**Autonomic Pharmacology 1**

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**Basic Anatomy of the ANS**

**Cholinergic Transmission**

- Nerves which use acetylcholine as a neurotransmitter

![Chemical Structure of Acetylcholine](attachment:acetylcholine.png)

**An approach to the cholinergic nerves**

1. **Supply** of transmitter precursor  
2. **Synthesis** of transmitter  
3. **Storage** of transmitter  
4. **Release** of transmitter  
5. **Inactivation** of transmitter  
6. **Feedback** inhibition of release

**1. Supply**

- Nerves cannot make enough choline  
- Choline has to be taken up from blood  
- Choline comes from diet and from liver  
- Uptake into nerve endings via a high-affinity carrier, Na$^+$-dependent process  
- **Hemicholinium:**  
  - is competitive inhibitor of the choline carrier  
  - Causes *activity-dependent block* of cholinergic transmission, due to depletion of ACh stores  
- No clinical use (as its actions are widespread)
2. Synthesis
Choline + acetylCoA $\rightarrow$ acetylcholine + CoA catalysed by choline acetyltransferase (ChAT)
• ChAT occurs in nerve cytoplasm
• Triethylcholine is also a substrate and this gives acetyltriethylcholine, a 'false transmitter' (see later)
• ChAT inhibitors are not used clinically

3. Storage
Storage of acetylcholine
Store is maintained by energy-dependent pump

Choline + acetylCoA $\rightarrow$ acetylcholine + CoA
Catalysed by choline acetyltransferase (ChAT)

4. Release
Always requires entry of Ca$^{2+}$ into nerve ending
Occurs by exocytosis:
fusion of vesicle membrane with cell membrane

4. Release
Drugs that affect the release of acetylcholine
• Massive release and depletion of vesicles evoked by black widow spider venom ($\alpha$-latrotoxin)
• Release blocked by botulinum toxin. Used clinically to treat blepharospasm, salivary drooling, axillary hyperhidrosis, achalasia (oesophageal spasm) and for cosmetic reasons; but it is also a biological warfare agent

5. Inactivation
How is ACh removed from the synaptic cleft?
• Diffusion is not important, unless cholinesterase is inhibited
• Main mechanism is hydrolysis by tissue acetylcholinesterase
  Acetylcholine $\rightarrow$ acetate + choline
This is non-reversible

5. Inactivation
Cholinesterases
• Acetylcholinesterase (AChE) present in nerve and muscle cells, red cell membrane
• AChE is mainly bound to cell membranes or to basement membrane
• Soluble form of AChE is secreted from neurons into CSF (diagnosis of spina bifida or CSF leak)
• Very specific for hydrolysis of ACh
**5. Inactivation**

**Cholinesterase inhibitors**
- Only work if there is pre-existing tonic release of ACh
- Clinically most important actions are on:
  - skeletal muscle (reverse neuromuscular blockade; diagnosis and treatment of myasthenia gravis)
  - CNS (treatment of Alzheimer’s disease)
  - Eye (treatment of glaucoma; pupillary constriction)
- Examples: neostigmine, physostigmine
- Many common insecticides (organophosphates) are cholinesterase inhibitors (eg. Parathion)

**Clinical Aside: Myasthenia Gravis**
- Cause: autoantibodies to skeletal nicotinic receptors
- Symptoms:
  - muscle weakness
  - rapid fatigue (eyelids first; ptosis)
- Diagnosis: Edrophonium (short acting AChEI; “Tensilon test”)
- Treatment: eg. Neostigmine (medium-duration AChEI)

**Topical Aside:**
**Allegations of Chemical Weapons use in Syria (2013)**
- Symptoms reported included “excess saliva, narrow pupils and vomiting” or “vomiting and have breathing problems” or “some appear to have constricted pupils”.
- “Those injured in the strike itself had responded ‘very quickly’ to treatment with atropine”
- All of these features are typical of organophosphate ‘nerve agents’, which act by irreversible acetylcholinesterase inhibition. Examples: sarin, soman.


**Butyrycholinesterase**
- Non-specific cholinesterase (wrongly called pseudocholinesterase)
- Found in blood plasma
- Hydrolyses many different choline esters
- Metabolises some drugs, e.g. suxamethonium
- Rare genetic forms without activity, so check before giving suxamethonium (neuromuscular blocker)

**6. Feedback**

**Cholinergic nerves have presynaptic (or prejunctional) receptors**
- ACh (muscarinic) inhibits release of ACh (enteric)
- ACh (nicotinic) increases the release of ACh (motor)
- ATP, adenosine inhibit release
- Morphine (opioids) inhibit release (autonomic), leads to constipation
- Noradrenaline (α-) inhibits release (autonomic) increases release (motor nerves) Consider what happens in heavy exercise

