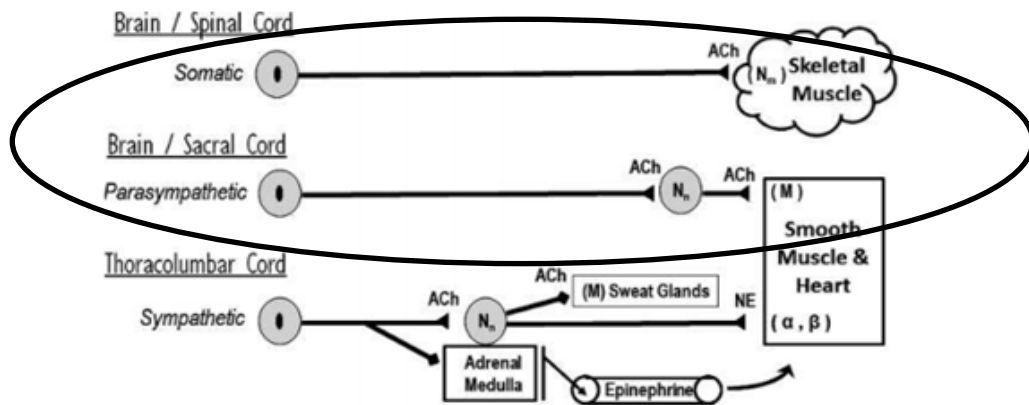


The Parasympathetic Nervous System and Associated Pharmacology

Dr Janieke van Nugteren

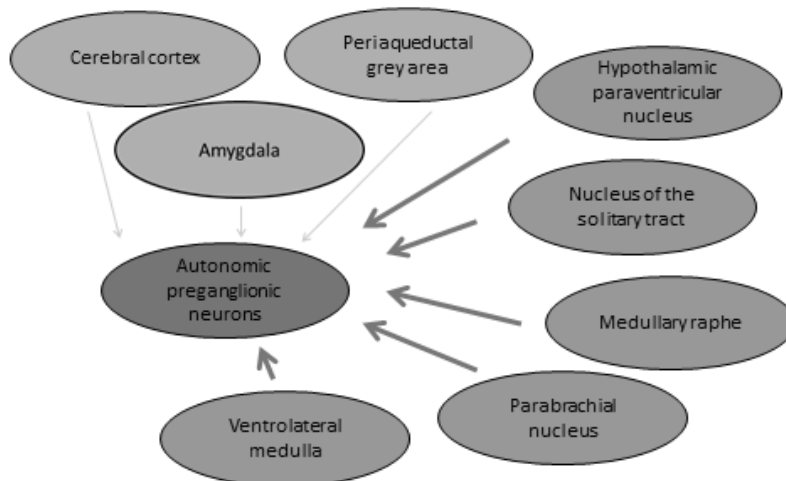
UCT Dept of Anaesthesia & Perioperative Medicine
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Becker DE. Basic and Clinical Pharmacology of Autonomic Drugs. *Anesthesia Progress*. 2012;59(4):159-169.

Pathways from the brain that control autonomic responses.

Brain origins of ANS



Indirect projections (thin arrows) Direct projections (thick arrows)

The parasympathetic nervous division of the autonomic nervous system (ANS) is sometimes called the craniosacral division of the ANS because of the location of the preganglionic neurons. The parasympathetic nerves supply the visceral structures in the head via the oculomotor, facial and glossopharyngeal nerves – and those in the thorax and upper abdomen via the vagus.

The sacral outflow supplies the pelvic viscera via branches of the 2nd-4th sacral spinal nerves.

