Parasympathetic Nervous System
Part I

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Parasympathetic Nervous System

Key Points
- Division – Anatomical
- Usually dual innervation
- Usually antagonistic
- Usually one dominates
- Usually some ANS “tone”

Cholinergic Neurotransmission

Rate limiting step
Uptake of choline into nerve terminal

Synthesis
Choline
Acetyltransferase

Termination
Enzymatic by acetylcholinesterase (AchE)
**Cholinergic Receptors**

- **Muscarinic** (7 transmembrane)
  - M₁ - autonomic ganglia, CNS
  - M₂ - heart
  - M₃ - smooth muscle, glands
  - M₄, M₅
  - M₁₃ → PLC, M₂₄
  - G-protein coupled

- **Nicotinic** (ion channel)
  - pentamer, 5 subunits
  - N₁ or N₂ - ganglia, adrenal medulla (α₂β₂, α₂β₁)
  - N₄ or N₃ - skeletal muscle (infant α₂β₂γ, adult α₂β₂γ)
  - α subunit, Ach binding (2)

**True Acetylcholinesterase (AchE)**

(Other: Pseudoacetylcholinesterase, circulating, plasma, butyrylcholinesterase)

<table>
<thead>
<tr>
<th>AchE</th>
<th>BuChE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nerves</td>
<td>Yes</td>
</tr>
<tr>
<td>NMJ</td>
<td>Yes</td>
</tr>
<tr>
<td>Circул</td>
<td>Little</td>
</tr>
</tbody>
</table>

**Muscarinic effects on organ systems**

- **Heart** (M2)
  - ↓ HR, ↓ contractility, ↓ conduction velocity

- **Vasculature** (not innervated)
  - vasodilation: nitric oxide (NO)

- **Other smooth muscle**

- **Eye**: pinpoint pupil (miosis), focus for near vision

- **GI-tract**: ↑ tone to intestine, bladder, ↓ tone to sphincters

- **Lung**: contract bronchial SM. → ↑ resistance, ↑ secretions

- **Exocrine glands**
  - ↑ sweating (cholinergic sympathetic)
  - ↑ salivation, ↑ gastric acid secretion (M1)

**Muscarinic receptor agonists**

- **Choline esters**
  - ACH (muscarinic & nicotinic action)
  - methacholine (not common)
  - carbachol (direct/indirect; muscarinic & nicotinic)

- **Alkaloids**
  - muscarine (mushrooms)
  - pilocarpine (DOC, used in glaucoma emergency)
  - oxotremorine (synthetic) CNS action (basal ganglia)

- **Uses**
  - ophthalmic (Ach, brief miosis)
  - diagnostic for belladonna poisoning (methacholine)
  - urinary retention (bethanechol)
  - reverse GIT depression (bethanechol)

**Cholinergic Stimulants**

- **Direct-acting** (receptor agonists)
  - Muscarinic
  - Nicotinic

- **Indirect-acting** (cholinesterase inhibitors)
  - Edrophonium
  - Physostigmine
  - Neostigmine

**Wild Mushrooms - Amanita**

- **WARNING! Picking and Eating Wild Mushrooms Can Kill You!**

  10,000 cases per year

  Muscarine poisoning
  5,000 mushroom species
  100 “bad”, 10 “deadly”
Adverse Reactions - Cholinergics

- Adverse reactions: (SLUDE)
  - Salivation
  - Lacrimation
  - Urination
  - Diarrhea
  - Emesis (vomiting)
  - Cardiac slowing (arrest, esp. bethanechol)
  - Nausea, cramps
  - Bronchoconstriction, can precipitate asthma
  - Involuntary defecation, urination
  - Tremor, CNS induced convulsions

Nicotinic receptor agonists

Ganglionic stimulants

- Clinically not important
- Acetylcholine (natural transmitter)
- DMPP (experimental)
- Nicotine (alkaloid, tobacco)
- Lobeline (tobacco)

Indirectly-Acting Parasympathomimetics

- Interact with acetylcholinesterase
  True and/or pseudocholinesterase (serum)
- Two sites:
  - Anionic site that binds the quaternary amine and positions the Ach molecule
  - Esteratic site which attacks the acyl carbon
- Inhibitors of cholinesterase:
  - Reversible inhibitors (eg. physostigmine)
  - Irreversible inhibitors (eg. organophosphates)

Reversible inhibitors

- Quaternary ammonium compounds
  - Edrophonium (synthetic, water stable, 5-10 min)
  - Tensilon test – Myasthenia gravis
  - Ambenonium (synthetic, 4-8 hr)
- Carbamates
  - Physostigmine (0.5-2 hr)
    (tertiary amine, well absorbed, CNS activity, can give topically)
  - Neostigmine (0.5-2 hr)
    (quaternary amine, no CNS activity, synthetic, some direct action)

Myasthenia gravis

Autoimmune disease

1:10,000 (250,000 USA)
- Antibodies to NMJ nicotinic receptors leads to degradation
- Simplified synaptic folds
- Normal nerve terminal and transmitter
- Wider synaptic junction
- Diagnosis: Edrophonium (Tensilon, short acting) is used for diagnosis and determination of maintenance dose
- Treatment: Neostigmine has direct (stimulates receptor) and indirect actions (inhibition of AchE). No CNS activity.

