles fuse to membrane and empty contents to exterior
- They diffuse across the synapse to reach the membrane of the effector cell (post-ganglionic or end-organ)

RECEPTORS

Cholinergic receptors are of 2 kinds, both activated by acetylcholine:

- Nicotinic

  At SNS and PsNS ganglia i.e. on postganglionic cell bodies & non-ANS sites e.g. motor end plate

- Muscarinic

  Found at all PsNS postganglionic nerve endings & SNS postganglionic cholinergic nerve endings

  i.e. on these effector cell membranes

DESTRUCTION OF TRANSMITTER

Short lived after secretion across the synapse:

- terminated by acetylcholinesterase in the post-synaptic environment. Re-used in the presynaptic nerve ending.

Also terminated by non-specific/pseudo/or butyrylcholinesterase found in the plasma. 10% population have inherited deficiency.

CHOLINERGIC DRUGS

Actions of cholinomimetic drugs:

- Eye: pupil constriction (miosis) ciliary muscle spasm (accommodation for near vision)
- Exocrine glands: increased secretions
- Heart: bradycardia, AV block
- Bronchi: bronchoconstriction, ↑ secretion
- GI tract: ↑ motility, ↓ sphincter tone
- Bladder: ↑ contraction & micturition

MUSCARINIC AGONISTS

- 3 types of receptor: M_1 (CNS), M_2 (heart), M_3 (smooth muscle)
- ACh has no therapeutic value:
  - widespread actions & rapid metabolism

Cholinomimetics:

- Methacholine – bronchial challenge studies
- Pilocarpine – miosis leads to↑ aqueous humour drainage in open angle glaucoma

MUSCARINIC ANTAGONISTS

- Competitive blocking action at effector cell (<u>not</u> nicotinic ganglionic receptor)
- 'Antimuscarinic' drugs

<u>ATROPINE</u>

- $T_{1/2}$ 2 hours
- Administered iv
- Poorly lipid soluble (less CNS penetration)

USES OF ANTIMUSCARINICS 1/2

- Organophosphate poisoning – atropine
- Parkinson's Disease – benzhexol (po), benzatropine (iv, im): rigidity & tremor
- Extrapyramidal side-effects of major tranquillisers – benzhexol, benzatropine, procyclidine, orphenadrine
- Bradycardia/heart block – atropine