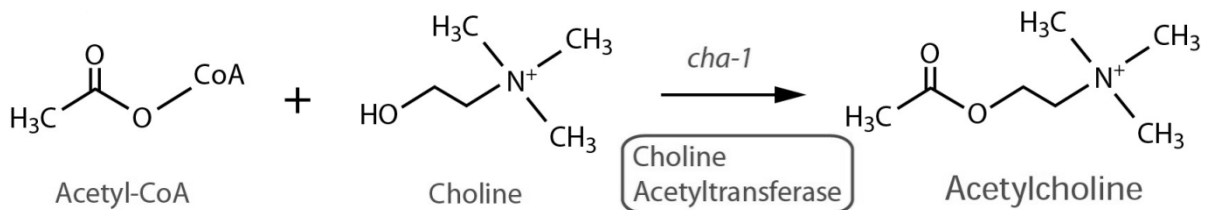
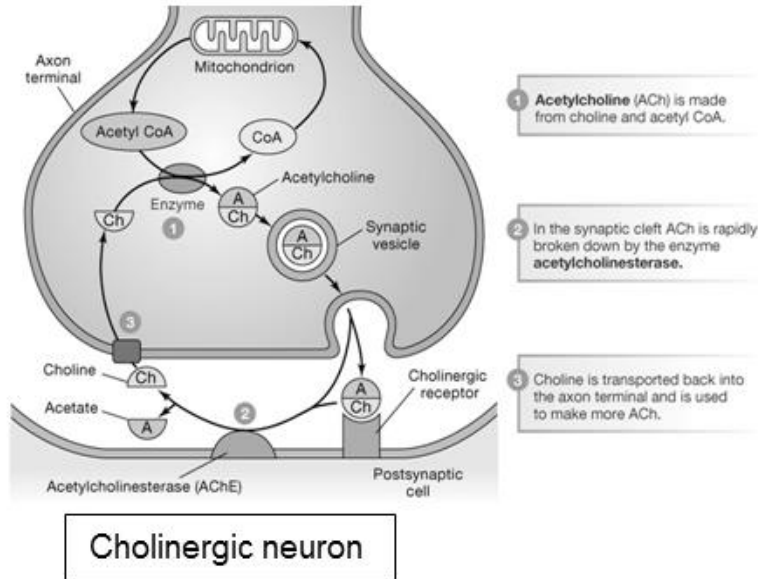
Parasympathetic preganglionic fibres synapse on ganglia clustered within wall of the visceral organs. This means that the parasympathetic postganglionic fibres are very short.

Neurotransmitters:

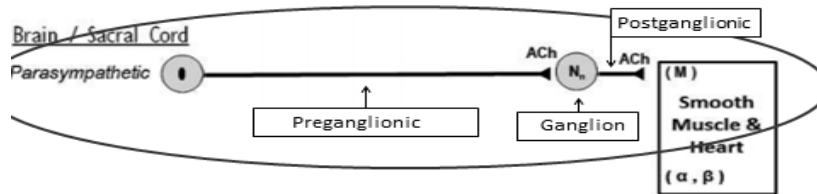
Acetylcholine is released at all preganglionic neurons, postganglionic parasympathetic neurons and a few post-ganglionic sympathetic neurons (sympathetic vasodilatory fibres and sweat glands).

The remaining sympathetic postganglionic neurons release **norepinephrine**.

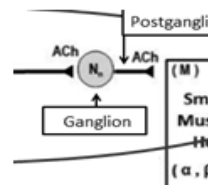
Acetylcholine is formed within cholinergic neurons and broken down within the synaptic cleft:



