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)
Cholinergic Receptors

- **Muscarinic** (7 transmembrane)
  - \(M_1\) -autonomic ganglia, CNS
  - \(M_2\) -heart
  - \(M_3\) -smooth muscle, glands
  - \(M_4, M_5\)
  - \(M_{135}\) \(\uparrow\) PLC, \(M_{24}\) \(\downarrow\) A/C
  - G-protein coupled

- **Nicotinic** (ion channel)
  - pentamer, 5 subunits
  - \(N_N\) or \(N_1\) -ganglia, adrenal medulla (\(\alpha_2\beta_3, \alpha_3\beta_2\))
  - \(N_M\) or \(N_2\) -skeletal muscle (infant \(\alpha_2\beta_0\delta\), adult \(\alpha_2\beta_0\gamma\))
  - \(\alpha\) subunit, Ach binding (2)

True Acetylcholinesterase (AchE)

(Others: Pseudocholinesterase, circulating, plasma, butyrylcholinesterase)

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

Quaternary group Acyl carbon

AchE: 300,000 Ach / enzyme / min (0.15 msec/cycle)
Muscarinic effects on organ systems

- **Heart (M<sub>2</sub>)**
  - ↓ 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 (M<sub>1</sub>)

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Cholinergic Stimulants

![Cholinergic Stimulants Diagram](image)

- **Muscarinic**
  - Choline esters
  - Pilocarpine
  - Muscarine

- **Nicotinic**
  - Alkaloids
  - Ach
  - Nicotine

- **Direct-acting** (receptor agonists)
  - Ganglionic
  - NMJ

- **Indirect-acting** (cholinesterase inhibitors)
  - Reversible
    - Edrophonium, carbamates
    - Physostigmine
    - Neostigmine
    - Edrophonium
  - Irreversible
    - Phosphates
    - Malathion
    - DFP
    - Nerve gas
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:** (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

Also: DUMBBELS, SLUGBAM and MTWtHF (nicotinic excess)
Symptoms of Parasympathetic Toxicity

SLUDGE

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

DUMBBELS

D - Diarrhea
U - Urination
M - Miosis
B - Bronchorrea (↑mucus)
B - Bradycardia
E - Emesis
L - Lacrimation
S - Salivation/sweating

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
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

- **Quarternary 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

Neostigmine

- Ach very fast 0.15msec
- Neostigmine undergoes metabolism 0.5 – 6 hr
- Enzyme becomes operational again

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
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

FIG. 19

Glaucoma treatment

1. $\alpha$-Agonist  
   ↑ Outflow

2. M-Agonists  
   ↑ Outflow

3. $\beta$-Blocker  
   ↓ Secretion

4. $\alpha_2$-Agonist  
   ↓ Secretion

5. PGs: ↑ Outflow

6. Carbonic acid inhibitors ↓ Secretion

Innervation of the iris
Acetylcholinesterase Inhibitors

<table>
<thead>
<tr>
<th>Alcohols</th>
<th>Uses</th>
<th>Duration of Action</th>
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<tbody>
<tr>
<td>Edrophonium (Tensilon)</td>
<td>Myasthenia gravis, ileus, arrhythmias</td>
<td>5-15 minutes</td>
</tr>
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</table>

| Carbamates and related agents | | |
| Neostigmine (Prostigmine, Prostigmin, Prostigmine, Demecarium) | Myasthenia gravis, ileus, NMJ reverse | 1/2-2 hours |
| Pyridostigmine (Mestinon) | Myasthenia gravis | 3-6 hours |
| Physostigmine (Eserine) | Glaucoma | 1/2-2 hours |
| Ambenonium (Mytelase) | Myasthenia gravis | 4-8 hours |
| Demecarium (Humorsol) | Glaucoma | 4-6 hours |

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<td>Echothiophate, DFP, Malathion (Phospholine), nerve gases etc.</td>
<td>Glaucoma</td>
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Toxicity & Treatment of AchE Inhibitors

- **Adverse reactions:** (SLUDGE)
  - 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

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