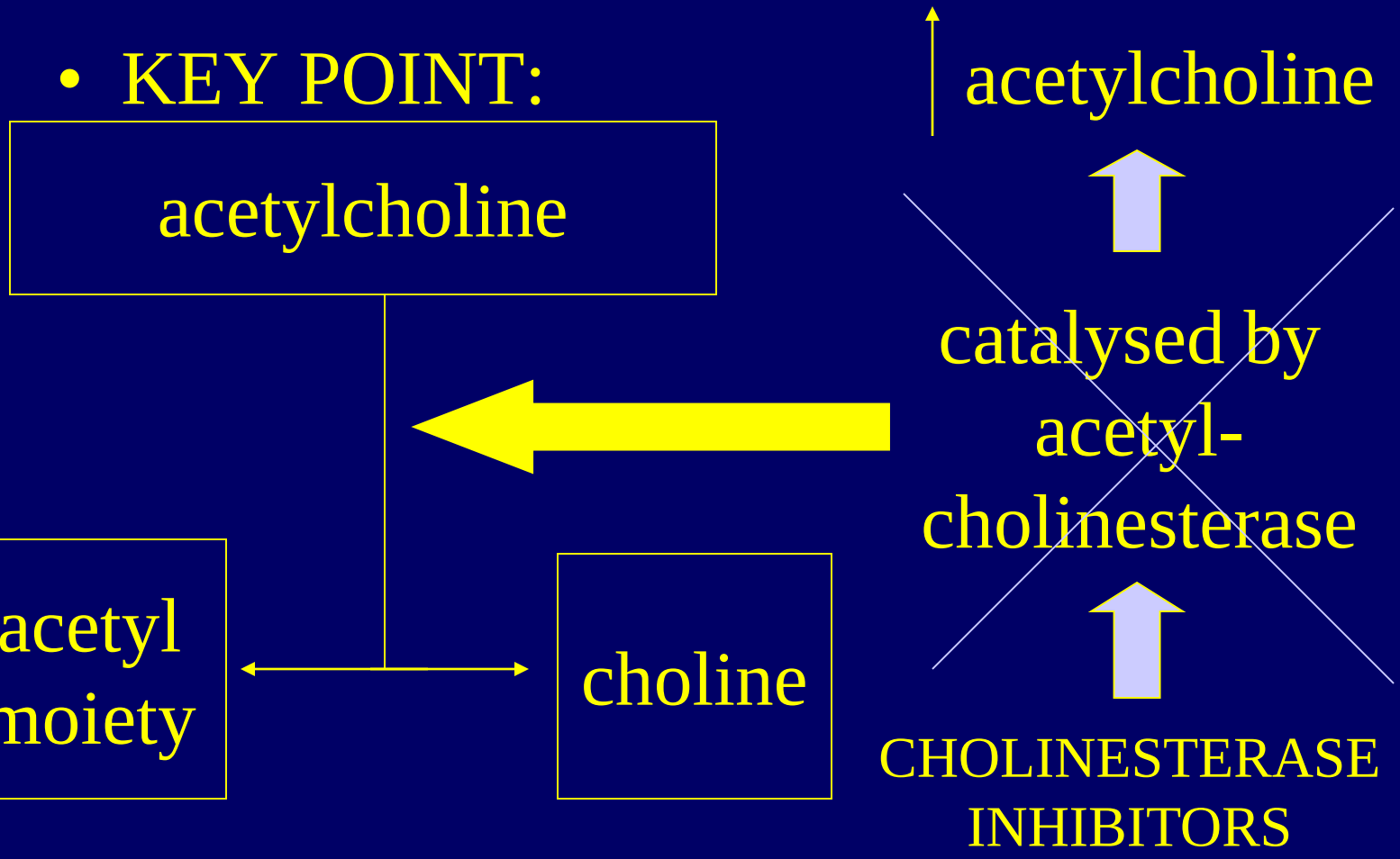
USES OF ANTIMUSCARINICS 2/2

- Anaesthetic premed & motion sickness - hyoscine (sedating)
- Bronchodilator – ipatropium (inhaled/neb)
- Eye – tropicamide, cyclopentolate (topically)

  dilate pupil (mydriasis) & paralyse accommodation (cycloplegia)
- Bladder – oxybutynin, detrusor muscle instability

CHOLINESTERASES INHIBITORS ARE CHOLINOMIMETIC

- KEY POINT:



WHICH DRUGS INHIBIT CHOLINESTERASE ?

Cholinesterase inhibitors or Anticholinesterases.

- increase muscarinic and nicotinic actions of ACh

‘Reversible’ Carbamates

- Clinically used – edrophonium, neostigmine, pyridostigmine, physostigmine (next lecture)
- Pesticides – Carbaril

‘Irreversible’ Organophosphates (OP)

- Pesticides – Parathion, Malathion
- Nerve gases – Sarin, Tabun

ANTICHOLINESTERASE POISONING

Organophosphates covalently phosphorylate serine in the active site of the acetyl-cholinesterase. Leads to irreversible inhibition of ACh destruction and prolonged effects.

‘Reversible’ carbamate poisoning only lasts a few hours.

- Features are of cholinergic overactivity

OUTLINE OF MANAGEMENT

- OP's are absorbed by the skin, lungs & GI tract, so wash skin & gastric lavage
- Atropine is the drug of choice, repeated frequently. Needs large doses.
- May need mechanical ventilation and treatment of convulsions

Pralidoxime is a cholinesterase reactivator. Dephosphorylates active site and allows ACh destruction. Only useful for OP poisoning.

NICOTINIC RECEPTOR ANTAGONISTS

(Next lecture)

ACh receptor blockers at nicotinic receptors on the motor end plate, causing muscle weakness

- Non-depolarising: tubocurarine, atracurium pancuronium
- Depolarising:suxamethonium(succinylcholine)

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