Parasympathetic nervous system



Nicotinic



Ganglion agonists

Nicotine	Stopping smoking
Lobeline	
Epibatidine	

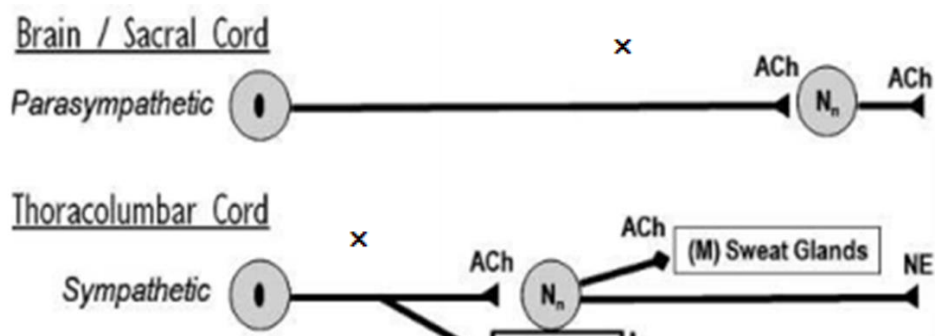
Ganglion antagonists

Hexamethonium	(First anti-hypertensive)
Trimetaphan	BP lowering

Ganglionic transmission is mediated via **nicotinic agonists** and blocked via **nicotinic antagonists**. None of these drugs other than nicotine (which is used in smoking cessation products) are used clinically anymore.

Ganglion antagonists block both SNS and PNS ganglia and so have the following clinical effects:

- Hypotension / ↓ HR
- Loss of cardiac reflexes
- Inhibition of secretions
- GIT paralysis
- Impaired micturition



Muscarinic agonists (Direct)

Muscarine was first isolated from the mushroom *Amanita muscaria*.



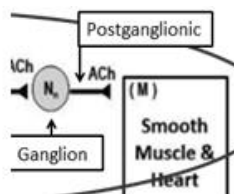
Anaesthetists do not use drugs in this class.

The majority of drugs which are used in this class are those that are used to treat glaucoma. The parasympathetic nerves to the eye supply the constrictor pupillae muscle which runs circumferentially in the eye. The ciliary muscle adjusts the curvature of the lens. In glaucoma drainage of aqueous humour becomes impeded with a dilated pupil. Activation of the constrictor pupillae muscles by muscarinic agonists lowers IOP.

Pilocarpine is a tertiary amine and crosses the conjunctival membrane and is used to treat glaucoma.

Bethanechol stimulates smooth muscle of the GIT and facilitates bladder evacuation in the absence of organic obstruction.

Muscarinic Agonists (Direct)



Muscarine	<i>Amanita muscaria</i>
Pilocarpine	Glaucoma
Bethanechol	Bladder and GIT hypotonia



Bezerkers

Muscarinic agonists (Indirect)

Anticholinesterases inhibit acetylcholinesterase (AChE) -the enzyme that causes hydrolysis of Ach to choline and acetic acid. Anticholinesterases inhibit hydrolysis by binding to the AChE and forming relatively stable complexes to prevent Ach reaching the catalytic site of the enzyme. They can be divided into:

- Reversible anticholinesterases
- Irreversible anticholinesterases – Organophosphates

Reversible anticholinesterases

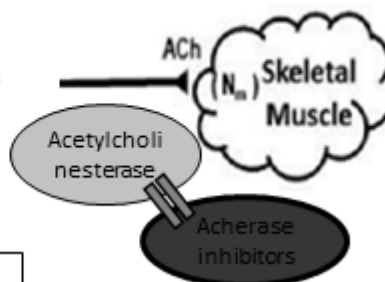
	Edrophonium	Physostigmine	Neostigmine	Pyridostigmine
Indications	Tensilon test: In MG helps to distinguish cholinergic crisis (too much Ach) and too little (Myasthenic crisis)	-Glaucoma -Postop shivering	-Reversal of NDMRs -Myasthenia Gravis	Myasthenia Gravis (drug of choice due to long DOA/ less muscarinic side effects)
Structure	Quaternary ammonium	Tertiary amine (crosses the BBB)	Quaternary ammonium	Quaternary ammonium
Predominant site of action	Presynaptic	Postsynaptic	Postsynaptic	Postsynaptic
Onset of action	80 seconds	Not known	120 seconds works at same time as glycopyrrolate	3-5 minutes(very slow)
Duration	60-120 min after IV	20-30 min	40-60 min IV 2-4 hours after oral	112 minutes

Adapted from Applied Pharmacology in Anaesthesiology and Critical Care: Multi author, Milner A, Welch EH 1st edition 2012

Irreversible anticholinesterases

Organophosphate poisoning is relevant to anaesthetists since these patients present to ICU. Examples of these pesticides are Parathion and Malathion.