Acetylcholinesterase and Reversible inhibitors

- Ach very fast 0.15ms
- Neostigmine undergoes metabolism 0.5 – 6 hr
- Enzyme becomes operational again
**Irreversible inhibitors**

- **Organophosphates**  
  (highly lipid soluble, >50,000 compounds)
  - Diisopropyl-fluorophosphate (DFP)
  - Ectothiophate (low lipid solubility, no CNS)
  - Sarin, Soman (nerve gases)
  - Malathion, Parathion (more toxic)
    - Inactive, converted to active compound in body \((S \rightarrow O)\)
    - Pesticides, very lipid soluble

**Acetylcholinesterase & Irreversible Inhibition**

**DFP, Isoflurophate**

**2-PEM**  
2-PAM  
Pralidoxime  
No CNS action

**DFP Aging**  
Nerve gas  
30-40 min

**Malathion**  
4 – 6 hr

**US Military 2-PAM / Atropine Injector**

**2.5 mg Atropine, 600mg 2-PAM**

**Clinical use: Acetylcholinesterase Inhibitors**

- **Eye**: miosis (sphincter contraction), accommodation block (ciliary muscle contraction)  
  Use: Glaucoma (wide-angle or secondary glaucoma)  
  Physostigmine or echorithiothéphate (long acting)
- **GI tract**: ↑ motility in paralytic ileus (post-op) or atony of urinary bladder. Neostigmine (bethanechol better)
- **Neuromuscular junction:**  
  - Neostigmine in Myasthenia gravis  
  - Edrophonium as diagnostic Myasthenia gravis  
  - Reverse NMJ block after surgery, Neostigmine
- **Reverse toxicity by anticholinergic agents:**  
  - ie. atropine, tricyclic antidepressants (high doses)  
  - Physostigmine is preferred (CNS action)

**Acetylcholinesterase Inhibitors**

<table>
<thead>
<tr>
<th>Uses</th>
<th>Approximate Duration of Action</th>
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<tbody>
<tr>
<td>Alcohols</td>
<td></td>
</tr>
<tr>
<td>Edrophonium</td>
<td>Myasthenia gravis, ileus, arrhythmias 5-15 minutes</td>
</tr>
<tr>
<td>Carbenes and related agents</td>
<td></td>
</tr>
<tr>
<td>Organophosphates</td>
<td></td>
</tr>
</tbody>
</table>
### Toxicity & Treatment of AchE Inhibitors

- **Adverse reactions:** (SLUDE)
  - Salivation (muscarinic)
  - Lacrimation (muscarinic)
  - Urination (muscarinic)
  - Diarrhea (muscarinic)
  - Emesis (vomiting) (muscarinic)
  - Cardiac slowing (muscarinic)
  - Hypertension / Hypotension (nicotinic)
  - NMJ paralysis (nicotinic)
  - Cramps (muscarinic)
  - Bronchoconstriction (muscarinic)
  - Tremor, nausea, CNS induced convulsions

- **Treatment:** Muscarinic antagonist ie. Atropine
  - AchE reactivator (Pralidoxime, 2-PAM)
  - Mechanical respiration

### Symptoms of Parasympathetic Toxicity

<table>
<thead>
<tr>
<th>SLUDGE</th>
<th>DUMBBELS</th>
</tr>
</thead>
<tbody>
<tr>
<td>S - Salivation</td>
<td>D - Diarrhea</td>
</tr>
<tr>
<td>L - Lacrimation</td>
<td>U - Urination</td>
</tr>
<tr>
<td>U - Urination</td>
<td>M - Miosis/muscle weakness</td>
</tr>
<tr>
<td>D - Diarrhea</td>
<td>B - Bronchorrea (↑mucus)</td>
</tr>
<tr>
<td>G - Gastric upset</td>
<td>B - Bradycardia</td>
</tr>
<tr>
<td>E - Emesis</td>
<td>E - Emesis</td>
</tr>
<tr>
<td>-</td>
<td>L - Lacrimation</td>
</tr>
<tr>
<td>-</td>
<td>S - Salivation/sweating</td>
</tr>
</tbody>
</table>