Parasympathetic Nervous System
Part I

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Cholinergic Neurotransmission

- Rate limiting step: Uptake of choline into nerve terminal
- Synthesis: Choline Acetyltransferase
- Termination: Enzymatic by acetylcholinesterase (AchE)

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)

Cholinergic Receptors

- Muscarinic (7 transmembrane)
  - M1, -autonomic ganglia, CNS
  - M3, -heart
  - M4, -smooth muscle, glands
  - M135 ↑ PLC, M34 ↓ A/C
  - G-protein coupled
- Nicotinic (ion channel)
  - pentamer, 5 subunits
  - N2 or N2 -ganglia, adrenal medulla (α2, β1, β2)
  - N2 or N2 -skeletal muscle (infant α2, adult α2β1δε)
  - α subunit, Ach binding (Z)

Cholinergic Stimulants

- Direct-acting
  - Muscarinic
  - Nicotinic
  - Reversible
- Indirect-acting
  - Cholinesterase inhibitors
  - Edrophonium, carbamates
  - Physostigmine
  - Neostigmine
  - Malathion
  - DFP
  - Nerve gas

True Acetylcholinesterase (AchE)

(Others: Pseudocholinesterase, circulating, plasma, butyrylcholinesterase)

Quaternary group

<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>Circul</td>
<td>Little</td>
</tr>
</tbody>
</table>

AchE: 300,000 Ach / enzyme / min (0.15 msec/cycle)
Muscarinic receptor agonists

- **Choline esters**
  - ACH (muscarinic & nicotinic action)
  - bethanechol (oral or sc, never iv or im → cardiac arrest)
  - methacholine (not common)
  - carbachol (direct/indirect; muscarinic & nicotinic)

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

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

Adverse Reactions – Cholinergics

- **Adverse reactions:** (SLUED)
  - Salivation
  - Lacrimation
  - Urination
  - Diarrhea
  - Emesis (vomiting)
  - cardiac slowing (arrest, esp. bethanechol)
  - nausea, cramps
  - bronchoconstriction, can precipitate asthma
  - involuntary defecation, urination
  - tremor, CNS induced convulsions

Also: DUMBBELS, SLUGBAM and MTWThF (nicotinic excess)

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)
  - 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)

Irreversible AchE inhibitors

• Organophosphates
  (highly lipid soluble, >50,000 compounds)
  - Diisopropyl-fluorophosphate (DFP)
  - Echothiophate (low lipid solubility, no CNS)
  - Sarin, Suman, Vx (nerve gases)
  - Malathion, Parathion (more toxic)
    Prodrugs, inactive, converted to active compounds in body (S → O)
    pesticides, very lipid soluble

Myasthenia gravis
Autoimmune disease

$\text{MY} \rightarrow \text{Ach} \rightarrow \text{NMJ} \rightarrow \text{Nerve terminal} \rightarrow \text{Transmitter}$

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

<table>
<thead>
<tr>
<th>Neostigmine</th>
<th>Edrophonium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ach very fast 0.15ms</td>
<td></td>
</tr>
<tr>
<td>Neostigmine undergoes metabolism 0.5 – 6 hr</td>
<td></td>
</tr>
<tr>
<td>Enzyme becomes operational again</td>
<td></td>
</tr>
</tbody>
</table>

Acetylcholinesterase & Irreversible Inhibition

DFP, Isoflurophate

$\text{DFP Aging}$

2-PAM Pralidoxime No CNS action

DFP Aging 30-40 min

Nerve gas secs / min

Malathion 4 – 6 hr

Clinical use: Acetylcholinesterase Inhibitors

• Eye: Miosis (sphincter contraction), accommodation block (ciliary muscle contraction)
  Use: Glaucoma (wide-angle or secondary glaucoma)
  Physostigmine or echothiophate (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)
**Actions on the Eye**

Glaucome treatment

1. α-Agonist
   - ↑ Outflow
2. M-Agonists
   - ↑ Outflow
3. β-Blocker
   - ↓ Secretion
4. α2-Agonist
   - ↓ Secretion
5. PGs: ↑ Outflow
6. Carbonic acid inhibitors ↓ Secretion

**Innervation of the Iris**

100 hours Glaucoma

**Echothiophate, DFP, Malathion (Phospholine), nerve gases etc.**

4-6 hours Glaucoma

**Demecarium (Humorsol)**

4-8 hours Myasthenia gravis

**Ambenonium (Mytelase)**

1/2-2 hours Myasthenia gravis

**Neostigmine (Prostigmine)**

1/2-2 hours Myasthenia gravis, ileus, arrhythmias

**Physostigmine (Eserine)**

1/2-2 hours Myasthenia gravis

**E触thiophate, DFP, Malathion**

100 hours Glaucome

**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**

**SLUDGE**

- S - Salivation
- L - Lacrimation
- U - Urination
- G - Gastric upset
- E - Emesis

**DUMBBELS**

- D - Diarrhea
- U - Urination
- M - Miosis/muscle weakness
- B - Bronchorrea (↑ mucus)
- B - Bradycardia
- E - Emesis

**Adverse Reactions – Cholinergics cont.**

- **SLUGBAM (muscarinic excess):**
  - Salivation, seizure
  - Lacrimation
  - Urination
  - GI distress: diarrhea, vomiting
  - Bronchoconstriction
  - Abdominal cramps
  - Miosis

- **MTWThF (nicotinic excess):**
  - Mydriasis
  - Tachycardia
  - Weakness (muscle paralysis)
  - Th Hyperthermia
  - Fasciculations

**Acetylcholinesterase Inhibitors**

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>Uses</th>
<th>Duration of Action</th>
</tr>
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<tbody>
<tr>
<td>Alcohols</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edrophonium (Tension)</td>
<td>Myasthenia gravis, ileus, arrhythmias</td>
<td>5-15 minutes</td>
</tr>
<tr>
<td>Carbamates and related agents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neostigmine (Prostigmine)</td>
<td>Myasthenia gravis, ileus, NMJ reverse</td>
<td>1/2-2 hours</td>
</tr>
<tr>
<td>Physostigmine (Eserine)</td>
<td>Glaucoma</td>
<td>1/2-2 hours</td>
</tr>
<tr>
<td>Organophosphates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E触thiophate , DFP, Malathion</td>
<td>Glaucoma</td>
<td>100 hours</td>
</tr>
<tr>
<td>(Phospholine), nerve gases etc.</td>
<td></td>
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