Muscarinic Agonists (Indirect)



Acetylcholinesterase inhibitors	
<i>Reversible</i>	
Neostigmine	Reverse NDMRs
Pyridostigmine	Myasthenia Gravis
Physostigmine	Glaucoma/ atropine poisoning
Edrophonium	Myasthenia Gravis diagnosis

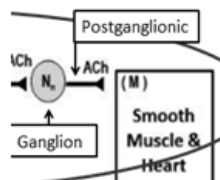
<i>Irreversible</i>	
Organophosphates	
Ecothiopate	Glaucoma
Parathion	Pesticides
Malathion	Pesticides

They combine with AChE at the esteratic site to form a stable phosphorylated inactive complex which cannot be hydrolysed.

Treatment in ICU involves atropine infusion which acts as a muscarinic antagonist.

Echothiopate is used by ophthalmologists to cause ciliary muscle contraction for treatment of glaucoma. It may enhance neostigmine's effect and should not be used prior to GA with neuromuscular blocking agents

Muscarinic Agonists



↓ HR ↓ cardiac output

Smooth muscle

↑ peristalsis, bladder, bronchial smooth muscle contracts

Glands

↑ Sweating, lacrimation, salivation and bronchial secretion



Constriction and ↓ intra-ocular pressure

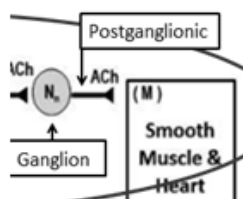
Muscarinic antagonists

Atropine and hyoscine are alkaloids from the belladonna plants (Nightshade family– which includes tomatoes and aubergine). They are muscarinic antagonists – resulting in competitive antagonism of muscarinic receptors- thus blocking the effect of ACh. In general they don't cause significant effects at the nicotinic receptors.

Atropine and hyoscine are tertiary amines which cross the blood brain barrier (BBB).

Ipratropium (Atrovent™) used to treat bronchospasm and glycopyrrolate are quaternary amines and do not cross the BBB.

Muscarinic Antagonists



Atropine	Anaesthesia/ Organophosphate poisoning
Glycopyrrolate	Anaesthesia
Hyoscine	Motion sickness
Oxybutynin	Bladder incontinence
Ipratropium	Bronchodilator (Atrovent™)
Tropicamide	Mydriasis
Pirenzepine	



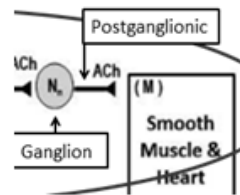
Nightshade family
Atropa belladonna
(Belladonna)



Red as a beet (Hyperthermia)
Dry as a bone (No sweating)
Mad as a hatter (crosses BBB)
Blind as a stone (mydriasis and poor near-sightedness).

Ways to remember the effects of atropine

Muscarinic Antagonists



↑HR ↑cardiac output

Smooth muscle

Decreased peristalsis, bladder, bronchial smooth muscle dilation

Glands

↓ Sweating, lacrimation, salivation and bronchial secretion



Dilation and ↑ intra-ocular pressure

Atropine

Glycopyrrolate

	Atropine	Glycopyrrolate
Onset	50-80 secs	90-120 secs
Duration	2-4 hours	Vagal block 2-3 hours Antisialagogue 7 hours (IM)
Dose	10-20 mcg/kg IV	4-6 mcg/kg
Characteristics	Tertiary amine- crosses BBB	Quaternary amine- does not cross BBB More powerful antisialagogue
Side effects	Dry mouth Relaxes LOS Relaxes bronchi (Inspissation of secretions) Confusion (elderly) Decreased sweating/ heatstroke	Dry mouth Relaxes LOS
Caution	IHD / High temp/ pyrexia/ obstructive uropathy/ glaucoma	Glaucoma/ CVS disease/ High temp/ pyrexia