Note possibility of feed-back inhibition of ACh release by ACh itself or by co-released ATP

**Nicotinic Allosteric Potentiating Ligands**
- Act on nicotinic receptors to increase their activity
- Many also have anticholinesterase activity
- Examples:
  - galanthamine (from the snowdrop)
  - rivastigmine
Acetylcholine Release and Modulation

Acetylcholine (ACh) is the transmitter at the following sites:
1) motor nerve endings in skeletal muscle
2) preganglionic autonomic
3) postganglionic parasympathetic (e.g. vagus to the heart)
4) postganglionic sympathetic (e.g. symp. vasoconstrictor)

In other words, skeletal muscle, heart and sympathetic ganglion cells must all have chemically-sensitive sites (receptors) for acetylcholine.

Nicotinic Receptor Antagonists

Selectively antagonised by:
1) Skeletal muscle:
   - decamethonium, α-bungarotoxin
   - atracurium, pancuronium, rocuronium

2) Autonomic ganglia (and CNS):
   - hexamethonium

Non-specific antagonists: d-tubocurarine

Ganglion blocking drugs

Hexamethonium was used to treat high blood pressure (hypertension). Problems:
1) very poorly absorbed from gut; have to be given by injection.
2) not only blocks sympathetic ganglia, but also parasympathetic ganglia, to give unpredictable side-effects.

Mechanism of action of Hexamethonium

- Blocks the ion channel
- Chief characteristics which distinguish channel block from competitive block are:
  1. Use dependent block
  2. Block becomes more effective as membrane hyperpolarized
Nicotinic cholinoceptors
Relative potencies series of agonists:
(1) Skeletal muscle:
nicotine > carbachol >> DMPP >>> methacholine
or
(2) Autonomic ganglia (and CNS):
nicotine, DMPP > carbachol >>> methacholine
muscarine

DMPP = dimethylphenylpiperazinium

Nicotinic Receptor Agonists
Eg. Nicotine
- Commonly cause desensitisation
- Ganglia are no longer targeted
Clinically because of wide-spread effects

Muscarinic Agonists
Parasympathomimetics
- G-protein-coupled
- 7 transmembrane segments.

Muscarine

Parasympathomimetics
- ACh
- Carbachol
- Methacholine
- Bethanecol
- Muscarine
- Pilocarpine
- Oxotremorine

All closely mimic effects of parasympathetic nerve stimulation

Effects of Parasympathomimetics
Cardiovascular - decreased heart rate, cardiac output
Smooth muscle - contracts, vascular dilates via endothelium (EDRF = NO)
Exocrine glands - secrete - sweating, lacrimation, salivation, bronchial secretion

Effects of muscarinic agonists
- increased secretions (eg. salivation!)
- increased gut motility
- slowing of the heart
- bronchoconstriction
- urinary frequency
- constriction of pupil
- vasodilation, via activation of receptors which are not innervated

NB: Many of these effects are also present with acetylcholinesterase inhibition
Clinical uses muscarinic agonists

- **Pilocarpine**
  - Topically for glaucoma (through an action on ciliary muscle and hence increasing aqueous humor drainage)
- Muscarinic agonists: for atonic bladder (to increase bladder contraction).

Uses of Parasympathomimetics

- **Glaucoma**
- Suppression of atrial tachycardia (rare use)

Muscarinic Antagonists

5 subclasses - 3 are particularly important

<table>
<thead>
<tr>
<th>Class</th>
<th>Location examples</th>
</tr>
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<tbody>
<tr>
<td>M&lt;sub&gt;1&lt;/sub&gt;</td>
<td>Stomach, salivary glands</td>
</tr>
<tr>
<td>M&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Cardiac</td>
</tr>
<tr>
<td>M&lt;sub&gt;3&lt;/sub&gt;</td>
<td>Smooth muscle</td>
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While there are subtype-specific antagonists, they are rarely used. However, the less-specific antagonists are used.

Clinical Uses of Antimuscarinic Drugs

- Asthma (ipratropium)
- To treat bradycardia (atropine)
- To decrease gut motility; decrease secretions (pirenzapine)
- During operations: decrease secretions, decrease AChEi side-effects (atropine)
- To dilate pupils (tropicamide)
- Urinary incontinence (oxybutynin)
- Motion sickness (hyoscine)

Summary

3 main types of receptors for ACh:

1. **Skeletal nicotinic**: α<sub>1</sub>
   - Ligand-gated ion channels
2. **Neuronal nicotinic**: α<sub>2-7</sub>
3. **Muscarinic**: M<sub>1-5</sub>
   - G-protein coupled receptors

Beware the partial agonist (or prolonged agonist exposure) blocking the functional response (e.g. nmj depolarization block)